BWP Belgian Week of Pathology

10th BELGIAN WEEK OF PATHOLOGY

18.10 > 19.10.19

@ WILD GALLERY - BRUSSELS

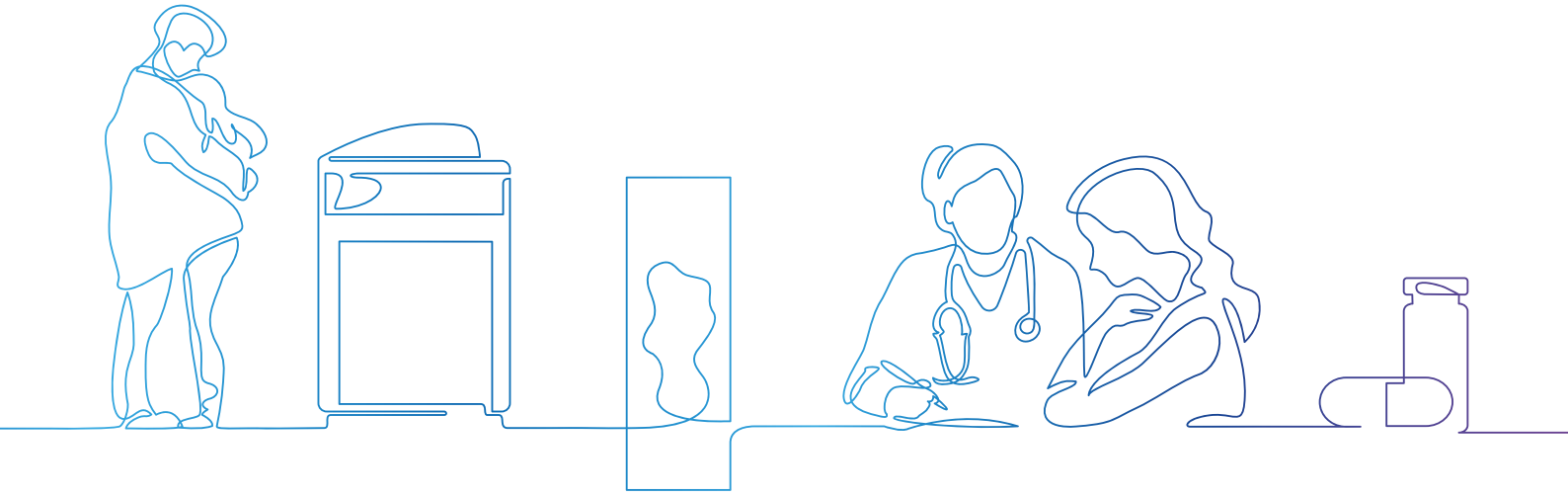
FRIDAY

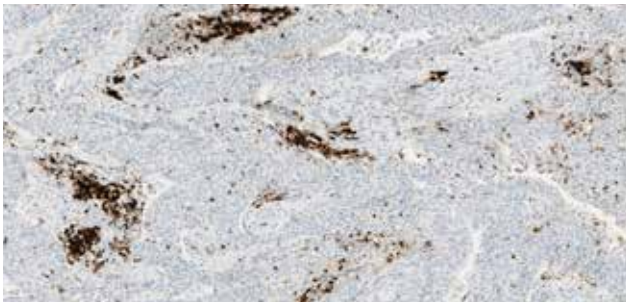
SATURDAY

www.bwpcongress.be

Predictive tests for your cancer patients

Your assay choice matters





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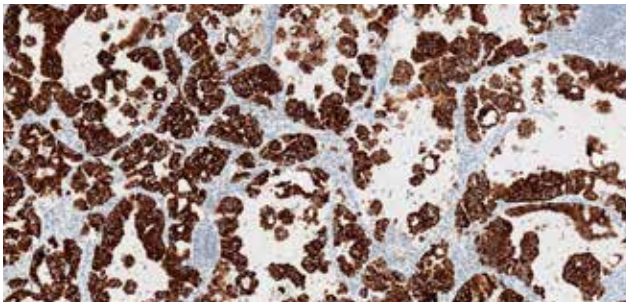

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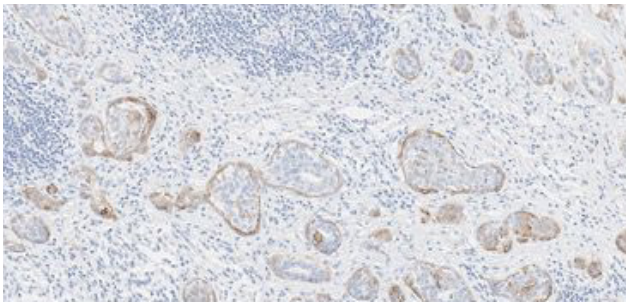

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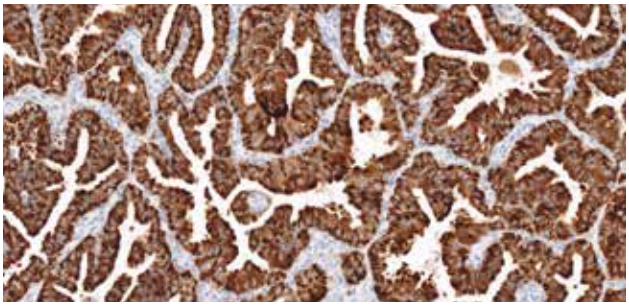

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JOIN US AT THE BOOTH

MKT_2019_171

WELCOME

Dear Colleagues and Friends,

It is our pleasure to invite you to the **10th Belgian Week of Pathology** in Brussels, the center of Europe. The congress will take place at the Wild Gallery on **October 18-19, 2019**.

The **KEYNOTE** lecture for BWP2019 will be on **Gynecological Pathology**. The world of pathology evolved from pure diagnostics to more complex precision and targeted pathology. The central role of the pathologist in the multidisciplinary management of patients is beyond dispute.

Prof. dr. Esther Oliva from Harvard in Boston, and **Prof. dr. Glenn McCluggage** from the UK, have demonstrated worldwide leadership and expertise in the field of gynecological pathology. The Belgian Society of Pathology wants to remain at the frontline in all subspecialties, and distinguished national and international experts are invited for State-of-the-Art lectures. Advances and new discoveries in Skin Lymphomas, Thyroid and Head & Neck Pathology and Molecular Pathology will be addressed.

We encourage residents to present their work by submitting abstracts, and multiple prices will be awarded not only for excellent research work but also for presenting difficult and rare disease entities.

The sponsoring companies are our partners in challenging the recent innovations to provide more accurate prognostic and predictive information to the patient. We thank them for their continuous involvement and renewed support.

The website is open for registration to the meeting. Don't forget to also book your place for the **Pathology Congress Dinner** on Friday evening.

We look forward to welcoming you in Brussels !

Koen VAN DE VIJVER
Belgian Week of Pathology President

GENERAL INFORMATION

Accreditation

Accreditation has been requested for ethics and economy as well a pathology.
Submission is done on the computers available in the exhibition area.
Submission is requested once a day. You will receive a confirmation e-mail after ending the procedure.

Language

The language of the congress is English (British spelling) for abstracts, slides and announcements.

Abstracts

Authors were invited to submit abstracts until June 30, 2019.
The result of evaluation was sent to the first authors on Augustus 23, 2019.

- Oral presentations will be presented during the related sessions
- e-Poster presentations will take place during the morning and afternoon coffee breaks and lunch of Friday October 18 and Saturday october 19.

e-Posters will be displayed during the congress on the assigned screens in the Exhibition Area.

The BWP / Belgian Society of Pathology will award:

- the Best Oral Presentation: Research (500€)
- the Best Oral Presentation: Case report (500€)
- Best e-Poster (500€).

Venue

Wild Gallery
11 rue du Charroi
B-1190 Brussels – Belgique

Parking available

Underground parking: Avenue du Pont de Luttre/ Luttrebruglaan 86
Outdoor parking: Rue du Charroi 21-23

Hotels

Pullman Brussels Centre Midi: Place Victor Horta 1 – 1060 Brussels – Belgium
Tel: +32 2 528 98 00

Event Coordinator

DME Events
Olivier Thomas – 57, Av. G. Demey – 1160 Brussels – Belgium
Tel: +32 471 46 02 72 / E-mail: o.thomas@medisquare.be

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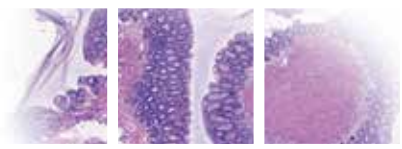

FRIDAY

SATURDAY

SBP-BVP Board

www.belgian-society-pathology.eu

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Foreign faculty

ALLORY Yves	Paris, France	**JUNG Alain**	Strasbourg, France
BOSSUYT Veerle	Boston, USA	**MCCLUGGAGE W. Glenn**	Belfast, UK
BULTEN Hans	Nijmegen, The Netherlands	**OLIVA Esther**	Boston, USA
CATHOMAS Gieiri	Liestal, Switzerland	**ORTONNE Nicolas**	Paris, France
ECKSTEIN Markus	Erlangen, Germany	**SADOW Peter**	Boston, USA
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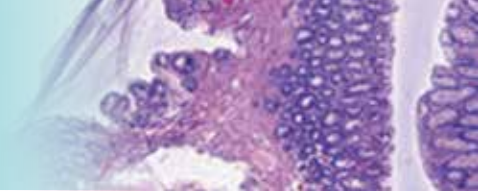
FRAITAG Sylvie	Paris, France	**VERGIER Béatrice**	Bordeaux, France
HASSELBLATT Martin	Munster, Germany		

Belgian faculty

BALDEWIJNS Marcella	Leuven, Belgium	**PAUWELS Patrick**	Antwerp, Belgium
BOURGAIN Claire	Brussels, Belgium	**SAHEBALI Shaira**	Brussels, Belgium
CREYTENS David	Gent, Belgium	**SIOZOPOULOU Vasiliki**	Antwerp, Belgium
HEBRANT Aline	Sciensano, Belgium	**VAN DOREN Waltruda**	RIZIV/INAMI, Belgium
HERFS Michaël	Liège, Belgium	**VAN EYCKEN Elizabeth**	Cancer Registry,
LAMMENS Martin	Antwerp, Belgium		Brussels, Belgium
MELENDEZ ASENSIO Barbara	Brussels, Belgium	**WEYNAND Birgit**	Leuven, Belgium

FRIDAY

SATURDAY



FRIDAY

FRIDAY October 18

	Auditorium 1	Auditorium 2
08.00-09.00	WELCOME	WELCOME
09.00-10.30	Dermato-/Hematopathology	Uropathology
10.30-11.00		**Sakura Satellite Symposium:** The Laboratory of the Future
10.30-11.15	BREAK + POSTERS SESSION	BREAK + POSTERS SESSION
11.15-12.30	Dermatopathology	Uropathology
12.45-13.30	**Educational GRANT Symposium:** Molecular testing: the NGS convention	
12.30-14.00	LUNCH + POSTERS SESSION	LUNCH + POSTERS SESSION
14.00-15.30	Surgical Pathology: Head & neck pathology	Molecular Pathology (Ethics and Economy requested: 1,5 pts)
15.35-16.05		**Astrazeneca Satellite Symposium:** Optimizing the pre-analytical phase in pathology to accommodate the next generation molecular testing
15.30-16.15	BREAK + POSTERS	BREAK + POSTERS
16.15-17.30	Surgical Pathology: Head & neck pathology	Neuropathology
17.45-18.45	KEY NOTE Lecture Gynaecological pathology	
18.45-19.30	RECEPTION	RECEPTION
19.30		**CONGRESS DINNER** at the Wild Gallery

SATURDAY October 19

	Auditorium 1	Auditorium 2
08.00-09.00	WELCOME	WELCOME
09.00-10.30	**Digestive pathology**	**Cytopathology (Ethics and Economy requested: 2,5 pts)**
10.30-11.00	**Roche Satellite Symposium (1):** Personalised Healthcare - Evolution of informed treatment decision	
10.30-11.15	BREAK + POSTERS SESSION	BREAK + POSTERS SESSION
10.45-11.05		**Announcement:** "Young Pathologists' section" in the BSP
11.15-13.00	**Breast pathology**	**Cytopathology (Ethics and Economy requested: 2,5 pts)**
12.45-13.30	**Roche Satellite Symposium (2):** PD-L1 testing in TNBC from the pathologist's perspective	
13.00-14.00	LUNCH + POSTERS SESSION	LUNCH + POSTERS SESSION
14.00-16.00	**Gynaecological pathology**	
16.00-16.15	**Awards Ceremony:** - BSP Prize: Best Oral Presentation: Research - BSP Prize: Best Oral Presentation: Case Report - BSP Prize: Best e-Poster Presentation	
16.15	CLOSING CEREMONY 10TH BWP	

Invitation

BELGIAN WEEK OF PATHOLOGY 10TH EDITION

Sakura Satellite Symposium at the 10th edition of the Belgian Week of Pathology

''The Laboratory of the Future"

Sakura Finetek Belgium invites you to attend the satellite symposium
The Laboratory of the Future on **Friday 18 October 2019, 10:35 am -11:05 am**

Speaker Paul Coombes, Director Sales & Marketing, North Region, Sakura Finetek UK

Abstract:

Behind every sample, tissue block and slide, lies a unique story. That of a person – young or old, woman or man, grandmother or son – who's anxiously awaiting their diagnosis. Because when you're waiting for results, every day, hour, and minute counts.

Sakura's mission is to constantly advance cancer diagnostics in anatomical pathology. We understand the necessity to enhance the efficiency of the current diagnostic processes and minimise the impact on people's lives. We are determined to make tomorrow's reality possible today by delivering the best solutions in the market. Smarter solutions and client-driven services that empower pathology professionals to deliver accurate and fast diagnoses to optimise treatment success for each life we touch.

Technology enables us to; constantly strive for better, faster and automated solutions like what the world is discovering in other areas of the medical field.

We look forward to seeing you there!

08.00-09.00 **WELCOME**

09.00-10.30

AUDITORIUM A

DERMATO-/HEMATOPATHOLOGY

Chairs: An Bervoets and Ivan Theate

09.00-09.45 • **Algorithmic approach of skin lympho-proliferations and skin B-cell lymphomas**
Béatrice Vergier (Bordeaux, France)

09.45-10.30 • **T-cell lymphomas, with a focus on TFH skin lymphomas**
Nicolas Ortonne (Creteil-Paris, France)

AUDITORIUM B

UROPATHOLOGY

Chairs: Sofie Verbeke and Thomas Gevaert

09.00-09.35 • **PD-L1 in bladder cancer**
Markus Eckstein (Erlangen, Germany)

09.35-10.15 • **Grading of papillary UC lesions**
Murali Varma (Cardiff, UK)

10.15-10.30 • ***Free Paper* - *An unexpected finding in the abdominal wall of a 45-year-old woman with endometriosis***
Angélique Dubail (Brussels, Belgium)

10.30-11.00 **SATELLITE SYMPOSIUM BY SAKURA (AUDITORIUM B)**

• **The Laboratory of the Future**
Paul Coombes (UK)

10.30-11.15 **COFEE BREAK (Exhibition Area)**

POSTER TOUR: P 01 to P 07 (e-Posters Area)

P 01 Intracranial desmoid tumor in a paediatric patient caused by heterozygous APC deletion
Stefanie Brock (Brussels, Belgium)

P 02 Synchronous presentation of endometrioid carcinoma of the ovary and carcinosarcoma of the uterus
Louise Cras (Brussels, Belgium)

P 03 Series of BCOR associated endometrial stromal sarcoma
Glenn Broeckx (Antwerp, Belgium)

P 04 Sebaceous adenoma of the parotid gland
Steff De Smet (Brussels, Belgium)

P 05 Metastasized angiosarcoma of the pericardium: report of a very rare case diagnosed post-mortem
Lotte Keulen (Antwerp, Belgium)

P 06 Onset of a psychiatric disease in a 52-years-old man: when autopsy revealed possible psychiatric disease!
Sophie Lecomte (Brussels, Belgium)

P 07 Esophageal melanoma: case report
Fanchon Noël (Liège, Belgium)

11.15-12.30

AUDITORIUM A

DERMATOPATHOLOGY

Chairs: Sofie De Schepper and Ursula Sass

11.15-11.40 • **What's new in Pediatric dermatopathology**
Sylvie Fraitag (Paris, France)

11.40-12.05 • **Update in cutaneous fibrohistiocytic tumours**
David Creytens (Ghent, Belgium)

12.05-12.15 • **New Belgian guidelines on 'dysplastic nevi'**
Vasiliki Siozopolou (Antwerp, Belgium)

12.15-12.30 • ***Free Paper* - *High resolution multiplexing of melanoma microenvironment in responders/non-responders to checkpoint therapy***
Yannick van Herck (Leuven, Belgium)

AUDITORIUM B

UROPATHOLOGY

Chairs: Sofie Verbeke and Thomas Gevaert

11.15-11.50 • **Benign lesions of the bladder**
Esther Oliva (Boston, USA)

11.50-12.30 • **Molecular classes of urothelial cancer, the clinical relevance and implementation in daily practice**
Yves Allory (Paris, France)

Educational Grant Symposium

Auditorium A

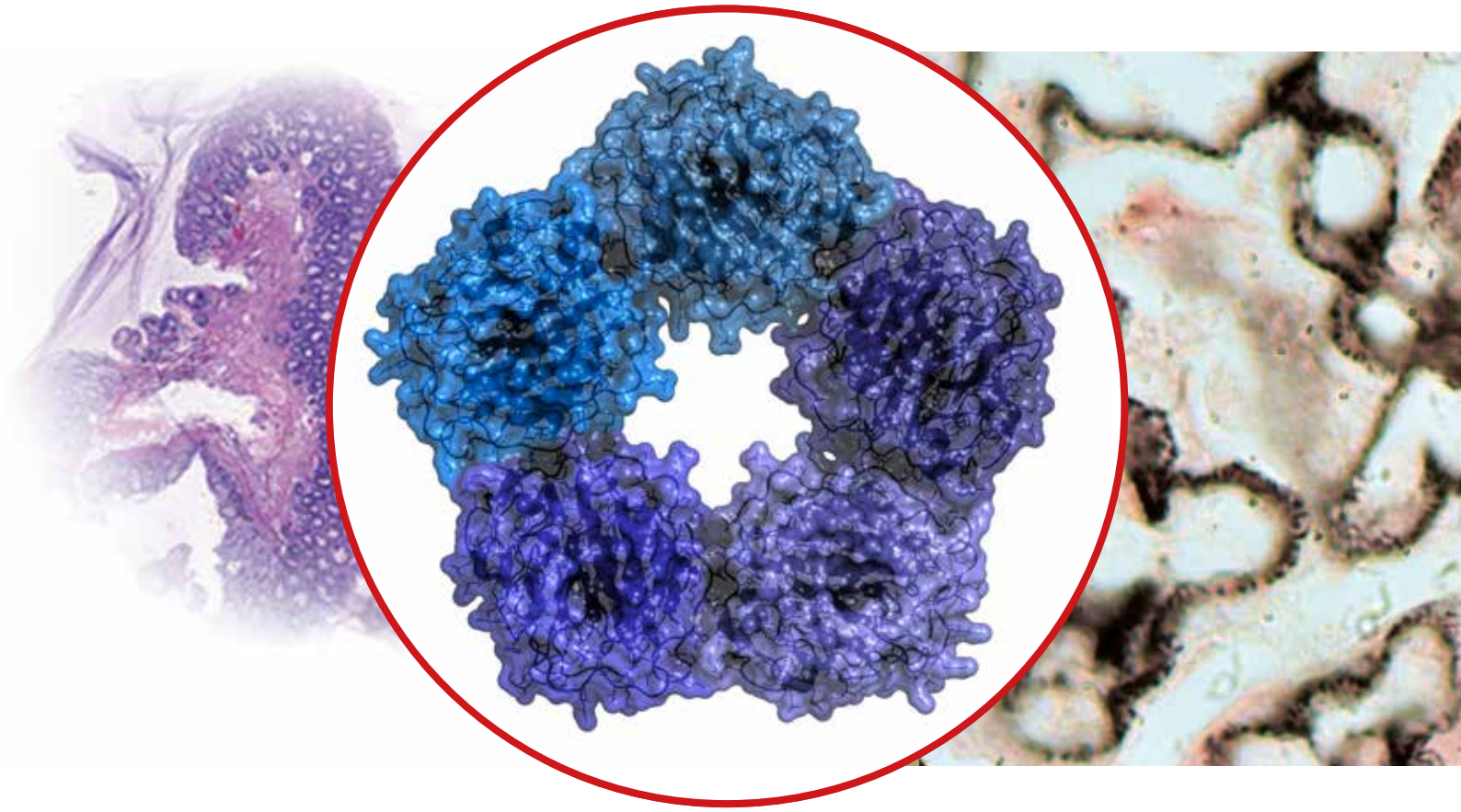
12.45-13.30

FRIDAY
OCTOBER 18

Molecular testing: the NGS convention

ALINE HEBRANT

WALTRUDA VAN DOREN



Organised thanks to the Educational Grant

with the kind support

AstraZeneca

Bristol-Myers Squibb

Roche

12.30-14.00 **LUNCH (Exhibition Area)**

12.45-13.30 **EDUCATIONAL GRANT SYMPOSIUM: Molecular testing: the NGS convention (AUDITORIUM A)**

With the kind support of: ASTRA ZENECA, BMS, ROCHE

Chairs: Patrick Pauwels and Koen Van de Vijver

- 12.45-13.05 • Molecular testing: development, use and updating of molecular algorithms and panels
  Aline Hebrant (Sciensano, Belgium)
- 13.05-13.25 • Molecular testing: the RIZIV/INAMI point of view on the NGS convention
  Waltruda Van Doren (RIZIV/INAMI, Belgium)
- 13.25 • Discussion

12.45-14.00 **POSTER TOUR: P 08 to P 14 (e-Posters Area)**

P 08 IMDM2 immunoexpression and gene amplification in a gastric wall tumor: an unexpected pitfall
Marie-Lucie Racu (Brussels, Belgium)

P 09 Molecular pathological approach of a rare tonsillar tumor
Maaike Ramael (Antwerp, Belgium)

P 10 A very rare case of intravascular NK/T-cell lymphoma: a case report and review of the literature
Stéphanie Rizzo (Liège, Belgium)

P 11 Synchronous thyroid carcinoma in a 13-year-old girl
H. Van Beveren (Ghent, Belgium)

P 12 Lipoblastoma-like tumor of the vulva in a 33-year-old woman
Hanne Van Beveren (Ghent, Belgium)

P 13 Primary cutaneous adenoid cystic carcinoma of the upper limb: common tumor, rare location
Annelore Vandendriessche (Antwerp, Belgium)

P 14 The Milan System for Reporting Salivary Gland Cytopathology: single centre experience with cell blocks
Marie Behaeghe (Leuven, Belgium)

14.00-15.30

AUDITORIUM A

SURGICAL PATHOLOGY: HEAD & NECK PATHOLOGY

Chairs: Philippe Delvenne and Ramses Forsyth

- 14.00-14.45 • Thyroid pathology: NIFTP
  Peter Sadow (Boston, USA)
- 14.45-15.30 • HPV-related HNSCC
  Alain Jung (Strasbourg, France)

AUDITORIUM B

MOLECULAR PATHOLOGY (ETHICS AND ECONOMY REQUESTED: 1,5 PTS)

Chairs: Karl Dhaene and Nicky D'Haene

- 14.00-14.30 • Fusion genes and the pathologist: good news!
  Patrick Pauwels (Antwerp, Belgium)
- 14.30-15.00 • Tumour mutational load, a burden?
  Barbara Melendez Asensio (Brussels, Belgium)
- 15.00-15.30 • When is molecular testing helpful in soft tissue tumour?
  Uta Flucke (Nijmegen, The Netherlands)

15.35-16.05 **SATELLITE SYMPOSIUM BY ASTRAZENECA (AUDITORIUM B)**

- Optimizing the pre-analytical phase in pathology to accommodate the next generation molecular testing
  Mark Kockx MD, PhD

15.30-16.15 **COFEE BREAK (Exhibition Area)**

POSTER TOUR: P 15 to P 21 (e-Posters Area)

P 15 Neuropathological findings in Leigh syndrome. A report of neonatal case
Mohamed Tahar Yacoubi (Sousse, Tunisia)

P 16 Hydrocephalus in fetuses revealing a spectrum of Walker-Warburg syndrome (Type II Lissencephaly): a fetal neuropathological study of 5 cases.
Mohamed Tahar Yacoubi (Sousse, Tunisia)

AstraZeneca Satellite Symposium

Optimizing the pre-analytical phase in pathology to accommodate the next generation molecular testing

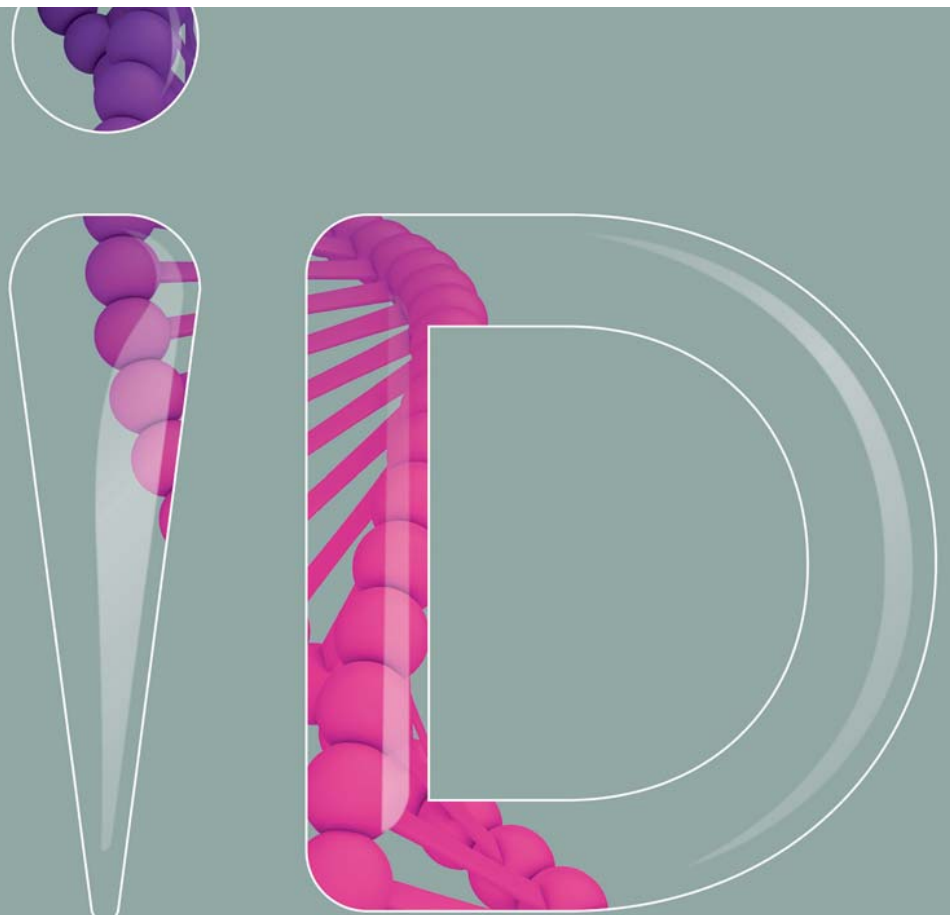
Mark Kockx, MD, PhD

In the age of molecular testing the DNA extracted from diagnostic biopsies has become an important source of information on tumour biology. It is therefore essential to preserve the quality of the DNA during sample processing critical steps like formalin fixation and paraffin embedding.

However little is known on the exact conditions required for each of these pre-analytical steps.

Dr Mark Kockx will share insights from literature and from his own work at HistoGeneX on how to create an optimal pre-analytical phase in the pathology lab today. Dr Kockx will also explain what is required for biopsy samples to be compatible with the molecular biology techniques of tomorrow.

Friday 18th of October
15h35 – 16h05
Auditorium B



P 17 Meningeal Hemangiopericytoma a pathological dilemma: immunohistochemical and genetic study
Mohamed Tahar Yacoubi (Sousse, Tunisia)

P 18 Immunohistochemistry accuracy in the diagnosis and histological classification of ovarian carcinoma
Mohamed Tahar Yacoubi (Sousse, Tunisia)

P 19 Prognostic impact of glioblastoma stem cell markers OLIG2 and CCND2
Christelle Bouchart (Brussels, Belgium)

P 20 Highlight of Mismatch repair (MMR) expression on biopsy or surgical specimen in CRC: similarity or difference in results?
Sarah Bouri (Gosselies, Belgium)

P 21 Clinicopathologic identification & risk gradation of naevus subtypes based on interdisciplinary data
Veronique Clauwaert (Ghent, Belgium)

16.15-17.30

AUDITORIUM A

SURGICAL PATHOLOGY: HEAD & NECK PATHOLOGY

Chairs: Philippe Delvenne and Ramses Forsyth

16.15-17.15 • **Overview of salivary gland tumours**
Peter Sadow (Boston, USA)

17.15-17.30 • ***Free Paper** - Thyroid-like low grade nasopharyngeal papillary adenocarcinoma: Report of a case*
Serife Kaçar (Brussels, Belgium)

AUDITORIUM B

NEUROPATHOLOGY

Chairs: Dietmar Thal and Julie Lelotte

16.15-17.00 • **The pathological diagnosis of Brain tumours after the WHO-classification 2016 and cIMPACT-now.**
Martin Hasselblatt (Münster, Germany)

17.00-17.15 • **The use of the WHO-classification of Brain tumours and the Belgian reimbursement rules**
Martin Lammens (Antwerp, Belgium)

17.15-17.30 • ***Free Paper** - In depth immunophenotypic analysis of the tumour microenvironment in primary central nervous system lymphoma*
Lukas Marcelis (Leuven, Belgium)

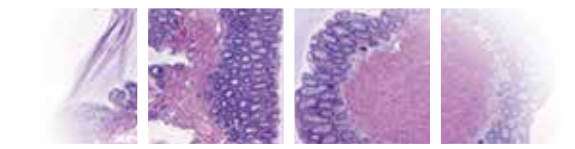
17.45-18.45 **KEYNOTE LECTURE: Gynaecological pathology (AUDITORIUM A)**

Chair: Jean-Christophe Noël

17.45-18.45 • **The spectrum of endometrial stromal tumours: utility of morphologic, immunohistochemical, and molecular features in their classification and differential diagnosis.**
Esther Oliva (Boston, USA)

18.45-19.30 **Reception in the Exhibition Area (Exhibition Area)**

19.30 **Congress Dinner at the Wild Gallery (AUDITORIUM B)**



FRIDAY OCTOBER 18

10TH ANNIVERSARY RECEPTION

18:45 - 19:30
IN THE EXHIBITION AREA

Everyone is welcome
in the Exhibition Area

SPECIAL 10TH EDITION

PRESIDENT'S DINNER

at the Wild Gallery

19:30
IN THE AUDITORIUM B

Introducing, someone you already know.

Meet Epredia. While you may not yet know the name ... you will likely recognise our legacy.

Epredia™ is the culmination of nearly a century of a singular focus on advancing technologies and products that enhance precision cancer diagnostics.

We are powered by many of the most-respected names in the industry – Shandon™, Richard-Allan Scientific™, Microm™, Menzel-Gläser™, and others. Together, these brands represent groundbreaking technologies, a remarkable commitment to quality, and a deep dedication to enabling our customers to achieve diagnostic excellence.

Discover our full portfolio, from specimen collection to processing, sectioning to staining, advanced imaging to archiving, we have solutions that help laboratories work more precisely, efficiently, and accurately.

We look forward to meeting you. Again.

Find out more at **Epredia.com**

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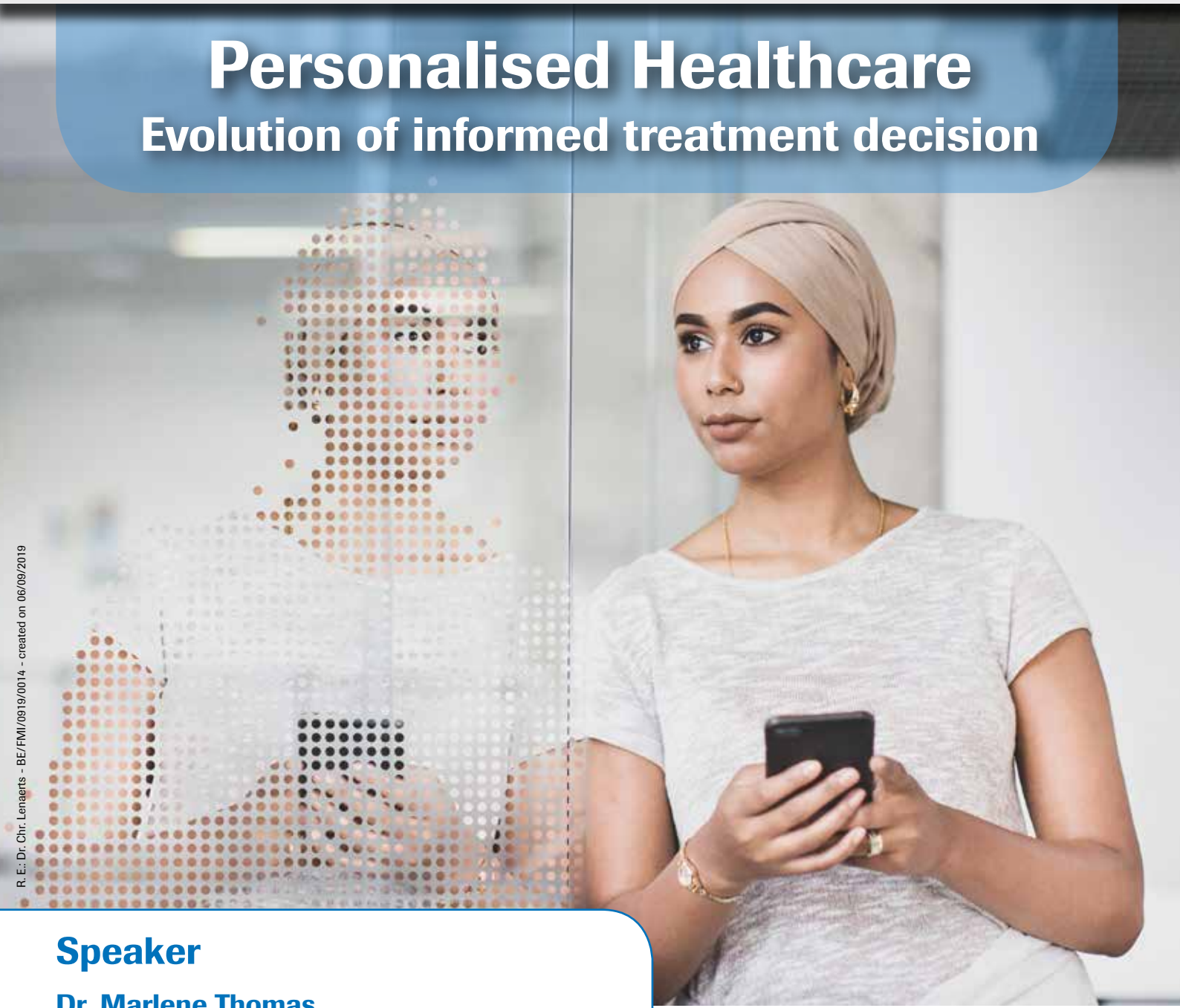
Enhancing precision cancer diagnostics

SATELLITE SYMPOSIUM

Roche

Personalised Healthcare

Evolution of informed treatment decision



R. E.: Dr. Chr. Lenaerts - BE/FMI/0919/0014 - created on 06/09/2019

Speaker

Dr. Marlene Thomas
Global Medical Affairs, F. Hoffmann - La Roche - CH

Saturday - October 19, 2019
10.30 - 11.00

Personalised
Healthcare

SATURDAY October 19 - Morning

08.00-09.00 **WELCOME**

09.00-10.30

AUDITORIUM A

DIGESTIVE PATHOLOGY

Chairs: Anne Hoorens and Ann Driessen

09.00-09.30 • **Pathology of infections of the colon and anal canal**
Gieri Cathomas (Liestal, Switzerland)

09.30-10.00 • **A dualistic model of squamous carcinoma and adenocarcinoma of the anal canal with implications for personalised medicine**
Michaël Herfs (Liège, Belgium)

10.00-10.30 • **Microsatellite instability in Lynch syndrome and gastro-intestinal cancer therapy**
Magali Svrcek (Paris, France)

AUDITORIUM B

CYTOPATHOLOGY (ETHICS AND ECONOMY REQUESTED: 2,5 PTS)

Chairs: Birgit Weynand and Shaira Sahebali

09.00-09.45 • **Screening in the setting of primary HPV-testing: a pathologist's perspective**
Hans Bulten (Nijmegen, The Netherlands)

09.45-10.30 • **Abnormalities in a HPV-vaccinated population**
Annabelle Farnsworth (Sydney, Australia)

10.30-11.00 SATELLITE SYMPOSIUM BY **ROCHE (1) (AUDITORIUM A)**

• **Personalised Healthcare - Evolution of informed treatment decision**
Marlene Thomas (Basel, Switzerland)

10.30-11.15 **COFEE BREAK (Exhibition Area)**

POSTER TOUR: P 22 to P 28 (e-Posters Area)

P 22 The assessment of stromal tumor infiltrating lymphocytes (sTILS) in invasive micropapillary carcinoma of the breast and correlation with prognosis and clinico-pathological features
Frederik Deman (Leuven, Belgium)

P 23 Prognostic value associated with the presence of hybrid EMT states in UCC
Louis Godin (Brussels, Belgium)

P 24 Impact of Next Generation Sequencing analysis for patients with an indeterminate cytological diagnosis
Philomène Lavis (Brussels, Belgium)

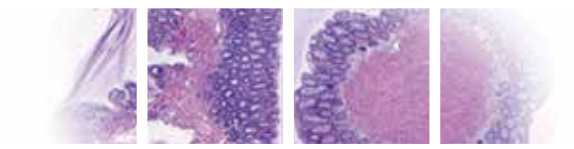
P 25 Proliferation index and expression of PD-L1: PDXs of head and neck, skin, esophagus and lung
Claire Royer-Chardon (Brussels, Belgium)

P 26 Clinical, morphological and immunohistochemical characterization of 58 pheochromocytomas and paragangliomas
Claire Royer-Chardon (Brussels, Belgium)

P 27 Olfactomedin 4 (OLFM4) expression is associated with nodal metastases in esophageal adenocarcinoma
Lucia Suzuki (Rotterdam, the Netherlands)

P 28 MicroRNA profiles do not predict Barrett's esophagus progression to esophageal adenocarcinoma
Lucia Suzuki (Rotterdam, the Netherlands)

10.45-11.05 **ANNOUNCEMENT:** "YOUNG PATHOLOGISTS' SECTION" IN THE BSP **(AUDITORIUM B)**



SATURDAY

SATELLITE SYMPOSIUM

Roche

Saturday – October 19, 2019

13.00 - 13.45

Speaker

Dr. Corrado D'Arrigo

Poundbury Cancer Institute, UK

PD-L1 testing in TNBC from the pathologist's perspective

PD-L1, programmed death ligand 1; TNBC, triple-negative breast cancer

R. E.: Dr. Chr. Lenaerts - BE/TCN/0919/0012 - created on 06/09/2019

11.15-12.30

AUDITORIUM A

BREAST PATHOLOGY

Chairs: Kathleen Lambein and Gert Van den Eynden

11.15-11.50 • **Pathology after neoadjuvant chemotherapy: BIG versus AJCC/UICC classification**
Veerle Bossuyt (Boston, USA)

11.50-12.15 • **Use of the AJCC/UICC classification after neoadjuvant chemotherapy**
Elizabeth van Eycken (Stichting Kankerregister, Belgium)

12.15-12.30 • ***Free Paper** - A fast, affordable and minimally-invasive diagnostic test for Cancer of Unknown Primary (CUP) using DNA methylation profiling*
Jilke De Wilde (Ghent, Belgium)

AUDITORIUM B

CYTOPATHOLOGY

Chairs: Birgit Weynand and Shaira Sahebali

11.15-11.35 • **Belgian survey on cervical screening in vaccinated women**
Shaira Sahebali (Brussels, Belgium)

11.35-12.15 • **Case presentations:**
S. Sahebali, M. Baldewijns, C. Bourgain, B. Weynand

12.15-12.30 • ***Free Paper** - ALK-positive histiocytosis: rare disease with tremendous implications. Case report*
Jimmy Liu (Antwerp, Belgium)

12.30-12.45 GENERAL ASSEMBLY **BSP ROCHE (AUDITORIUM B)**

12.30-14.00 **LUNCH (Exhibition Area)**

13.00-13.45 SATELLITE SYMPOSIUM BY **ROCHE (2) (AUDITORIUM A)**

• PD-L1 testing in TNBC from the pathologist's perspective
Corrado D'Arrigo (Poundbury Cancer Institute, UK)

13.00-14.00 **POSTER TOUR: P 29 to P 35 (e-Posters Area)**

P 29 The use of immunohistochemistry in the assessment of BRAF V600E and P53 mutations in melanomas
Stefan Rusu (Brussels, Belgium – Tirgu Mures, Romania)

P 30 The use of deep learning to recognize inflammatory breast cancer cells in H-DAB stained images
Christophe Van Berckelaer (Antwerp, Belgium)

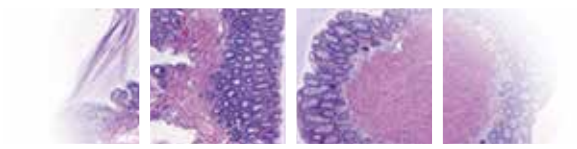
P 31 Infiltrating immune cells in the tumor emboli of inflammatory breast cancer.
Christophe Van Berckelaer (Antwerp, Belgium)

P 32 High-throughput analysis of an aetiology driven ductular reaction and its niche in the human liver disease spectrum
Matthias Van Haele (Leuven, Belgium)

P 33 Histopathologic assessment of unused donor lungs: when to decline or not?
Arno Vanstapel (Leuven, Belgium)

P 34 Intra-alveolar fibrin and organizing pneumonia in lung allograft biopsies
Arno Vanstapel (Leuven, Belgium)

P 35 The daily practice reality of PD-L1 evaluation in non-small cell lung cancer: a retrospective study
Camille Verocq (Brussels, Belgium)



EXHIBITION FLOOR

FRIDAY

SATURDAY

Gold Partners

A1	ROCHE Diagnostics+Pharma+Oncology

Silver Partners

B1	ADAMAS INSTRUMENTEN bv
B2	BMS
B3	SAKURA
B4	BD Diagnostics-Biosciences
B5	ASTRAZENECA
B6	AGILENT/DAKO
B7	EPREDIA
B8	MSD

Bronze Partners

C3	DEUTSCHE TELEKOM HEALTHCARE
C4	LEICA BIOSYSTEMS
C6	PROPATH
C7	MIPS
C9	HOLOGIC
C12	WHAT'S UP DOC
C13	HAMAMATSU
C14	SECTRA
C15	EXCILONE
C16	FUJIREBIO
C17	Alliance MERCK/PFIZER
C20	PHILIPS HEALTH SYSTEMS

GOLD

SILVER

BRONZE

ALLIANCE MERCK / PFIZER - DEUTSCHE TELEKOM HEALTHCARE - EXCILONE - FUJIREBIO - HAMAMATSU - HOLOGIC - LEICA BIOSYSTEMS - MEDISQUARE - MIPS - PHILIPS HEALTH SYSTEMS - PROPATH - SECTRA - WHAT'S UP DOC

14.00-16.00 **AUDITORIUM A**

GYNAECOLOGICAL PATHOLOGY

Chairs: Jean-Christophe Noël and Claire Bourgain

14.00-15.00 • **Ovarian cancer: tumour typing, site assignment and reporting following the ICCR datasets (International Collaboration on Cancer Reporting)**
Glenn McCluggage (Belfast, UK)

15.00-16.00 • **Mucinous tumours of the ovary**
Esther Oliva (Boston, USA)

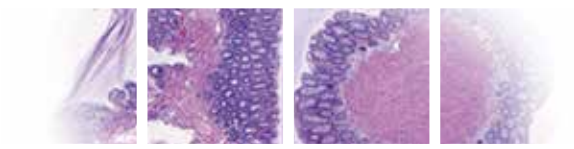
16.00-16.15 **AWARDS CEREMONY: (AUDITORIUM A)**

- **BSP Prize: Best Oral Presentation: Research**
- **BSP Prize: Best Oral Presentation: Case Report**
- **BSP Prize: Best e-Poster Presentation**

CLOSING CEREMONY 10TH BWP

BWP Belgian Week of Pathology

SATURDAY



SAVE THE DATE

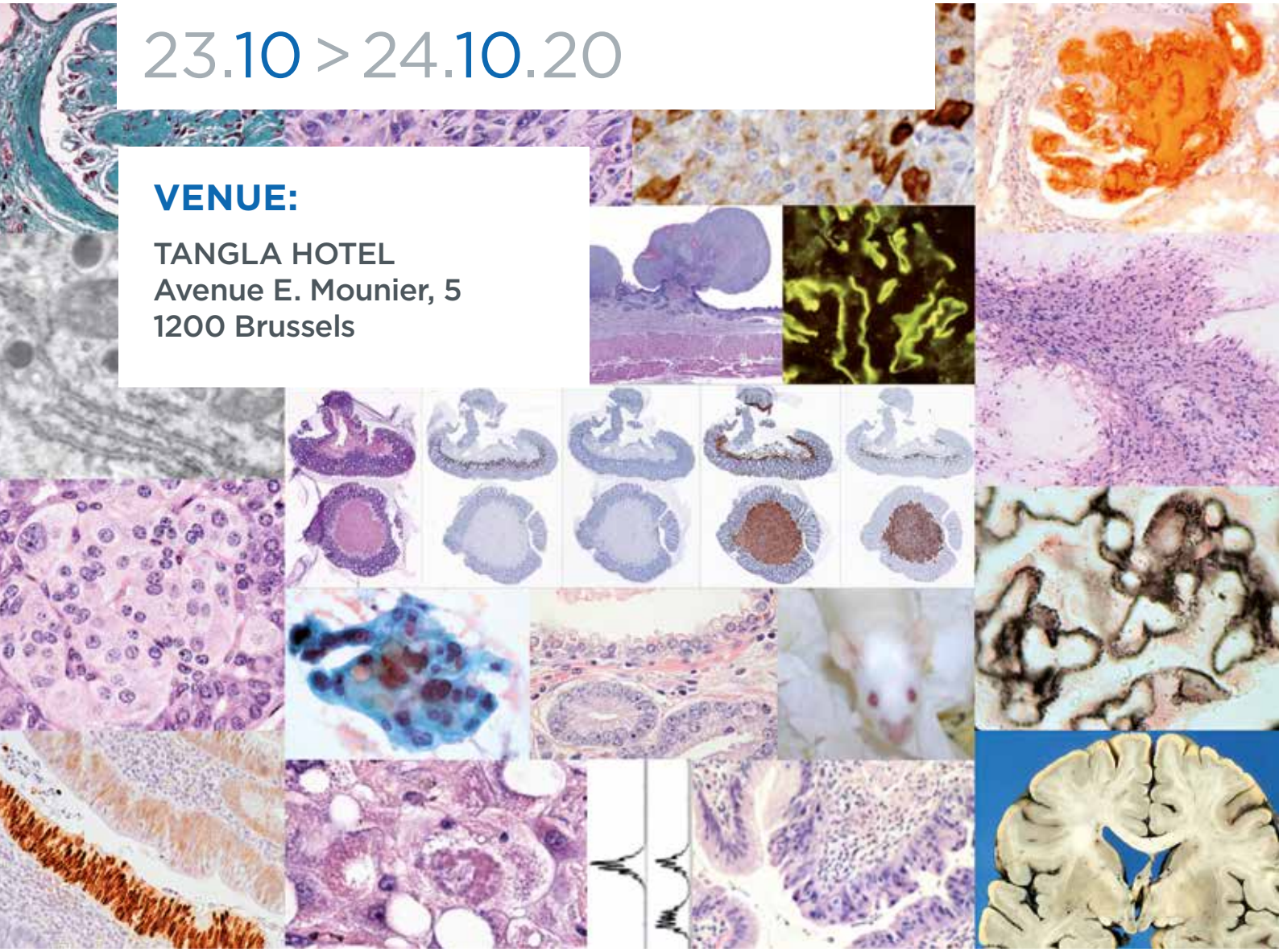
CONGRESS

11TH EDITION

BWP Belgian Week of Pathology

BELGIAN WEEK OF PATHOLOGY

23.10 > 24.10.20



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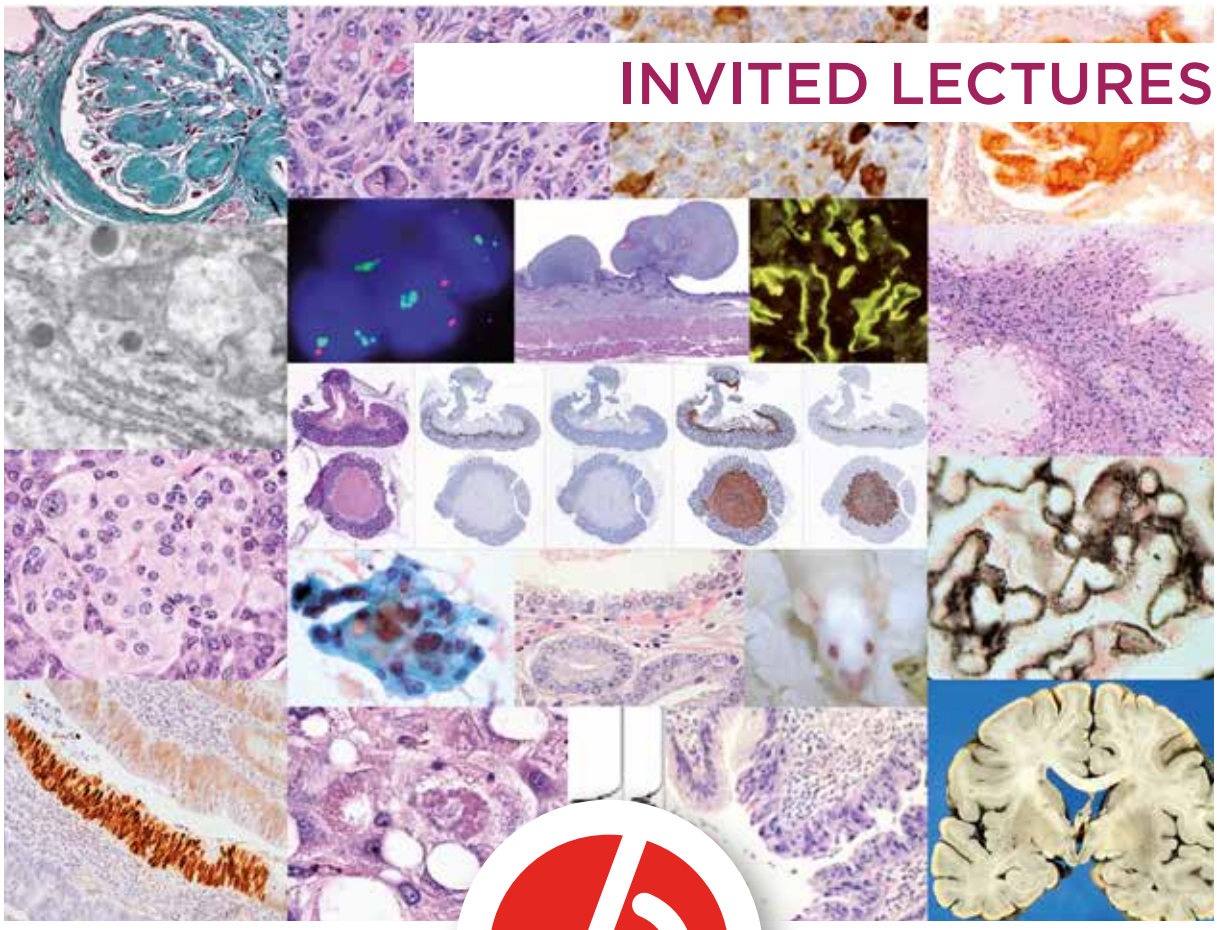
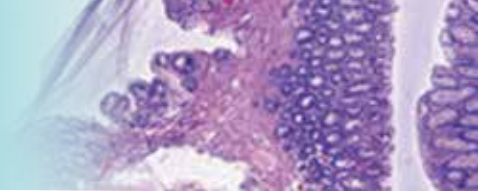

INVITED LECTURES



INDEX - Friday 18/10

Uropathology

Allory Y. / Paris, France

Molecular classes of urothelial cancer, the clinical relevance and implementation in daily practice

The urinary bladder cancer, with or without muscle invasion, is a heterogeneous disease with a range of therapeutic modalities, treatment responses and outcomes. In the last 10 years, many international teams tried to set up a bladder cancer molecular classification, mainly using transcriptomic profiling, to stratify cases according to prognosis and treatment options (ref. listed in 1). We aim to provide an update regarding the current molecular classification, the interest in clinical setting, the molecular or immunohistochemistry tools available, and the challenges for the transfer to clinical practice.

For the muscle invasive bladder cancer (MIBC), up to six distinct classification systems were reported including 2 to 10 molecular subtypes with different names even for the same entities. In 2015, the different teams launched an initiative to achieve an international consensus on MIBC molecular subtypes that reconciles the published classification schemes. They identified recently a consensus set of six molecular classes (1): luminal papillary (24%), luminal non-specified (8%), luminal unstable (15%), stroma-rich (15%), basal/squamous (35%), and neuroendocrine-like (3%). This consensus system offers a robust framework to foster our understanding of MIBC biology but also for the future development of diagnostic and predictive biomarkers. A single-sample classifier that assigns a consensus class label to a tumour sample's transcriptome is now available. Of note, several studies have highlighted the clinical significance of molecular stratification of MIBC by suggesting that responses to chemotherapy in neoadjuvant setting and immunotherapy may be enriched in specific MIBC subtypes (1, 2, 3, and 4). However, these promising results needs to be confirmed in prospective studies before recommending the use of molecular classification in clinical setting (5). Just as different histological variants might be admixed within a same bladder cancer, some studies reported a significant proportion of cases with spatial and temporal tumour heterogeneity with admixed molecular subtypes and discrepancies between primary and lymph node metastasis (6). This heterogeneity might be confusing for treatment response prediction. In comparison with MIBC, there are still few studies regarding molecular classification in non-muscle invasive bladder cancer (cf. references in 1) and a consensus system is still expected for NMIBC. Several teams proposed to extend the luminal versus basal MIBC molecular classification to NMIBC but this should be validated.

If the interest to classify at molecular level the MIBC and NMIBC is confirmed, tools based on mRNA signatures or immunohistochemistry panel should be provided (3, 4, 7). A simple approach is to discriminate luminal and basal tumours using antibodies associated with urothelial (i.e. GATA3, FOXA1 or CK20) and basal differentiation (CK5/6, CK14 or CD44) (2, 8, 9). However, these panels and the positivity thresholds must be validated in comparison with molecular classification to assess their respective sensitivity and specificity. On the opposite, the Lund group proposed an extensive panel including 13 antibodies specific for FGFR3, CCND1, RB1, p16, FOXA1, GATA3, CK5, CK14, VIM, ZEB2, CDH1, EPCAM, TUBB2B with the aim to discriminate all the subtypes (7, 10).

Studies evaluating the treatment response prediction to chemotherapy and/or immunotherapy using these mRNA signatures or antibody panels are now mandatory to determine at which extent it is useful at clinical level to distinguish the multiple molecular subtypes within the two main luminal and basal molecular groups.

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Dermatopathology

Creytens D. / UZ Gent

Update in cutaneous fibrohistiocytic tumours

Fibrohistiocytic tumors are among the most frequent soft tissue tumors encountered in the skin. "Fibrohistiocytic" is an entirely descriptive term devised to designate a group of heterogeneous tumors that share morphological features of histiocytes and fibroblasts on light microscopy. Unlike most similar designations (e.g. vascular, adipocytic,....), it does not cover a definitive line of differentiation. In fact, most tumors in this category are of uncertain histogenesis and over the years it has become apparent that many so-called 'fibrohistiocytic' tumors are largely composed of relatively undifferentiated mesenchymal cells, and can also show areas of myofibroblastic differentiation. Based on their histological features, cutaneous fibrohistiocytic tumors fall into benign, intermediate and malignant subcategories. Diagnostic difficulties carrying potential therapeutic implications are not infrequent in fibrohistiocytic lesions, due to the large number of variants/entities and histologic overlap between benign and malignant entities. This lecture will cover the clinical and histological features as well as differential diagnosis of these so-called fibrohistiocytic tumors, including common fibrous histiocytoma, histological variants of fibrous histiocytoma (cellular, aneurysmal, epithelioid, atypical subtypes), metastasizing fibrous histiocytoma, dermatofibrosarcoma protuberans, angiomatoid fibrous histiocytoma, plexiform fibrohistiocytic tumor, atypical fibroxanthoma and pleomorphic dermal sarcoma.

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Uropathology

Dr. Markus Eckstein - Instiute of Pathology - University Hospital Erlangen
Friedrich-Alexander-Universität Erlangen-Nürnberg

PD-L1 in Bladder Cancer

PD-L1 is a central immune checkpoint protein which is expressed on several immunological (macrophages, dendritic cells) as well as other cells like fibroblasts, different somatic tissues and tumor cells. PD-L1 plays a central role in the adaptive immune response to prevent overwhelming immune responses. Cancer tissues are known to upregulate PD-L1 on the cell surface to actively suppress anti-tumoral immune infiltrates and to evade the immunosurveillance. Therefore, therapeutic inhibition of PD-L1 and its receptor PD-1 have become widespread in different solid cancer types and specific hematological neoplasias. This kind of unspecific immunotherapy has also entered the field of metastatic urothelial carcinoma and represents a new standard treatment especially in the second line. Although PD-L1 expression on tumor cells showed good correlation with therapy response and outcome in other cancer types like non-small cell lung carcinoma, the predictive and prognostic value of PD-L1 assessment in bladder cancer is consistently inconsistent. Most studies clearly showed that patients with high PD-L1 expression have a higher likelihood to respond, while only a minority of studies revealed a better prognosis dependent on the PD-L1 status. Initially, PD-L1 testing was therefore not indicated, but in 2018 the FDA and EMA restricted the first line use of Pembrolizumab and Atezolizumab in cis-platinum ineligible patients with metastatic urothelial carcinoma to patients with high PD-L! expression as determined by one of the approved companion diagnostic assays (CDA; Atezolizumab: >=5%-IC/ CDA: pharmDX 22c3; Pembrolizumab CPS >=10/ CDA Ventana SP142). CDAs from DAKO/pharmDX can only be performed on DAKO autostainers while Ventana assays can exclusively be performed on Ventana autostainers. Therefore, pathological laboratories who want to perform all CDAs need a variety of expensive autostainers. According to the European law and the EMA, a strict CDA testing is not necessary, if institutions ensure to deliver the same testing quality like the validated CDAs. Therefore, it is important to know whether different PD-L1 assays are interchangeable. Recent studies showed that all commercially available PD-L1 assays (pharmDX 28-8, 22c3; Ventana SP142, SP263) are comparable to score immune cells. The SP142 assay targets another PD-L1 splice variant, thus not detecting PD-L1 expression on tumor cells like the other CDAs. Therefore, the SP142 shouldn't be used for applying scoring algorithms including tumor cell positivity (CPS).

Beside differences in the CDAs, the scoring algorithms for different drugs vary greatly. A recent study showed that the Ventana IC score (needed for 1-line Atezolizumab) and the CPS (needed for 1-line Pembrolizumab) showed concordant scoring results (positive with both algorithms) in only appr. 48%. The other patients were exclusively eligible for one of the both drugs based on the scoring results. Although the different CDAs are more or less interchangeable, the huge differences between scoring algorithms could be a major reason for inconsistent results on te predictive and prognostic value of PD-L1 expression in urothelial bladder cancer.

Beside PD-L1 there are numerous other potential players in the tumor immune microenvironment which can influence the response to checkpoint inhibition. New approaches try to characterize the immunological attractivity of tumors by evaluating the tumor mutational burden which is considered to cause a high neoantigen burden (TMB). However, for urothelial bladder cancer TMB has shown promising results in retrospective analysis, but prospective trials are still ongoing. Recently reported results in NSCLC on prospective trials using TMB as biomarker failed to demonstrate TMB as a discriminating biomarker (congress news WCLC, Barcelona 2019). Whether TMB can add useful information for bladder cancer patients has still to be investigated. Other biomarkers like the composition of the extracellular matrix and other immune evasion mechanisms are evaluated in phase-I trials. First results are expected for 2020.

Taken together, integrative analysis of the tumor immune microenvironment using multiple markers will be necessary to identify patients who really benefit from immunotherapy.

FRIDAY

Molecular pathology

Flucke U. / Nijmegen, the Netherlands

When is molecular testing helpful in soft tissue tumours?

Soft tissue tumors are relatively rare and interpretation of morphology and immunohistochemistry can be challenging, especially in cases with an aberrant clinicopathological setting.
Molecular confirmation by conventional methods or next generation sequencing leads to the correct diagnoses which has therapeutic implications.
In the recent years molecular testing has improved leading to better insight into biology of lesions and possible tailored treatment options. By using advanced next generation sequencing techniques, a growing number of new fusion genes or recurrent mutations have been and will be identified and new entities have been and will be created. Clinical impact have mutations which are targetable, e.g KIT, PDGFRA/B, NTRK. Methylationprofiling is another new method to define entities by clustering of cases. This can be useful when the other mentioned techniques are not applicable or failed.

Dermatopathology

Fraitag S. / Paris, France

What's new in pediatric dermatopathology

Fibroblastic connective tissue nevi were described in 2012 as a solitary slowly growing, painless, plaque or nodule mostly localized on the trunk or head and neck. Histologically it is mainly situated in the reticular dermis and superficial subcutis and is characterized by a proliferation of bland fibroblastic/myofibroblastic cells arranged in short intersecting fascicles with no significant cytologic atypia. Cells express CD34 or SMA. FISH analysis is mandatory to rule out DFSP. This entity overlaps with many different entities, such as: medallion-like dermal dendrocyte hamartoma, plaque-like CD34 positive dermal fibroma, fibrous hamartoma of infancy, lipofibromatosis (infantile fibromatosis) and lipofibromatosis-like neural tumour.

Plaque-like myofibroblastic tumor of infancy is a newly recognized entity with early onset. The lesion is mostly located on the back (middle lower back region) or hip and present as a pinkish-brown poorly marginated plaque containing firm nodules. There's no spontaneous disappearance, so the diagnosis is sometimes made lately even during adulthood. Histologically this lesion is very close to a dermatofibroma.

Kaposiform hemangioendothelioma and tufted hemangioma may both lead to a severe coagulopathy called Kasabach Merritt syndrome. Actually they are two ends of a same spectrum called "vascular tumours associated to the Kasabach Merritt syndrome" and always express podoplanin into the lobules and outside them. At birth they may be confused with a congenital hemangioma which can also show thrombocytopenia. This disorder shows numerous lymphatics as well, stained by D2-40 antibody but only outside of the lobules. Lymphatic immunostaining is a very helpful tool for differentiating these different entities before starting a treatment (Sirolimus).

Inheritate palmoplantar keratodermas are a group of different disorders and the role of histopathological diagnosis has been traditionnaly limited. However we can recognize epidermolytic PPK usually related to KRT 1 or 10 mutation. **Striate palmoplantar keratodermas** has been recently recognized as an uncommon group of genodermatoses with autosomal inheritance. Clinically there is a linear hyperkeratosis of the palms and diffuse yellowish thickening of the soles. Mutations in genes encoding desmoglein 1, desmoplakin and keratin 1 have been found. Histologically the lesion can be easily recognized showing widening of intercellular spaces and incomplete acantholysis in the spinous cell layers. Because desmosomal proteins, such as desmoplakin or plakoglobin, are present together in skin, hair and heart, their mutations are responsible for different syndromes that can affect both skin, hair and, importantly, heart. Consequently patients may die from arrhythmogenic cardiomyopathy and recognizing such PPK may serve as warning signal for a close follow-up and a self-implantable defibrillator.

Lymphocytic cutaneous infiltrates in children: beware of mimickers! Subcutaneous panniculitis-like T-cell lymphoma, also called in paediatrics "clonal cytophagic histiocytic panniculitis", is characterized histologically by subcutaneous nodules/plaques often associated with systemic symptoms and hemophagocytic syndrome. This is likely that this aspect corresponds in children to a reactive clonal proliferation rather than to a true lymphoma as it is often preceded by an infection (chicken-pox, other virus) and may show spontaneous regressions. In addition some cases were reported in association with immunodeficiencies. Recently mutation in Tim3 was described in some young patients with a severe hemophagocytic syndrome. These cases mustn't be treated by chemotherapy.

Lipoatrophic Panniculitis of Childhood is characterized by erythematous nodules and plaques followed by a circumferential band of permanent lipoatrophy around the lower legs and ankles. Histologically the feature may simulate a subcutaneous panniculitis-like T-cell lymphoma.

Finally, regarding **histiocytic infiltrates**, histiocytic phenotype (cytology and immunohistochemistry) is not sufficient on its own to classify histiocytoses. Looking for BRAFV600E or other mutations in the MAPkinase pathway (MAP2K1 (Mek)) in all histiocytic infiltrates with difficult diagnosis and in all patients with failure of first-line treatment, is nowadays mandatory.

Neuropathology

Hasselblatt M. / Münster, Germany

The pathological diagnosis of brain tumors after the WHO-classification 2016 and cIMPACT-now

The 2016 WHO classification of central nervous system tumors for the first time uses molecular parameters in addition to histology to define many tumor entities. Furthermore, in order to evaluate and recommend proposed changes to future CNS tumor classifications, cIMPACT-NOW (the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) was established. The cIMPACT consortium already published four updates from 2016 to 2019. In this talk, I will give an overview on these recent developments and their impact on routine surgical neuropathology.

Educational Grant Symposium

Hebrant A. / Sciensano, Belgium

The pathological diagnosis of brain tumors after the WHO-classification 2016 and cIMPACT-now

In order to advise the Federal Government on the reimbursement of molecular tests related to Personalized Medicine in Oncology, the Commission of Personalized Medicine (ComPerMed), represented by Belgian experts, has developed a methodology to classify molecular testing in oncology. The different molecular tests per cancer type are represented in algorithms and are annotated with a test level reflecting their relevance based on current guidelines, drug approvals and clinical data. The molecular tests are documented with recent literature, guidelines and a brief technical description. This methodology was applied on different solid tumors for which molecular testing is a clear clinical need.

Surgical Pathology: Head & Neck

Jung A. / Strasbourg, France

HPV-related HNSCC

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cancer in the world, with over 600.000 cases diagnosed each year. They define a heterogeneous group of malignancies that arise from the epithelium that delineates the upper aero-digestive tract (oral cavity, pharynx and larynx). The major risk factors are the heavy consumption of tobacco smoke and alcohol, and the infection by Human Papillomaviruses (HPV). HPV-related head and neck cancers define a clinical subgroup of HNSCC. Fewer patients have a history of tobacco smoking and alcohol drinking. HPV-positive tumors mainly arise in the oropharynx, and especially in the palatine and lingual tonsils, display poorly differentiated histology and are often associated to lymph node invasion (N>1). Yet, despite these adverse features, HPV-positive patients have an improved outcome with a significantly longer survival.

HPV oral infection is thought to be acquired during sexual intercourse, since sexual behavior measured as vaginal sex, oral sex, and life-time sex partners have been shown to correlate with increased odds for HPV-related head and neck cancer. The prevalence of oral HPV infection has been described to be ~7.5%, and the prevalence of the HPV16 viral type (which is found is >80% of HVP-related HNSCC) to range between 0.2 and 17%, according to a bimodal age distribution. However, tonsillar crypts, which are thought to be the target of HPV, show infrequent HPV-positivity, and the analyses of HPV-positivity in paired gargle and tonsil fresh tissue samples have yielded conflicting results. Therefore, despite a relatively frequent detection of HPV in the oral microbiota, persistent tonsil keratinocyte infection is thought to be a rare event.

HPV-dependent carcinogenesis relies on the expression of the E6 and E7 oncoproteins that respectively target the p53 and pRb tumor suppressors and induce their proteasomal-dependent degradation. This specific HPV oncoprotein-driven carcinogenesis is likely to explain why HPV-related head and neck cancers have a lower mutational burden compared to HPV-negative HNSCC. Interestingly, we have shown that only HPV-positivity defined by the detection of both the viral genome (DNA+) and the expression of the transcripts that encode E6 and E7 (RNA+) is associated to a fewer chromosomal alterations, a distinct gene expression profile and to improved patient prognosis. Conversely, features of HPV DNA+ RNA- tumors are similar to HPV-independent HNSCC, suggesting that these lesions might not have been triggered by HPV infection. It has since been acknowledged that the detection of HPV viral RNA expression is a gold standard for the identification of bona fide HPV-related oropharyngeal tumors.

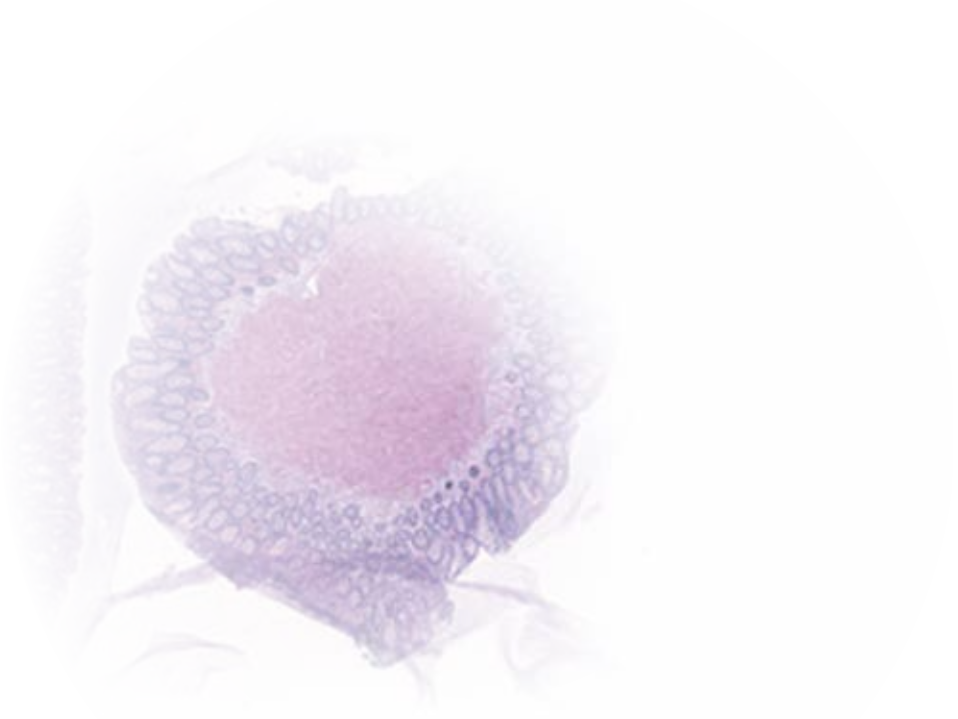
The comparison of the transcriptomes of HPV-positive and –negative HNSCC has highlighted that HPV-related cancers are characterized by the deregulation of specific sets of genes. Our analyses have shown that the top impacted molecular pathways include networks of factors involved in the regulation of the cellular cytotoxic immune response. This reflects the fact that HPV-positive oropharyngeal cancers are more frequently and more importantly infiltrated by CD8+ T lymphocytes. Interestingly, we could show that the expression of the CD8 gene correlates with improve prognosis, suggesting that the immune response plays a role in the outcome of HPV-positive patients. Interestingly, we also could observe that good- and poor-prognosis HPV-positive patients could be stratified on CD8 expression, suggesting that the clinical situation and prognostic impact of HPV in oropharyngeal cancer is more complex than initially envisioned. These observations also stress out that biomarkers are needed to more accurately stratify patients with HPV-positive head and neck cancers in order to provide them with tailored therapy.

Molecular Pathology

Meléndez Asensio B. / ULB Erasme, Brussels

Tumor mutational load, a burden?

Immune checkpoint inhibitors (ICIs) block the interactions between the inhibitory receptors expressed on T cells and their ligands on cancer cells, which promote a tumor-targeted immune response. Therapies based on blockade of immune checkpoints have shown impressive increased response rates in patients with different types of advanced cancers such as melanoma or non-small-cell lung cancer, among others. However, there is a high variability of response to ICIs among patients, and only a minority of them benefits long term, while some may even experience early disease progression. Therefore, it is crucial to identify reliable predictive biomarkers of response. The tumor mutational burden (TMB), i.e., the total number of mutations per coding area of a tumor genome, is emerging as a useful biomarker for the identification of patients that may benefit from immunotherapy. The rationale behind it comes from the evidence that tumors with higher TMB also carry higher neoantigen loads, with clonal T-cell expansion and sustained antitumor response. The TMB was initially determined by whole exome sequencing, but in an effort to implement it into a clinical routine setting, targeted-gene panel sequencing assays are currently being used. The accurate measurement of TMB for clinical implementation is, however, not trivial. On the one hand, the use of different platforms and technologies may have a high impact on TMB measure, and it requires a robust analytical validation, standardization and harmonization among laboratories and tests. On the other hand, there is a great variability of TMB among neoplasms, and therefore there is an urgent need to establish and clinically validate tumor-specific cut-offs that may direct clinical decisions. The different factors with an impact on the implementation of TMB as a biomarker in a clinical routine setting will be addressed here.



Dermatopathology

Ortonne N. / Paris, France

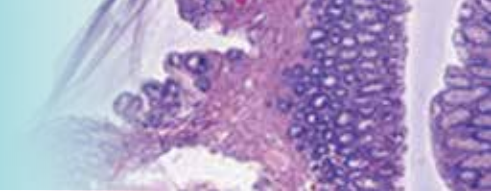
Update on cutaneous T-cell lymphomas

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of peripheral T-cell lymphomas, now grouped in the common WHO classification of tumours of haematopoietic and lymphoid tissues, updated in 2017 (1). Beyond the T-cell lineages of origin, CTCL segregates into two separate groups in terms of frequency and aggressiveness. Among the most frequent CL entities in western countries, non-transformed mycosis fungoides (MF), primary cutaneous - CD30+ lymphoproliferative disorders (LPD), follow an indolent course, contrasting with Sézary syndrome (SS) and rare T-cell lymphomas which require systemic treatments and hospitalization. Among CTCL, the current classification defines provisional diseases and some CTCL remains challenging to classify. Rare CTCL with a TFH signature actually cannot be classified as angioimmunoblastic T-cell lymphoma (AITL) or as a primary cutaneous CD4+ lymphoproliferative disorder.

What's new with phenotype and cytogenetics of primary cutaneous T-cell lymphomas?

The identification of an aberrant expression of cell surface leukocyte receptors may help for the histological diagnosis of CTCL, especially for those lacking a specific morphological and phenotypical signature. For example, a complete loss of T-cell antigens can be seen in some rare MF cases described as "null T-cell phenotype" MF (2). The diagnostic specificity of the Tox transcription factor (3) and CADM1 (4) for the diagnostic of early, non-transformed MF remains to be proven. In contrast to MF, SS usually have an unfavorable prognosis. The neoplastic T-cells of Sézary syndrome have a particular phenotype that is helpful for diagnosis on peripheral blood lymphocytes. The loss of CD26 is a classical marker of SS using flow cytometry, and the CD4+CD26- percentage more accurately delineates the blood burden than cytomorphology (Sézary cell count) or CD4+CD7- (5). The neoplastic Sézary cells strongly express PD1, and may exhibit CD7 and more rarely CD2 T-cell antigen losses (6). The Natural killer cell receptor CD158k/KIR3DL2 was shown to be expressed by the neoplastic clonal T-cells of SS in the skin (7), and blood (8). This receptor can also be expressed in other CTCL subtypes, such as primary cutaneous anaplastic large cell lymphomas (PC-ALCL), transformed MF (9), adult T-cell leukemia lymphomas (10). Interestingly, KIR3DL2 now represents a new therapeutic target of interest, following the development of humanized antibodies allowing the efficient killing of Sézary cells by antibody dependent cytotoxicity (11).

New phenotypic variants of lymphomatoid papulosis (LyP) have been described in the past recent years. Traditionally, 3 histological types are distinguished: the type A, B and C. The new type D refers to LyP with massive epidermotropism and a CD8+ cytotoxic phenotype (12). The type E is another cytotoxic variant characterized by angioinvasion and necrosis with large necrotic skin lesions (13). LyP follows a benign course but may reveal an underlying lymphoma, especially, Hodgkin lymphomas, systemic ALCL and MF (14). So far, these variants were not shown to have any clinical or prognostic significance although the type D may be less frequently associated to another lymphoma (14). They may however be confused with rare aggressive cytotoxic cutaneous lymphomas, especially the primary cutaneous aggressive epidermotropic T-cell lymphoma (PCAETCL) for the type D, and NK/T-cell lymphomas for the type E. On nosological grounds, the identification of the type D variant of LyP, together with the description of frequent CD30 expression in pityriasis lichenoides acuta (15), may be regarded as the "missing links" between the two diseases. The integration of pityriasis lichenoides as a variant of LyP remains debated in the literature. The ALK rearrangement which characterizes a subset of the systemic anaplastic T-cell lymphoma is extremely rare in cutaneous ALCL. It may be discovered in seldom cases, especially in young adults and infants. By contrast, the DUSP22 rearrangement at the 6p25.3 locus (DUSP22-IRF4 translocation) is present in up to 5% of LyP and nearly 25% of cutaneous ALCL (16,17). This aberration can be present in systemic ALK negative systemic ALCL and is associated with a better prognosis. The LyP cases associated with a DUSP22 rearrangement are considered as a separate entity (18). The DUSP22 rearranged LyP and PCALCL are histologically characterized by a particular biphasic histological pattern, including pagetoid reticulosis-type epidermal infiltration.



A large series PCAETCL was recently published by Guitart J et al. (1). This series has shed new lights on the clinical-pathological presentation of this extremely rare but severe lymphoma (19). In about one third of patients, the lymphoma may be preceded by inflammatory lesions simulating a psoriasis or eczema, so that a diagnosis of MF may be rendered at this stage. In one third of patients, mucosal lesions (oral or genital) are present. Histologically, PCAETCL may have a double negative CD4-CD8- or TCR phenotype, so that the disease may be renamed as "primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma" in the future. Although the prognostic is poor, patients may respond to allogeneic stem cell transplantation.

What's new in terms of molecular signature of cutaneous T-cell lymphomas?

AITL is the most common peripheral T-cell lymphoma in western countries. AITL commonly invades the skin, so that dermatologists may be involved in its diagnosis which may be very challenging both clinically and histopathologically. The molecular alterations associated with AITL are amongst the best described to date. They schematically involve alterations of 1) epigenetic regulators, especially TET2, DNMT3A, IDH2 mutations, 2) TCR signaling partners, and 3) the RHOA p.G17V hot spot mutation, reported in up to 70% of AITL cases. We recently have shown that the RHOA p.G17V and IDH2 p. R172K/S hot spot mutations can be identified in skin infiltrates of AITL (20). The use of a monoclonal antibody that specifically reacts with the IDH2 R172K mutant protein delineates the neoplastic T-cells in situ, thus providing new interesting tools for diagnosis.

High-throughput sequencing studies in SS and MF have revealed a heterogeneous pattern of gene mutations and focal copy-number variants. Some of the molecular alterations were previously identified in other B or T-cell lymphomas, but contrasting with AITL and DLBCL-LT, the mutational landscape of MF and SS appears to be very heterogeneous with rare recurrent events. To date, none of these molecular alterations has proven to be of diagnostic or prognostic value in routine practice. As in AITL however, there appears to be selection for genes involved in 1) epigenetic processes and 2) T-cell signaling, 3) deregulation of genome stability and 4) cell survival and proliferation.

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Molecular Pathology

Pauwels P. / Antwerp, Belgium

Fusion genes and the pathologist: good news!

Fusion genes are made of two genes, or part of genes, that have become fused together. This is commonly the result of chromosomal translocations, when two chromosomes have broken and the cell has put them back together incorrectly. The fused gene can give raise to a fusion protein. The general rule in oncogenic fusion genes is that one gene contains the code for the kinose domain, while the other partner contains frequently a dimerization domain. The fusion gene is under control of an active promotor. This fact makes fusion proteins amenable for detection by immunohistochemistry. Well known examples of fusion proteins that can be detected that way are ALK, ROS1 and TRK fusion proteins. Unfortunately, this is not the case for RET. Altough we are fixed on ALK en ROS1 in lung cancer, it must be remembered that these fusions can occur in other tumors. This is even more pronounced in RET, NTRK and FGFR fusions.
These are several fusion variants. Fortunately, exactly knowing the partner in for example ALK fusions is clinically mostly not relevant but things are changing.
From a clinical point of view, the good news is that drugs inhibiting tyrosin kinose activity of the fusion protein are very successful, so it is really worth looking for them.

Dermatopathology

VERGIER B. / Bordeaux, France

Algorithmic approach of cutaneous lymphoproliferations and focus on cutaneous B-cell lymphomas.

The French Study Group of Cutaneous Lymphoma (GFELC) is a multidisciplinary group including Dermatologists, Pathologists and Molecular Biologists from 39 centers from France, 3 from Belgium and 3 from Swistzerland. Every suspected diagnosis of cutaneous lymphoma is registered in the Lymphopath database (allowing a double histopathological diagnosis: D1, the initial diagnosis and D2, a 2° opinion of an expert pathologist) and is discussed in a collegial clinical / therapeutical GFELC multidisciplinary meeting (mdm) at a regional or national level.

One of the GFELC objectives is to improve the accuracy of the diagnosis of cutaneous lymphoproliferative disorders (CLPD) by non-expert Pathologists. In order to evaluate Pathologists general knowledge of these disorders, GFELC's Pathologists performed a retrospective study including 2760 samples of CLPD from 2010 to 2011, sent to expert Pathologists, in order to analyze the main problematic lesions and most frequently asked questions and to find a way to focus and orientate teaching lessons on these problems. We proposed (and tested) algorithms for the 6 main frequent problematic diagnoses. The aims of such algorithms were first to help non-expert Pathologists to make a diagnosis, but also to teach how to reach a histopathological diagnosis of CLPD without having to request a second opinion when it is not necessary.
The principles of such algorithms is :

- it is simple to use in the context of the daily routine, with entries via clinical or histopathological data
- it proposes an important set of informations to reach a diagnosis including morphological, immunohistochemical, clinical, molecular data and helps to decide whether to discuss the case in mdm (using a color code) or not
  -> However, it can not be exhaustive and unfortunately can not give a magical gift to always make the right diagnosis in all the cases and at the first time (it would be too simple indeed).

These algorithms are home made by French Pathologists and Dermatologists but can surely be adjusted to various countries practice.
These series and algorithms were published in French in 2015 (Ann Pathol 2015 ;35(2) : 141-47) and in the new edition of "pathologie cutanée tumorale" and are available for free on our GFELC website ("ressources"/"recommandations anatomopathologiques").
Moreover, we also analyzed 5640 CL cases included in the Lymphopath/GFELC database between 2015 and 2017 to know whether diagnosis problems found before (from 2010 to 11) were similar, but also to verify the efficiency of our algorithms and perhaps to evaluate the necessity of adapting or improving them. During the talk I will explain how to use these algorithms focusing on cutaneous B-cell lymphoproliferations with a presentation of cases.

The classification of cutaneous B-cell lymphoproliferations depends on the proportion of large lymphocytes (centroblasts/immunoblasts) and we proposed 2 main algorithms : one exploring differential diagnosis of cases with a majority of small lymphocytes (fig 1) and the other with a majority of large lymphocytes (fig 2, modified in 2019).
Primary cutaneous small B-cell lymphoproliferations raise the question of differential diagnosis including a reactive nodular B-cell Lymphoproliferation (Reactive Lymphoid Hyperplasia, HLR), a Marginal Zone or a Follicle Centre B-cell Lymphoma. A 4th differential diagnosis to think of showing features of a mixture of B and T-cells is the T- Helper Follicular (TFH) lymphoproliferation which will be described later by Pr Nicolas Ortonne. On the other hand, the difficulty in the case of a primary cutaneous large B-cell lymphoma is to differentiate a Follicle Center large B-cell Lymphoma with a good prognosis from a diffuse large B cell Lymphoma Leg-type, which is associated with a poorer prognosis. Part of the clues of such a differential diagnosis are morphology, phenotypic and molecular features. We recently tried to evaluate the best reproducible way to reach the right diagnosis in this context, which we converted in a brand new algorithm (fig 2, Menguy S and coll. Histopathology 2019 Jun;74(7):1067-1080).

Figure 1: small B-cell cutaneous lymphoproliferation

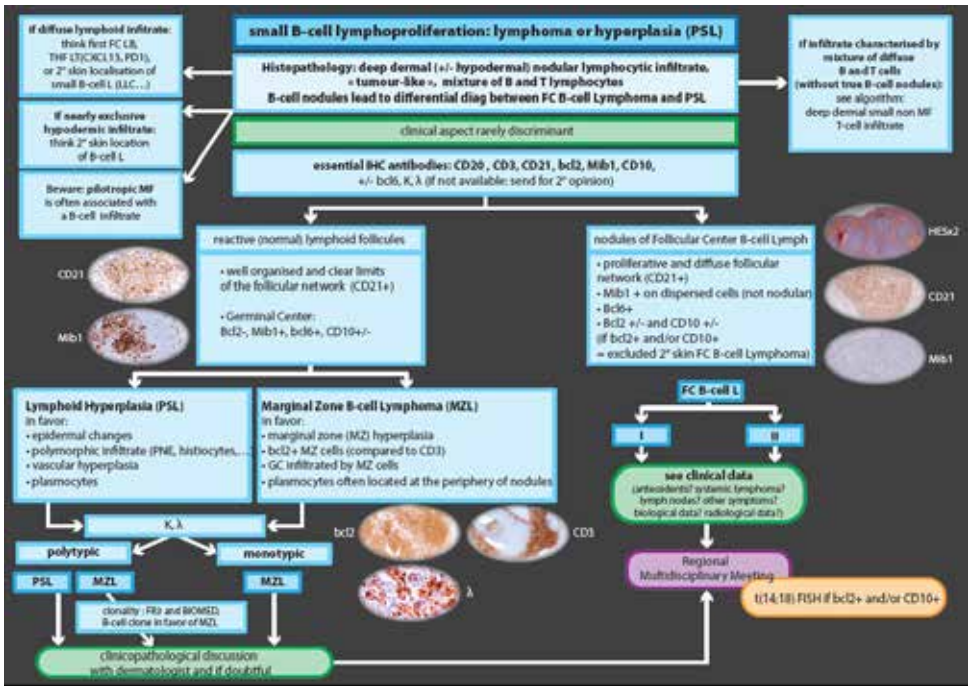
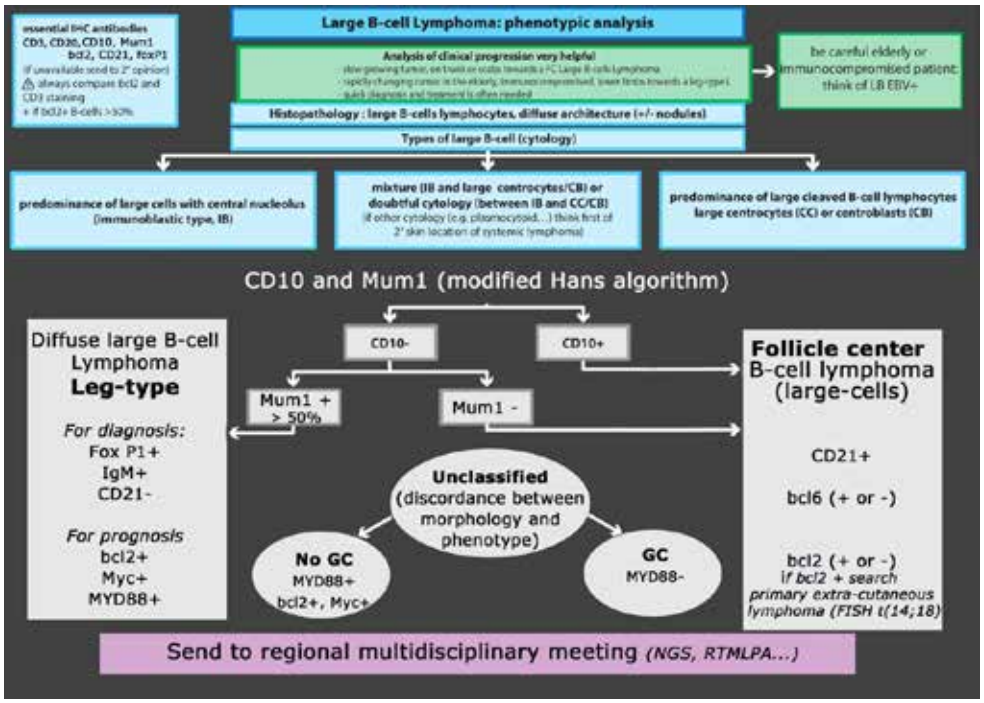


Figure 2: large B-cell cutaneous lymphoma



INVITED LECTURES

FRIDAY

Neuropathology
LAMMENS M. / Antwerp, Belgium

Keynote Lecture
OLIVA E. / Boston, USA

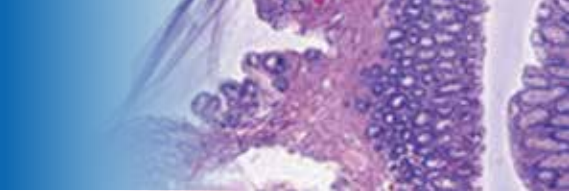
Surgical Pathology: Head & Neck
SADOW P. / Boston, USA

Dermatopathology
SIOZOPOULOU V. / Antwerp, Belgium

Educational Grant Symposium
VAN DOREN W. / RIZIV/INAMI, Belgium

Uropathology
VARMA M. / Cardiff, UK

NOTES



FRIDAY

SATURDAY

Educational Grant Symposium

Auditorium A

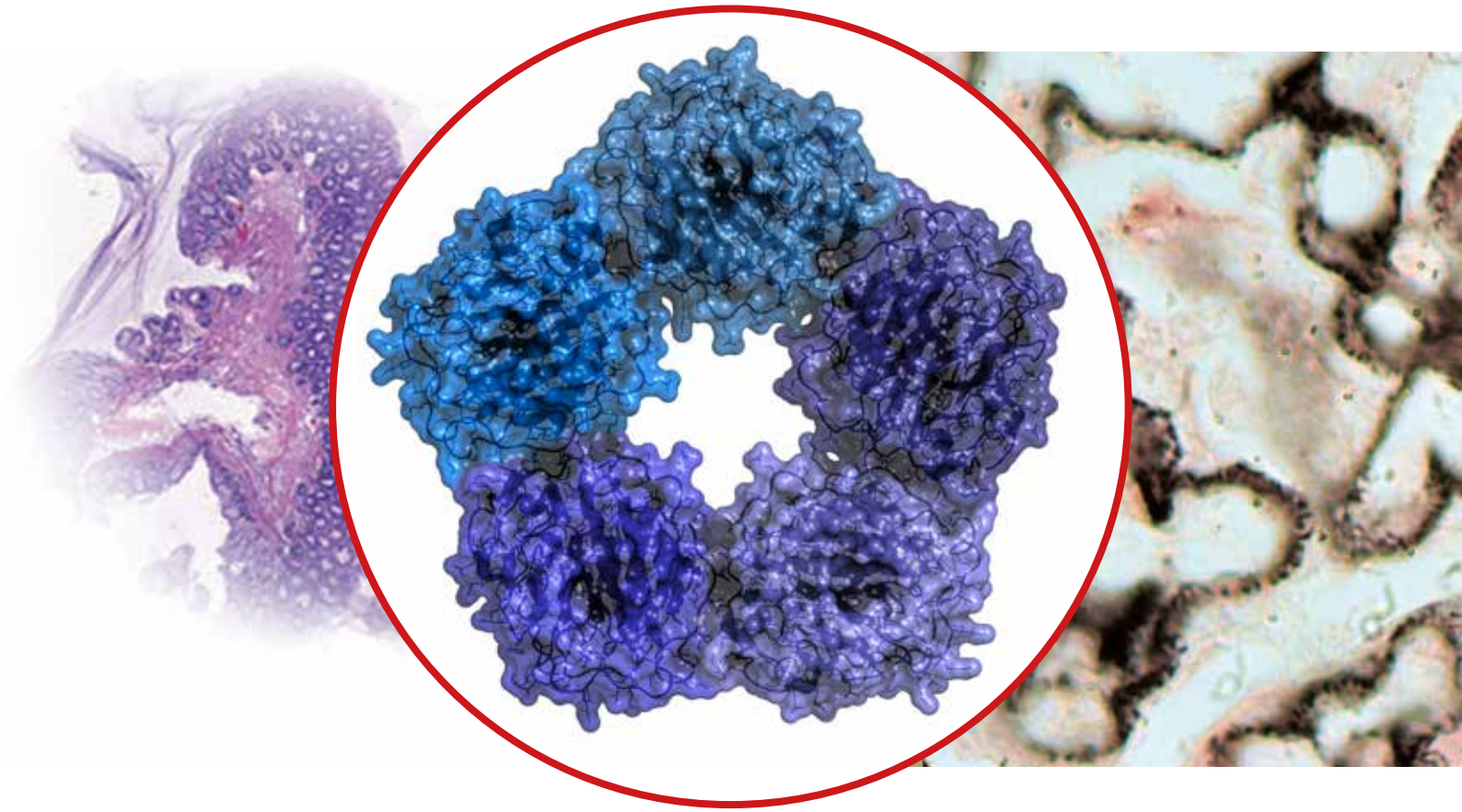
12.45-13.30

FRIDAY
OCTOBER 18

Molecular testing: the NGS convention

ALINE HEBRANT

WALTRUDA VAN DOREN



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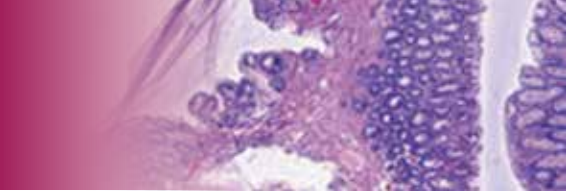

INDEX - Saturday 19/10

Cytopathology

Bulten H. / Nijmegen, The Netherlands

Cytopathology: Screening in the setting of primary HPV-testing: a pathologist's perspective.

At the start of 2017, the Dutch population screening for cervical cancer completely switched to primary HPV screening. Before 2017, the cervical smear was first cytologically assessed, followed by an hrHPV test as triage. Now the presence of hrHPV is first tested. If hrHPV is detected in a smear, the same sample is examined for cytologically abnormal cells.

Around 700 women in the Netherlands are diagnosed with cervical cancer. Without this population screening, around 1300 women would get cervical cancer per year. With the renewed hrHPV population screening, an additional 100 cases of cervical cancer are prevented each year. Every year about 250 women die from cervical cancer in the Netherlands and without the population screening this would be over 500.

In addition to the primary screening for hrHPV, population screening has also undergone significant changes in three other areas. Every 5 years the woman receives an invitation to participate in this population screening from her thirtieth to sixty years. If the woman does not have hrHPV at 40 and 50, she will not receive another invitation until 10 years later. Without HPV, a smear is only needed 5 times instead of 7 times. If the woman does not want to go to her general practitioner, she can also request a self-sampling device (ZAS) that is tested for hrHPV. If this is positive for hr HPV, the involved woman is still invited to have a smear made by her general practitioner for a cytological assessment. The number of performing laboratories has fallen from nearly 40 to 5, which are distributed regionally across the Netherlands.

The results of the first year (2017) of primary screening for HPV in the Netherlands will be presented. Furthermore, the roles of the cytological analysts and pathologists will be discussed. Finally, some important issues from the new Dutch cervical guidelines will be explained.

Breast Pathology

Bossuyt V. / Boston, USA

Pathology after neoadjuvant therapy: BIG versus AJCC/UICC classification

Systemic adjuvant therapy for breast cancer may be given before or after surgery. When neoadjuvant systemic therapy is given before surgery response to treatment can be evaluated. However, some prognostic information (for example pathologic tumor size pretreatment) is then lost and pathologic evaluation of breast specimens after neoadjuvant therapy is more difficult. For HER2 positive and triple negative tumors requiring neoadjuvant systemic therapy giving the treatment before surgery identifies a high-risk group of patients that can receive additional adjuvant therapy after surgery. Recent clinical trials have demonstrated that this approach improves survival. Now pathologic evaluation of response to neoadjuvant systemic therapy directs treatment received after surgery. Pathologists can refine our evaluation from binary, residual disease or pCR to a more nuanced approach in a practical and meaningful way. Residual Cancer Burden and AJCC/UICC stage provide complementary information.

Cytopathology

Farnsworth A. / Sydney, Australia

Cervical Cancer Prevention in Australia 2019

The Australian Cervical Screening Program changed significantly in December 2017 switching from biennial cytological Pap testing of asymptomatic women aged 18 to 69 years to five yearly primary Human Papillomavirus (HPV) testing of women aged 25 to 74 years. Although Australia had a highly successful cervical screening program based on cytology, this major change was taken after a formal review, in the context of a highly successful HPV Vaccination Program, operating in Australia since 2007 combined with improved understanding of HPV epidemiology and advances in molecular detection of HPV.

The primary HPV testing that was introduced in Australia includes partial genotyping (for HPV 16, 18 and other) followed by reflex liquid based cytology (LBC) if any oncogenic HPV is detected. Women are assigned a risk category of significant cervical abnormality and managed accordingly. The renewed program also introduced a co-testing arm (HPV testing and LBC) for women who are being followed up after histologically proven high grade abnormality or who have any symptoms or clinical signs possibly associated with cervical cancer.

Other crucial parts of the renewed program are a self-testing option for under screened or never screened women to increase participation in the program, policies to increase participation in Australia's indigenous population and the establishment of a National Cancer Screening Register to improve recruitment, follow up of women and monitoring of the program.

Although the program has successfully HPV tested over 2.5 million women, issues have arisen. These include limitations of self-testing due to laboratory validation criteria and problems of strict categorisation of testing (screening v non screening).There have been high levels of colposcopy referrals and ongoing management of HPV positive older women with no identifiable disease has created concerns.

Problems with the National Cancer Screening Register associated with an underestimation of the complexity of developing such a large population database, has meant that national data for tracking of the performance of the program is currently not available. Douglass Hanly Moir is the largest cervical screening laboratory in Australia and an analysis of the first six months of test results has been undertaken. These results have recently been reported (Machalek et al doi:10.594/mja2.50223). All HPV testing was performed on the Roche Cobas 6800. Reflex cytology is reported using ThinPrep with Imager. 80% of tests were primary screening and 20% were in the non-screening arm of the program. The HPV positivity rate varied significantly amongst these two groups with the screening positivity rate being 8% compared to 21% in the non-screening group.

Preliminary work has also begun on histological follow up of the approx. 4,006 women who were classified as higher risk in the screening population. Preliminary results show an overall positive predictive value (PPV) of 25%. The results also, highlight the importance of cytology triage as the PPV showed significant differences according to the cytology findings varying from 6% with negative cytology to 75% with High grade cytology. Analysis of the PPV of HPV primary screening also would appear to show significant variation with age.

In conclusion, these results represent the first report of the results from a population based HPV primary screening program. The changes to the program have been largely positive given the magnitude of the task to make such a significant paradigm shift. Issues have arisen however that should be taken into account in any country considering using HPV primary screening.

Digestive Pathology

Herfs M. / Ulg Liège

A dualistic model of squamous carcinoma and adenocarcinoma of the anal canal with implications for personalised medicine

Account for approximately 2% of all gastrointestinal malignancies, the incidence of anal squamous cell carcinoma (SCC) and its precursors is increasing worldwide. Most anal canal SCC (~90%) are etiologically linked to human papillomavirus (HPV) 16 infection and, for still undetermined reasons, a subgroup of patients is associated with a poor outcome. Interestingly, principal component analysis of the whole proteome significantly revealed a subclassification of anal cancers based on their cellular origin. These latter results were further confirmed by the region-specific immunoreactivity displayed by selected biomarkers (keratin filaments). Neoplasms arising from the transitional zone displayed a significantly higher proliferative index, a poor/basaloid differentiation and were associated with reduced disease-free and overall survivals. Altogether, two region-specific subtypes of anal canal SCC were, for the first time, identified (Herfs et al. J Pathol 2017).

Beside squamous neoplasms, a few thousands of primary anal canal adenocarcinoma are also diagnosed each year worldwide. More aggressive than SCC, these rare tumours still represent a diagnostic and therapeutic challenge due to the lack of in-depth characterization. As highlighted in a recent study (Herfs et al. Brit J Cancer 2018), phenotypic analysis revealed two region-specific subtypes of anal canal adenocarcinoma. The significant differences in the HPV status, density of tumour-infiltrating lymphocytes, expression of immune checkpoints and mutational profile of several targetable genes further supported the separation of these latter neoplasms into two distinct entities. Importantly, anal gland/ transitional-type cancers, which poorly respond to standard treatments, displayed less mutations in downstream effectors of the EGFR signalling pathway (i.e., KRAS and NRAS) and demonstrated a significantly higher expression of the immune inhibitory ligand-receptor pair PD-1/PD-L1 compared to their counterparts arising from the colorectal mucosa.

Gynaecological Pathology

McCluggage W.G. / Belfast, United Kingdom

Ovarian cancer: tumour typing, site assignment and reporting following the international collaboration on cancer reporting (ICCR)

A comprehensive pathology report is essential for optimal patient management, cancer staging and prognostication. In many countries, proforma reports are used but these vary in their content. The International Collaboration on Cancer Reporting (ICCR) is an alliance formed by the Royal College of Pathologists of Australasia, the Royal College of Pathologists of the United Kingdom, the College of American Pathologists, the Canadian Partnership Against Cancer and the European Society of Pathology, with the aim of developing an evidence-based reporting dataset for each cancer site. This will reduce the global burden of cancer dataset development and reduplication of effort by different international institutions that commission, publish and maintain standardised cancer reporting datasets. The resultant standardisation of cancer reporting will benefit not only those countries directly involved in the collaboration but also others not in a position to develop their own datasets. I will discuss the development of a cancer dataset by the ICCR expert panel for the reporting of primary ovarian, fallopian tube and peritoneal carcinoma and present the "core" and "non-core" elements to be included in the report (1). The widespread implementation of this dataset will facilitate consistent and accurate data collection, comparison of epidemiological and pathological parameters between different populations, facilitate research, and hopefully will result in improved patient management.

I will also cover tumour grading and controversial areas of tumour typing, including discussion of seromucinous carcinoma which was introduced as a new tumour type in WHO 2014 (2,3) and the recently described mesonephric-like carcinoma (4,5); both of these are closely related to endometrioid carcinomas. I will address issues regarding assignment of the primary tumour site in extrauterine high-grade serous carcinomas. It is now well established that a significant majority of so-called "ovarian" high-grade serous carcinomas arise from the distal fimbrial end of the fallopian tube from a precursor lesion known as STIC (serous tubal intraepithelial carcinoma). Criteria for site-assignment in extrauterine high-grade serous carcinoma have been proposed (6-9) and the use of these criteria result in a high-proportion (approximately 80%) being classified as tubal in origin while primary peritoneal high-grade serous carcinomas are exceedingly rare; this diagnosis should only be made when there is no ovarian parenchymal high-grade serous carcinoma and no mucosal STIC or high-grade serous carcinoma within either tube, both of which should be grossly visible in their entirety and examined in total histologically using a SEE-FIM protocol. I will discuss the chemotherapy response score (CRS) which is of prognostic significance in high-grade serous carcinoma treated by neoadjuvant chemotherapy (10,11).

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Cytopathology

Sahebali S. / Brussels, Belgium

Belgian survey on cervical screening in vaccinated women

Currently the prevention of cervical cancer is undergoing important changes. Research into the carcinogenic role of HPV has led to the development of vaccines. At the same time, in several countries testing for high-risk HPV has become the primary instrument in the screening for precursor lesions.
In order to optimally prepare for the changes in the screening population caused by HPV vaccination, the Cytology Working Group conducted a survey among Belgian pathology laboratories on the current practical experiences with that part of the screening population, which has been vaccinated. Do they still harbour lesions and if so, what kind of lesions. Do these still contain HPV?

Digestive Pathology

Svrcek M. / Paris, France

Microsatellite instability in Lynch syndrome and gastro-intestinal cancer therapy

Microsatellite instability (MSI), which is caused by deficiency of the DNA Mis-Match repair (MMR) system, is the molecular abnormality observed in tumors associated with Lynch syndrome (LS). LS affects approximately 3% of all patients with colorectal cancer (CRC), making it the most common hereditary syndrome predisposing individuals to develop CRC. These patients and their at-risk relatives can develop additional LS-related tumors, thus requiring specific care and genetic counseling. Moreover, research has recently increasingly focused on MMR deficiency due to its positive predictive value for the efficacy of immune checkpoints inhibitors (ICKi) in metastatic tumors, regardless of their primary origin. MSI has also been demonstrated to constitute an independent prognostic factor in several tumor types, being also associated with alternative response to chemotherapy. These observations have led many professional medical organizations to recommend universal screening of all newly diagnosed CRC for dMMR/MSI status and increasing evidence support the evaluation of MSI in all human tumors regardless of the cancer tissue of origin. Consequently, testing for dMMR/MSI is now increasingly being incorporated into routine oncological care of patients with solid tumors across a broad spectrum of cancers. In most instances, pathologists play a key role in this screening.
Two standard reference methods are currently recommended for the detection of dMMR/MSI in CRC: testing for MSI using Polymerase Chain Reaction (PCR), according to international criteria, and screening for loss of MMR protein expression using immunohistochemistry with antibodies directed against MLH1, MSH2, MSH6 and PMS2. These methods are equally valid as the initial screening test for dMMR/MSI in CRC. By contrast, there is no recommendation for detection of the dMMR/MSI phenotype in the great majority of other tumor types. We will present a comprehensive overview of the methods used for the evaluation of tumor dMMR/MSI status in CRC, as well as in other tumor types. We will see that the evaluation of this status remains challenging in some clinical settings and that the accuracy of standard IHC and PCR methods for detection of this phenotype has to be further investigated. Finally, we will talk about emerging techniques developed for improving MSI detection in some specific contexts.

Breast Pathology

Van Eycken E. / Belgian Cancer Registry

Use of the AJCC/UICC classification after neoadjuvant chemotherapy

The 8th edition of the UICC/AJCC TNM classification was first published in December 20171,2. There were very limited changes in the T-, N- and M-categories for breast cancer when compared to the 7th edition. Besides the classic description of the anatomic extent of disease in 'stages', AJCC also integrated in this edition the tumour grade, HER-2, ER and PR hormonal receptor status in prognostic groups.

Some clarifications on post neoadjuvant therapy classification were also made. They can be found in the recently published 5th edition of the UICC TNM supplement3, and more extended in the updated and freely available version of the AJCC breast cancer chapter4.

Post neoadjuvant pathological T-category (ypT) can only be determined if the primary site is resected after completing neoadjuvant therapy. It should be based on the measurement of the largest continuous focus of residual invasive cancer, if any. Treatment related fibrosis adjacent to residual invasive carcinoma or between foci of residual cancer is not included to determine the ypT maximum dimension because its extent may overestimate the residual tumour. When multiple foci of residual tumour are present, then the (m) modifier should be used.

A patient with no residual disease identified is classified as ypT0. When the only residual cancer in the breast is intravasular or intralymphatic (LVI), then the ypT0 category is assigned, but the case cannot be classified as a complete pathological response.

The assignment of the post neoadjuvant pathological N-category (ypN) is based on a similar approach as for the ypT-category. The largest continuous focus of residual cancer in the lymph nodes, if present, is used for ypN categorization. Treatment related fibrosis adjacent to residual nodal tumour deposits or between foci of residual cancer is not included in the ypN dimension and classification.

It is recommended to include in the pathology report a description of the extent of residual tumour (including a description of the distance over which tumour foci extend, number of tumour foci or the number of slides/blocks in which tumour appears) and to explain the basis for the assignment of the ypT and ypN category. This information may also orient the clinician to estimate the extent of disease after neoadjuvant therapy. Applying the AJCC/UICC rules to assign the ypT and ypN-categories -as uniform as possible- will improve the comparability of the post neoadjuvant TNM classification data.

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3. *Wittekind Ch, Brierley JD, Lee A, Van Eycken E, eds. Union for International Cancer Control (UICC) TNM Supplement, A commentary on Uniform Use, 5th edition, Wiley Blackwell, 2019*
4. *TNM classification 8th edition, Breast Cancer, updated version AJCC Cancer Staging Manual, 8th edn. https://cancerstaging.org/references-tools/deskreferences/Pages/Breast-Cancer-Staging.aspx*

INVITED LECTURES

Cytopathology
BALDEWIJNS M. / Leuven, Belgium

Cytopathology
BOURGAIN C. / Brussels, Belgium

Digestive Pathology
CATHOMAS G. / Liestal, Switzerland

Gynaecological Pathology
OLIVA E. / Boston, USA

Cytopathology
WEYNAND B. / Leuven, Belgium

SATURDAY

ORAL PRESENTATIONS

Oral Presentations: case report series

O 01	A. Dubail	An unexpected finding in the abdominal wall of a 45-year-old woman with endometriosis
O 02	S. Kacar	Thyroid-like low grade nasopharyngeal papillary adenocarcinoma: Report of a case
O 03	J. Liu	ALK-positive histiocytosis : rare disease with tremendous implications. Case report

Oral Presentations: research abstracts

O 04	Y. Van Herck	High resolution multiplexing of melanoma microenvironment in responders/non-responders to checkpoint therapy
O 05	L. Marcelis	In depth immunophenotypic analysis of the tumor microenvironment in primary central nervous system lymphoma
O 06	J. De Wilde	A fast, affordable and minimally-invasive diagnostic test for Cancer of Unknown Primary (CUP) using DNA methylation profiling

O 01

AN UNEXPECTED FINDING IN THE ABDOMINAL WALL OF A 45-YEAR-OLD WOMAN WITH ENDOMETRIOSIS.

A. Dubail[1], E. Wacheul[1], P. Jadoul[2], A. Stainier[3], M. Van Bockstal[1], L. Libbrecht[1], E. Marbaix[1]

1. Department of Pathology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.
2. Department of Gynaecology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.
3. Department of Urology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.

Background and objective

A 45-year-old woman underwent a non-radical hysterectomy with adhesiolysis because of postcoïtal abdominal pain and bleeding. Clinically, endometriosis was suspected. During the surgery, a small abdominal mass above the bladder was discovered and biopsied. Here, we describe the clinico-pathological findings of a villous adenoma in the urachal ligament. Moreover, a focus of mucinous adenocarcinoma was found in the subsequent surgical resection.

Materials and methods

Endometriosis of the peritoneum was confirmed histopathologically. Upon evaluation of the abdominal biopsy, a villous adenoma within the urachal ligament was suspected. Immunohistochemistry was undertaken to confirm this hypothesis. The surgical resection specimen allowed evaluation of the lesion's size and its resection margins.

Results

The abdominal biopsy showed a villous lesion with pseudostratification of atypical columnar epithelial cells. This lesion presented extensive cytoplasmic immunostaining for cytokeratins 7 and 20, and strong nuclear expression of CDX2. Expression of PTEN and DNA mismatch repair proteins (MLH1, PMS2, MSH2, MSH6) was preserved. A wild-type nuclear staining pattern was observed for p53. Expression of oestrogen (ER) and progesterone receptors (PR) was absent. This immunohistochemical profile excluded an endometrioid lesion. The patient underwent medical imaging (MRI) to evaluate the location and size of the lesion. After clinico-pathological correlation, a diagnosis of villous adenoma with moderate to severe dysplasia of the urachal ligament was established.
The subsequent resection specimen revealed extracellular mucin lakes containing scattered atypical cells near the adenoma, indicating an invasive mucinous adenocarcinoma.

Conclusions

An adenocarcinoma within a urachal villous adenoma is very rare. This lesion was incidentally diagnosed in a woman with endometriosis who complained of postcoïtal pain and bleeding. This early diagnosis probably prevented a worse outcome, since we hypothesize that mucinous adenocarcinomas of the urachus might be a rare cause of pseudomyxoma peritonei, thereby mimicking a low-grade appendiceal mucinous neoplasm.

O 02

THYROID-LIKE LOW GRADE NASOPHARYNGEAL PAPILLARY ADENOCARCINOMA: REPORT OF A CASE.

S. Kacar[1], P. Brihaye[2], N. De Saint-Aubain De Somerhausen[1]

1. Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium 2. Reine Fabiola University Hospital of Children, Université Libre de Bruxelles, Brussels, Belgium

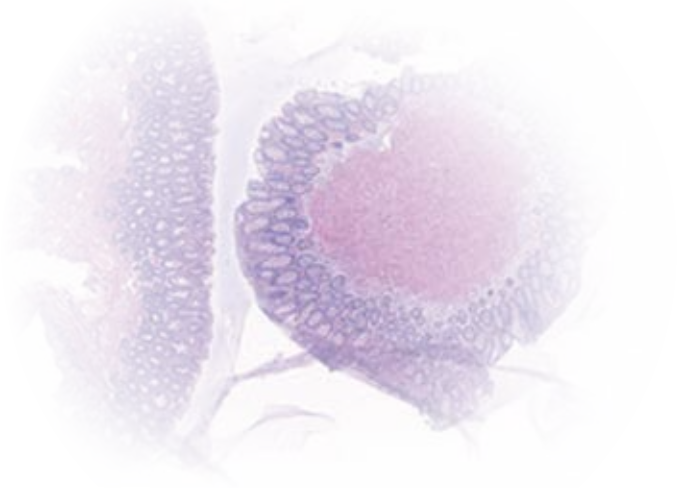
A case of nasopharyngeal low-grade papillary adenocarcinoma is presented. A 16 years old boy referred with a complaint of bilateral nasal obstruction for a few years, recently aggravated. The allergic markers levels, including IgE, were increased at 274kU (N <100).
A pediculated lesion originating from the roof of the rhino pharynx and filling the left choana was detected by MRI. The patient underwent a complete endoscopic resection.

Histopathological examination of the surgical specimen demonstrated an unencapsulated polypoïd lesion, characterised by both papillary and glandular architecture, lined by columnar epithelial cells with thin fibrovascular cores. Tumor cells were organized in single layer, exhibiting uniform small round nuclei and an eosinophilic cytoplasm. Cellular pleomorphism was mild to moderate and occasional mitotic figures were seen, but atypical mitoses and necrosis were absent.

Immunohistochemically, the neoplastic cells were strongly and diffusely positive for TTF-1, with no positivity for Thyroglobulin and PAX-8.
Thyroid-like low-grade nasopharyngeal papillary adenocarcinoma (TL-LGNPPA) is a rare entity (less than 30 cases in the literature). Patients often present obstruction, nasal fullness, and epistaxis.

There is a histologic similarity with metastatic papillary thyroid carcinoma and overlapping immunohistochemical studies, and it is important to distinguish between the two because of different treatment modalities and prognosis. Both entities express TTF-1, but TL-LGNPPA does not stain for Thyroglobulin and PAX-8.

TL-LGNPPA have an excellent prognosis, exhibiting indolent growth, with low metastatic rate and low recurrence after surgical excision (30%). The 3-year survival rates is 70 to 90%. Death due to disease is rare, occurring in less than 5% of cases, caused by uncontrollable local invasion.



O 03

ALK-POSITIVE HISTIOCYTOSIS : RARE DISEASE WITH TREMENDOUS IMPLICATIONS. CASE REPORT.

J. Liu[1], K. Norga[2], X. Bich Trinh[3], M. Ruppert[4], V. Siozopoulou[1,5]

1. Department of Pathology, University Hospital of Antwerp 2. Department of Paediatric Oncology, University Hospital of Antwerp 3. Department of Gynaecological Oncology, University Hospital of Antwerp 4. Department of abdominal, paediatric and plastic surgery, University Hospital of Antwerp 5. Centrum For Oncological Research, University of Antwerp

Introduction

ALK-positive histiocytosis is a newly described non-Langerhans cell tumor. It mainly affects children or adolescents and can be localized or systemic with involvement of many organs such as skin, liver, spleen and bone marrow and in disseminated cases can even lead to death.

Material and Methods

We report a case of a 2 years old girl with a small vulvar lesion, clinically described as a cyst. There was no medical history. The lesion was excised and sent for further histopathological investigation.

Results

The microscopy showed a non-circumscribed dermal lesion consistent of round to spindle cells with pale eosinophilic or amphophilic cytoplasm. The nuclei had irregular contours with occasionally nuclear grooves. Cytomorphologic atypia was not apparent, but there were scattered mitotic figures.

Immunohistochemistry showed positivity of the cells for CD68 without S100 expression. These cells were also diffusely and strongly ALK-positive. Further molecular analysis with NGS revealed a KIF5B-ALK gene fusion. The diagnosis of an ALK-positive histiocytosis was then suggested.

The patient underwent computed tomography, ultrasonography and blood sampling, which demonstrated hepatosplenomegaly and slight elevated level of eosinophils in the blood. Liver and bone marrow biopsies showed no signs of the lesion. Our patient showed no relapse 4 months after the initial diagnosis.

Conclusions

So far only 10 cases of ALK-positive histiocytosis were reported in the English literature. Six cases showed a *KIF5B-ALK* gene fusion. Those patients could benefit from therapy with ALK-inhibitors. Still, given the rarity of this entity, there is limited information about the possible therapeutic options and the prognosis of the localized or disseminated (systemic) disease. Awareness of the lesion would help in better recording of the disease.

O 04

HIGH RESOLUTION MULTIPLEXING OF MELANOMA MICROENVIRONMENT IN RESPONDERS/NON-RESPONDERS TO CHECKPOINT THERAPY

Y. van Herck[1,2], A. Antoranz[1], O. Bechter[2], M. M. Bolognesi[3], S. Lynch[4], A. Rahman[4], W. Gallagher[4], G. Cattoretti[3], J. van den Oord[1], F. M. Bosisio[1,2]

1. Laboratory of Translational Cell and Tissue Research, KU Leuven, Leuven, Belgium 2. University Hospital of Leuven, Leuven, Belgium 3. Università degli studi di Milano-Bicocca, Milan, Italy 4. University College of Dublin, Dublin, Ireland

Background and objective

An *in situ* "high resolution" investigation of the tumor microenvironment has been urged in recent years by the previously failed attempt to find solid histological biomarkers for immunotherapy response. Our objective is to characterize the melanoma microenvironment with a multi-omics approach to find significative differences between responders and non-responders.

Matherial and Methods

23 metastases were collected from patients that underwent PD-1 inhibition (10 complete/partial responders, 13 progressive disease) prior the start of the therapy. A Nanostring PanCancer Immune profiling panel was performed on fresh frozen material. On the same patients, a panel of 80 markers was performed according to the MILAN multiplex technique on formalin-fixed, paraffin-embedded material. A bioinformatic pipeline was applied to the first technique to find differences in gene expression between responders and non-responders, and to the second technique to phenotype the inflammatory populations present in the tissue and to investigate the spatial relationships between them.

Results

Several genes implicated in adaptive immunity/T cell activation were found to be differentially regulated in the responders. This was confirmed also by pathway analysis. In tissue sections, part of the proteins on the 80 selected for the panel showed a differential expression in the responders, in particular the immune checkpoint molecule TIM3. The level of CD8+ lymphocytes (cyT) exhaustion was higher in responders before treatment. In an active microenvironment, melanoma cells are in contact not only with active cyT, but also with active T helpers, that tend to fade away with the transition towards exhaustion, while myeloid cells express progressively higher levels of TIM3, assuming an immune suppressive role, and increase their interaction with cyT in all their functional statuses.

Conclusions

Associating the analysis of the phenotypical and functional heterogeneity of the immune infiltrate to the spatial distribution of each cell type could improve tissue-based biomarkers discovery.

O 05

IN DEPTH IMMUNOPHENOTYPIC ANALYSIS OF THE TUMOR MICROENVIRONMENT IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

L. Marcelis[1], A.-M. Delsupehe[2], P. Biesemans[1], K. Debackere[3], F. M. Bosisio[1,2], D. Dierickx[4], T. Tousseyn[1,2]

1. KU Leuven, Department of Imaging and Pathology, Translational Cell and Tissue Research Lab, Leuven, Belgium 2. UZ Leuven, University Hospitals, Department of Pathology, Leuven, Belgium 3. VIB-KU Leuven, Department of Human Genetics, Laboratory of Molecular Biology of Leukemia, Leuven, Belgium 4. UZ Leuven, University Hospitals, Department of Hematology, Leuven, Belgium

Background

Primary central nervous system lymphoma (PCNSL) is a rare lymphoma with an aggressive clinical course and poor prognosis. The central nervous system (CNS) is an immuneprivileged site, partially responsible for the unique clinical and pathological characteristics of PCNSL. Advances in the field of immunotherapy have led to increased interest in the cellular tumor microenvironment (TME) in different lymphoma subtypes, including PCNSL. Prognostic and predictive TME-specific biomarkers are however lacking in PCNSL.

Methods

We performed and in-depth review of 126 tissue biopsies from patients with CNS lymphoma diagnosed in the university hospitals Leuven. Subsequently, we selected a first cohort of 36 patients: 26 patients with PCNSL and 10 secondary CNS lymphomas based on biopsy size. The tumor microenvironment was characterized in a 2-step approach: First an initial broad analysis of 447 regions with immunostainings for CD8, PD-1, CD4, FoxP3, CD163, PD-L1 using digitalized pathology images and automated analysis system (QuPath). Secondly a single cell resolution, high-multiplex analysis of cytotoxic T-cells and macrophages using the novel MILAN method was performed for a more detailed characterization using CD8, CD68, CD163, PD-1, OX40, CD69, TIM3, LAG3 and PD-L1.

Results

A considerable intra- and inter-tumoral heterogeneity was observed for cytotoxic T-cells, T-helper lymphocytes and macrophages in selected areas. Both low tumor infiltrating lymphocytes and presence of necrosis correlated with shorter survival in PCNSL and differences between primary and secondary CNS lymphomas with potential implications for immune-checkpoint therapy were observed.

Conclusions

Initial results reveal the impact of multiple factors in TME composition of CNS lymphoma with potential therapeutic implications. We also provide further evidence for a prognostic role for CD8+ infiltrating immune cells.

O 06

A FAST, AFFORDABLE AND MINIMALLY-INVASIVE DIAGNOSTIC TEST FOR CANCER OF UNKNOWN PRIMARY (CUP) USING DNA METHYLATION PROFILING

J. De Wilde[1,2,3], R. Van Paemel[1,3,4], C. Vandeputte[1,3], A. De Koker[5], J. Van der Meulen[3,6], M. Van der Linden[1,2], N. Callewaert[5], J. Van Dorpe[2,3], D. Creytens[2,3], B. De Wilde[1,3,4], K. De Preter*[1,3]*

*1. Department of Biomolecular Medicine, Ghent University, Ghent, Belgium 2. Department of pathology, Ghent University Hospital, Ghent, Belgium 3. Cancer Research Institute Ghent (CRIG), Ghent, Belgium 4. Pediatrics department, Ghent University Hospital, Ghent, Belgium 5. VIB-UGent Center for Medical Biotechnology, Ghent, Belgium 6. Molecular Diagnostics, Ghent University Hospital, Ghent, Belgium * shared last author*

Background

Three to five percent of all cancers are CUPs, i.e. metastasized cancers of which the tissue-of-origin cannot be determined. A biopsy of the tumor for pathological examination can take up to two weeks to plan, execute and analyze. Diagnosis usually requires multiple rounds of immunostaining, but still the tissue-of-origin remains unknown in 34% of cases. Moreover, a biopsy is not always possible due to the clinical condition of the patient or the difficult location of the tumor.

Matherial and Methods

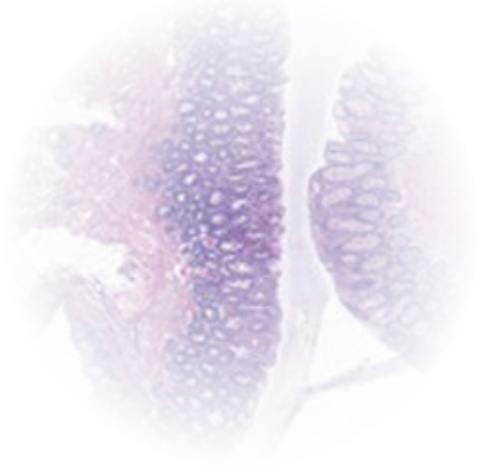
Studies have shown that the DNA methylation profile is a unique 'fingerprint' that can be used to classify tumors. A novel technique developed at the UGent-VIB, called cfRRBS, identifies the methylation profile starting from minimal amounts of highly fragmented DNA. Both DNA extracted from paraffin-embedded (FFPE) tumor tissue as well as cell-free DNA (cfDNA) isolated from liquid biopsies (such as blood) can thus be profiled. In our proof-of-concept study we have collected FFPE-tissue from breast, lung, colon, prostate, esophagus and pancreas adenocarcinomas and melanomas (n=45) and for the same tumor entities we are currently collecting plasma samples.

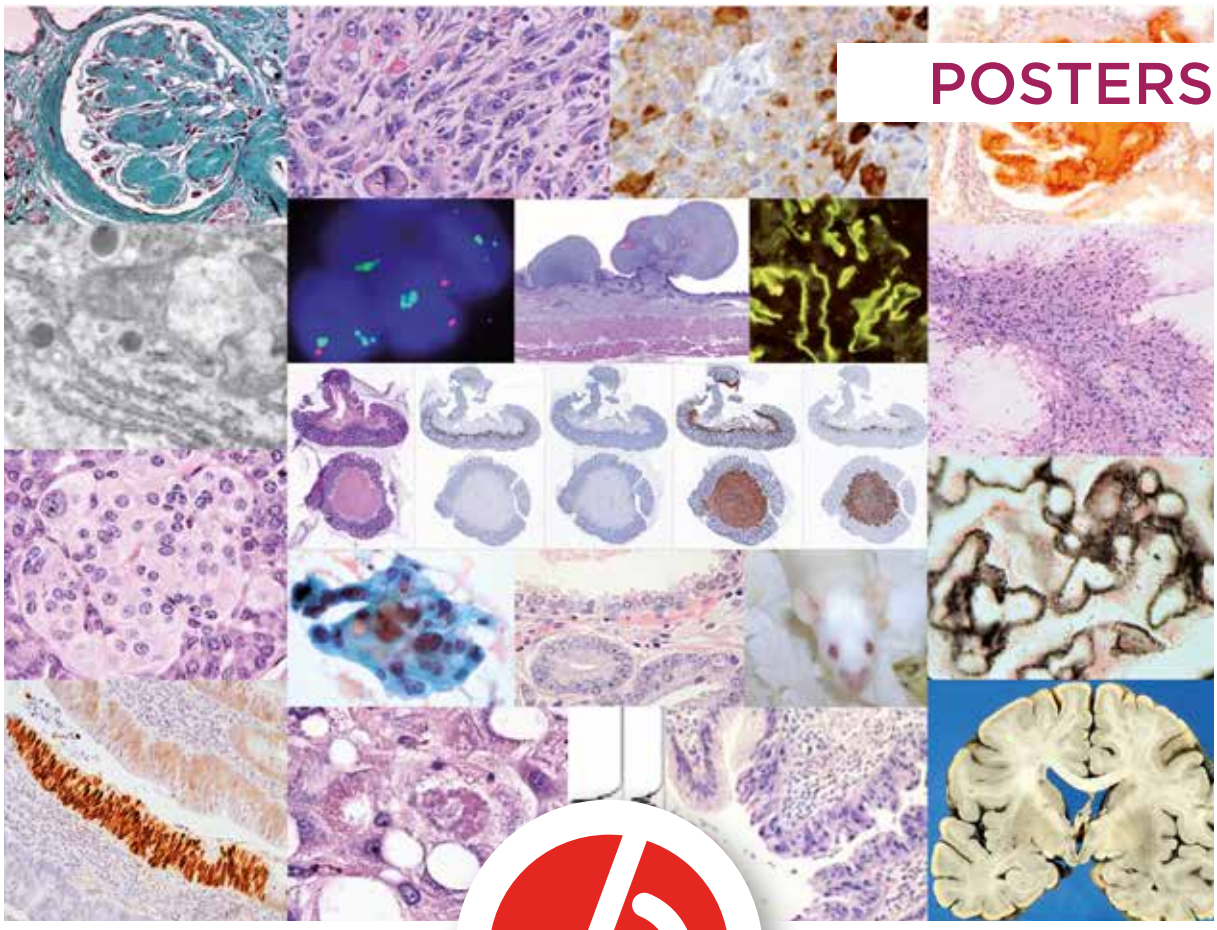
Results

NNLS (non-negative least squares) classification based on a reference dataset of TCGA tumor methylation profiles could correctly predict the tumor origin in 95,5% of the FFPE samples (32/34 primary tumors and 11/11 clinical CUPs). Moreover, the same method applied to cfDNA from plasma samples has shown that 1ng of DNA with a tumor fraction of 10% can be sufficient for diagnosis, but more samples are needed to support this statement.

Conclusions

cfRRBS methylation profiling could be a valuable addition to the pathologist's toolbox in the diagnosis of CUPs. Future research will focus on the optimization of computational classification algorithms and exploring the lower limits of the cfDNA tumor fraction, in order to further improve the performance of this diagnostic test.




POSTERS

P 01	S. Brock	Intracranial desmoid tumor in a paediatric patient caused by heterozygous APC deletion
P 02	L. Cras	Synchronous presentation of endometrioid carcinoma of the ovary and carcinosarcoma of the uterus
P 03	G. Broeckx	Series of BCOR associated endometrial stromal sarcoma
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P 01

INTRACRANIAL DESMOID TUMOR IN A PAEDIATRIC PATIENT CAUSED BY HETEROZYGOUS APC DELETION

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Background and objective

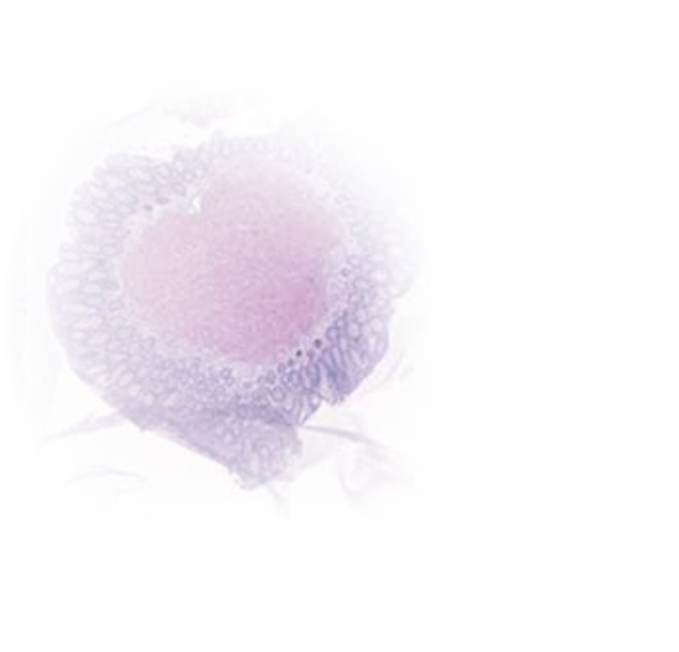
Paediatric desmoid tumors are benign but locally aggressive neoplasms originating from a proliferation of well-differentiated myofibroblasts. Up to 30% of desmoid tumors are found in the head and neck region. However, intracranial localisation is rare. Desmoid tumors are associated with familial adenomatosis polyposis (FAP) caused by germline APC variants, sporadic variants in the *CTNNB1* gene, previous trauma and irradiation.

Methods and Results

A two-year old patient presents with an extra-axial, fronto-parietal tumor with invasion of the skull. Microscopically, the tumor consists of spindle cells with variable cellularity. Focally, the stroma shows a myxoid component, other regions are rich of thick collagen bundles. Blood vessels exhibit a hemangiopericytomal change with a prominent surrounding eosinophilic matrix. Immunohistochemically, beta-catenin is overexpressed in the nuclei. The tumor cells are positive for SMA and vimentin. Staining for CD68 and CD117 shows the presence of a few mast cells. Comparative genomic hybridization (CGH) array of tumor samples demonstrated a heterozygous interstitial deletion of 5q21.1 - 5q23.1 including the APC gene. The patient also carries the probably germline APC variant c.3949G>C (p.Glu1317Gln) which is predicted to be benign but has also been reported to be involved in desmoid tumor development. Variants in beta-catenin were excluded.

Conclusions

(Intracranial) desmoid tumors are rare in the pediatric population. The presence of a desmoid tumor caused by an APC variant can be an early presentation of FAP and should prompt the exclusion of germline APC variants. Detection of the additional p.(Glu1317Gln) variant, although predicted to be benign, supports the hypothesis that this variant is implicated in desmoid tumor development in conjunction with a deleterious APC variant.



P 02

SYNCHRONOUS PRESENTATION OF ENDOMETRIOID CARCINOMA OF THE OVARY AND CARCINOSARCOMA OF THE UTERUS

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Introduction

Endometrioid adenocarcinoma presenting with a synchronous carcinosarcoma is extremely rare. It requires distinct diagnostic work-up and treatment.

Case

A 53-year old woman with a coagulopathy consulted the emergency department. She was diagnosed with bilateral pulmonary embolism. Imaging identified a possible bilateral ovarian cystadenocarcinoma. Significant anemia and interim bleeding also yielded suspicion of a gynecological lesion. Familial history identified a mother with endometrioid carcinoma at age 32 and an aunt with breast carcinoma.
Further gynecological investigation revealed bilateral ovarian masses of 10 cm, with a multi-cystic component. CA125 was 115.52 kU/L. A thickened endometrium could not be assessed further, due to a stenotic and displaced cervix and compression by the intra-abdominal mass.
A total hysterectomy with lymfnode resection was performed. Macroscopy identified a polypoid mass in the uterus and nodular masses of both ovaries.

Histology showed two malignant lesions. The ovaries contained a low-grade endometrioid adenocarcinoma. It was immunoreactive for ER, PR, bètacatenin and negative for TP53 and PTEN. Molecular analysis found a major ATM mutated clone and a minor clone with a PIK3CA (exon 9) mutation.

The uterus contained a high-grade malignant mixed Müllerian tumor (carcinosarcoma). The carcinomatous component was positive for TP53, bètacatenin, PTEN and negative for WT1, ER, PR. The sarcomal part was CD10 (+)/ CD117 (-). It contained a major clone with TP53 and PIK3CA (exon 21) mutations.

Conclusion

Both malignancies show significant microsatellite instability. There are no BRCA mutations. The ovarian neoplasm has a MSI/hypermutated profile, whereas the uterine tumor has a serous profile, which is characterized by high copy number alterations.
After multidisciplinary consultation, chemotherapy with six cycles carboplatin/taxol was started to treat the ovarian carcinoma. Afterwards adjuvant radiotherapy will follow to diminish the recurrence risk of the carcinosarcoma. Further genetic testing for Lynch syndrome is highly indicated in this case.

P 03

SERIES OF BCOR ASSOCIATED ENDOMETRIAL STROMAL SARCOMA

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Abstract

Endometrial stromal sarcoma (ESS) is a less common malignant mesenchymal tumour of the uterus. According to the 2014 World Health Organization classification of tumours, ESS is categorized, based on morphology, clinical behaviour and genetic alterations, into low-grade ESS (LG-ESS), the reintroduced high-grade ESS (HG-ESS) and undifferentiated uterine sarcoma (UUS) as an exclusion diagnosis.

Whereas 50% of the LG-ESS have a t(7;17) chromosomal translocation, resulting in gene fusions JAZF1-SUZ12, JAZF1-PHF1, EPC1-PHF1, MEAF6-PHF1 and MBTD1-CXorf67, USS has no defining genetic hallmarks. In 2014, reintroduction of HG-ESS was based on the discovery of the translocation t(10;17) in these tumours with fusions in the YWHAE and NUTM2 genes.

Cases of HG-ESS lacking a YWHAE fusion, have been described in the literature. These cases usually harbour rearrangements or internal tandem duplications (ITD) in the BCOR gene. Both genetic alterations can be found by immunohistochemistry with high specificity. Immunohistochemistry does not differentiate rearrangements from ITD.

We report a series of 3 BCOR associated ESS; BCOR alteration was confirmed on immunohistochemistry. All cases had a different morphology. A first case had a LG appearance with fibromyxoid growth pattern and high mitotic activity. The tumour cells were immunoreactive for CD10, but not for ER, PR, CD117 and Cyclin D1. A second case showed a multinodular tumour: high grade nodular areas with immunoreactivity for Cyclin D1 and CD117, but negative ER/PR, alternated with lower grade spindle cell areas that were ER/PR and CD10 positive, but Cyclin D1 and CD117 negative. FISH did not show YWHAE rearrangement. The third case had an undifferentiated morphology. Despite their variable morphological appearance, all cases had a clinical aggressive behaviour.
Literature suggests that BCOR associated malignant tumours might benefit from therapy with immunologic checkpoint inhibitors. Since robust scientific evidence for the benefit of immunotherapy in ESS is lacking, its role in BCOR associated ESS has yet to be evaluated.

P04
SEBACEOUS ADENOMA OF THE PAROTID GLAND

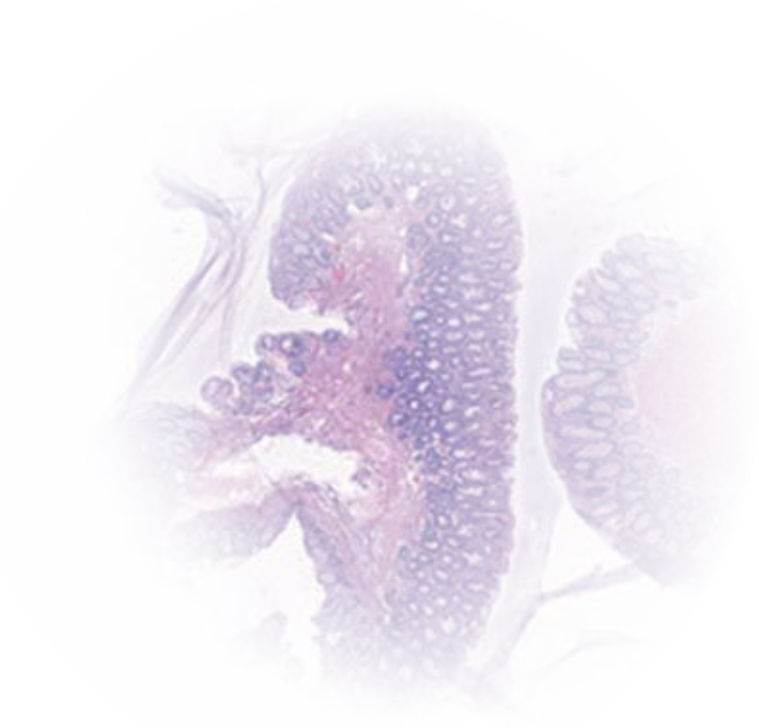
S. De Smet, C. Geers, S. Sahebali, W. Waelput, P. Lefesvre, R. Forsyth

A 58-year-old man presented with a painless, progressively enlarging right neck mass. Medical imaging showed a sharply demarcated, solid lesion, located in the superficial part of the parotid gland. Next to this, the patient was known with mental retardation, Guillain-Barré syndrome, transverse myelitis, meningoencephalitis and diabetes mellitus type 2.

As a first approach, fine needle aspiration was performed. Cytologic examination showed inflammation mixed up with the presence of multinucleated giant cells suggesting a ruptured (inclusion) cyst.

In a second stage surgery was performed. During this procedure, a frozen section was asked of this parotid lesion. It showed no clear evidence for malignancy. Subsequently, superficial parotidectomy was performed with preservation of the facial nerve.

Macroscopic examination of the surgical specimen showed a soft, encapsulated, yellowish mass of 2.9 x 2.5 x 2.5 cm. Histological examination found sebaceous lobules in a fibrous stroma surrounded by a thin fibrovascular capsule and normal parotid gland tissue. The lesion was finally diagnosed as a sebaceous adenoma. Parts of the lesion were infiltrated by numerous inflammatory cells and multinucleated giant cells as was seen in the FNAC, probably in response to extravasated sebum. Sebaceous cells occur in salivary glands and could be precursors of this rare neoplasm. Differential diagnoses are sebaceous lymphadenoma, sebaceous (lymph)adenocarcinoma and focal sebaceous differentiation in other tumors.



P 05

METASTASIZED ANGIOSARCOMA OF THE PERICARDIUM: REPORT OF A VERY RARE CASE DIAGNOSED POST-MORTEM

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Keywords

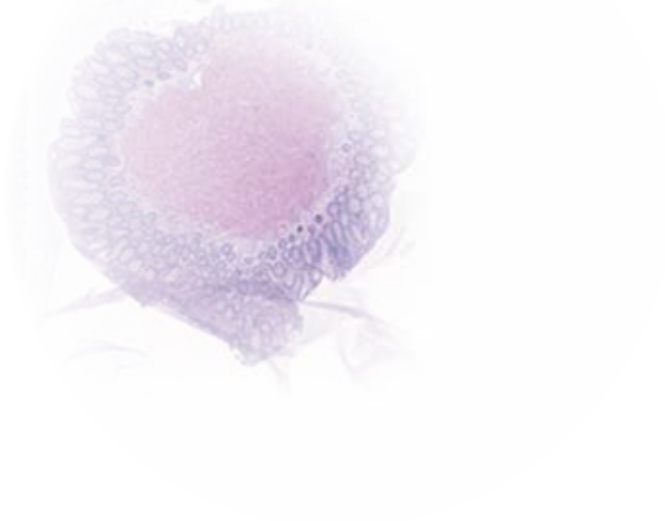
Angiosarcoma, pericardium, metastasized

Introduction

Angiosarcomas of the pericardium are very rare tumors, arising from endothelial cells of blood vessels. Only few cases have been reported, some of which were cases of the more common cardiac angiosarcoma with pericardial involvement. Patients are usually diagnosed in a late stage of the disease. Prognosis is poor.

Material and methods

We report a case of a 55-year old male patient that was admitted to hospital for pericardial effusion with cardial tamponade and obstructive shock. Previous evalution of the pericardial fluid gave no diagnosis. Quick deterioration of the patient lead to urgent sternotomy where biopsies were taken. The patient died a short time after surgery. An autopsy was performed.



Results

Both during surgery and autopsy no normal pericardium was seen. On autopsy the heart was surrounded by a thick, thrombus-like material. No normal pericardium was found. The heart itself showed no macroscopic anomalities. Also numerous enlarged lymphnodes in the mediastinum and multiple nodules in both lungs were found.

Microscopic investigation of the thrombus-like material from the pericard revealed proliferation of strongly atypical, spindle shaped cells. These cells had pleiomorphic nuclei with pseudo-inclusions and prominent nucleoli. There was scant cytoplasm. Multiple, sometimes atypical, mitotic figures were seen. Additional immunohistochemical staining for CK-Pan was negative. ERG-immunohistochemical staining was strongly positive in all atypical nuclei, supporting the diagnosis of an angiosarcoma.

Conclusions

Pericardial angiosarcoma is a rare and difficult diagnosis often made in a late stage of disease. The differential diagnosis proposed by the clinicians, based on symptoms, was either thrombosis or infection. In this case the pericardial effusion was also infected, which complicated the diagnosis even further. Based on cytology of pericardial effusion alone this diagnosis is hard to make. A biopy of thrombus-like material with strongly atypical endothelial cells should point in the right direction.

P 06

ONSET OF A PSYCHIATRIC DISEASE IN A 52-YEARS-OLD MAN: WHEN AUTOPSY REVEALED POSSIBLE PSYCHIATRIC DISEASE!

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A 52-year-old man was referred to our institution because of hypoxemic pneumonia. He was recently interned in a psychiatric institution due to schizophrenic symptoms. The patient complained of chest pain and breathing issues without pyrexia lasting for a week. Physical examination, radiological studies and biological explorations supported the diagnosis of pulmonary infection. First, antibiotics slightly improved patient's biological results but patient remained dependent on oxygen support. The patient died two weeks after his admission.

Autopsy showed mainly weighty lungs (left: 928g, right: 866g) without other macroscopic abnomalities in other organs as well as in brain. Microscopic examination however displayed extensive vascular invasion by isolated large neoplastic cells. Immunohistochemical ancillary studies confirmed B phenotype of these cells which were mature B lymphocytes. Peculiar distribution of B lymphocytes within the lumina of almost all vessels, led us to diagnose a rare type of extranodal large B-cell lymphoma (LBCL): the intravascular LBCL (ILBCL). This type of lymphoma is usually widely disseminated in the blood vessels, sparing the lymph nodes.

In its classic form, symptoms are related to the main organ involved, predominantly neurological or cutaneous. B-symptoms, in particular fever, are very common. This tumor is generally aggressive and has a poor prognosis mainly due to the lack of detectable tumors masses and the variability of the symptoms delaying a timely and accurate diagnosis (usually at autopsy).

According to the patient's psychiatric file, his psychiatric symptoms began only fifteen months earlier. Psychiatrists concluded on late onset of schizophrenia after extensive exploration (MRI, metabolic, infectious and chemical exploration ...) turned out negative.

Unfortunately, brain tissue samples for microscopic examination were not performed for lack of macroscopic alterations so we couldn't be certain that the neurological symptoms were related to the lymphoma.

This rare case emphasize the importance of brain microscopy at autopsy even in absence of macroscopic lesion and particularly when recent psychiatric symptoms are newly diagnosed.

P 07
ESOPHAGEAL MELANOMA: CASE REPORT

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3. Department of pathology, Jules Bordet Institute, Brussels, Belgium

A 81-year-old man was hospitalized for weightloss, inappetance, impaired general condition and dysphagia since 10 days. A gastroscopy was performed and showed a non ulcerated, 2 cm high, hemicircumferential esophageal achromatic mass, localised at 32 centimeters of dental arches.

The histological examination of the biopsy revealed a poorly differentiated neoplasic proliferation, formed by round and spindle cells with hyperchromatic nuclei.

Immunohistochemistry markers were positive for S100, SOX10, HMB-45 and melan-A and negative for cytokeratins, CD117 and DOG1.

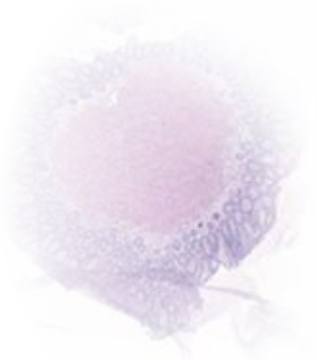
The histologic diagnosis retained was melanoma. A total body pet-scanner was performed to exclude a metastatic origin. It highlighted only the esophageal tumor without any distant lesion. An echo-endoscopic examination demonstrated that the lesion was limited to the mucosa, leaving the submucosa and muscularis propria free. The lesion measured 17.5 x 7.7 mm. There were three regional infracentimetric lymph nodes. A final diagnosis of primitive esophageal melanoma was suggested.

Primitive esophageal melanoma is a rare entity whose incidence is 0.1 to 0.4% of all esophageal neoplasia. Its main symptomes are common to the other esophageal tumors, namely dysphagia, weightloss, retrosternal pain, and more rarely bleeding.

The differential diagnosis of esophageal spindle cell melanoma is to be made with other malignant or borderline tumors, including the following :

- Sarcomatoid carcinoma
- Gastrointestinal stromal tumor (GIST)
- Malignant peripheral nerve sheath tumor (MPNST)
- Leiomyosarcoma
- Synovialosarcoma

The best therapy recommanded is extensive surgery with lymph node resection. Prognosis and survival rates are really poor. Patients who have had surgery have between 9 to 14 months of mean survival, and the 5-year survival rate is estimated at 4%.
Due to poor general condition and cardiovascular disease, surgery was not performed. A treatment by anti-PDL1 immunotherapy was started.



P 08

MDM2 IMMUNOEXPRESSION AND GENE AMPLIFICATION IN A GASTRIC WALL TUMOR: AN UNEXPECTED PITFALL

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Introduction

Mouse double minute 2 (MDM2) is a protein implicated in the negative regulation of tumor suppressor p53. *MDM2* amplification has been mainly described in two histological subtypes of one of the most common sarcoma: well differentiated and dedifferentiated liposarcoma. However, *MDM2* amplification has been described in other sarcomas.

Case presentation

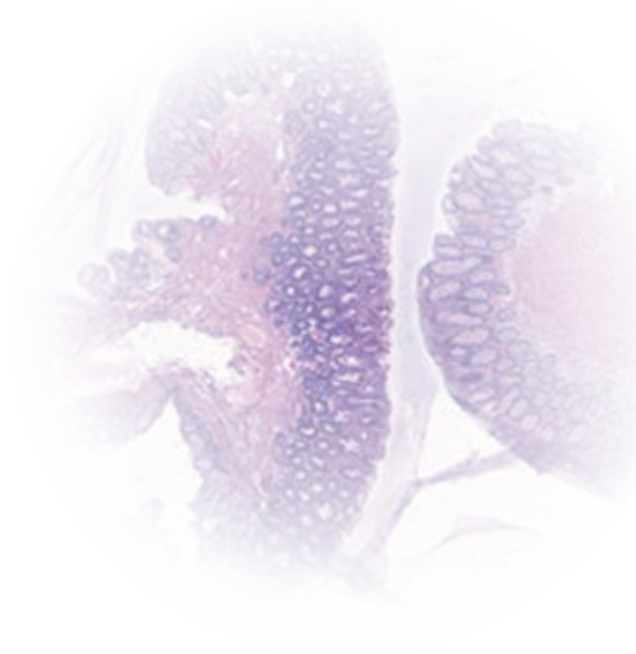
We report the case of a 50-year-old male referenced to our institution for the characterization of a voluminous gastric tumor. Based on imagery, gastrointestinal stromal tumor (GIST) was the initial most probable diagnosis. The morphological and immunohistochemical profile on fine needle aspiration of the tumor suggested liposarcoma, with positive *MDM2* expression in immunohistochemistry and *MDM2* amplification confirmed by CISH. Surgical resection of the tumor is obtained by gastrectomy. The morphology of the tumor on specimen suggested epitheloid GIST, but the immunohistochemistry profile and molecular biology analysis remained atypical. Indeed, positive *MDM2* expression in immunohistochemistry and *MDM2* amplification by CISH was again found, but the histological appearence wasn't compatible with a liposarcoma. In addition, Next Genome Sequencing (NGS) didn't highlight any gene mutations, especially C-kit or PDGFRA, which was against GIST. Slides are then sent for second opinion. The differential diagnosis between dedifferenciated liposarcoma and follicular dendritic cell sarcoma is evoked. After complementary stainings (CD21 and CD23), the diagnosis of *MDM2* amplified follicular dendritic cell sarcoma of the stomach is proposed.

Discussion

When morphology of the specimen is challenging, *MDM2* immunoexpression and gene amplification can be a diagnostic pitfall, especially if from an abdominal/retroperitoneal location.

Conclusion

Although *MDM2* amplification has been mainly associated with liposarcoma subtypes, it should not be forgotten that it has been described in other less frequent sarcomas. Therefore, one must remain critical and an extensive immunohistochemical panel may be required to propose an adequate diagnosis.



P 09

MOLECULAR PATHOLOGICAL APPROACH OF A RARE TONSILLAR TUMOR

M. Ramael[1], T. Puls[2], W. Dietmaier[3], W. Develter[4], H. Van Steelandt[5], D. Obbels[6], J. Frans[6], M. Ramael[1,4]

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Background and objective

Squamous cell carcinomas are the most common malignant tumors of the palatine tonsil. Muco-epidermoid carcinoma of the palatine tonsil is an extremely rare tumor. A literature search revealed only three cases of muco-epidermoid carcinoma of the palatine tonsil. We describe another case and searched for molecular markers.

Case Description

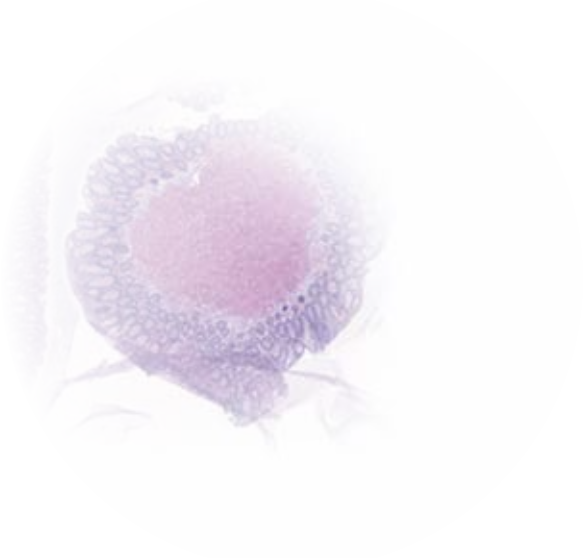
A 77 year old woman visited the outpatient clinic and presented with vague complaints of pharyngeal discomfort. CT-Imaging revealed a tumour in the right palatine tonsil. Tonsillectomy was performed. The tonsil (3 × 2.5 × 1.5 cm) was diffusely infiltrated by a malignant epithelial tumor with both squamous and mucinous differentiation suggesting muco-epidermoid carcinoma. After two months the patient underwent right neck dissection for removal of suspicious lymph nodes. One of five lymph nodes was invaded by muco-epidermoid carcinoma.

Results

Immunoreactivity was found for p16 and for stem cell associated markers CD44, CD133 and ALDH-1 but not for CD10. Real time PCR disclosed HPV 16 DNA confirming the immunoreactivity for p16 protein. Tumor mutational burden (TMB) was investigated both in the primary tumor (All mutations : 539.75/MB, Non-synonymous mutations (TMB-score): 2.33/MB mutations) as well as in the lymph node metastasis (All mutations : 553.99/MB, Non-synonymous mutations (TMB-score): 2.37/MB)

Conclusions

Muco-epidermoid carcinoma of the palatine tonsil is an extremely rare tumor but has to be considered in the differential diagnosis of tonsillar tumors. Our case might be an example of a 'stem cell tumor'. There is immunoreactivity for several cancer stem cell markers (ALDH, CD44) which can be found in tumorigenic cancer stem cells of muco-epidermoid carcinoma. The oncogenic process is probably initiated by HPV 16 infection.



P 10

A VERY RARE CASE OF INTRAVASCULAR NK/T-CELL LYMPHOMA: A CASE REPORT AND REVIEW OF THE LITERATURE

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Background

Intravascular NK/T-cell lymphoma is a rare and aggressive form of lymphoma with only about 30 cases described in medical literature so far.

Case presentation

We present a case report of a 29-years-old female, presenting with diffuse abdominal pain, headache, fever and pruritis lasting for several months. Clinical examination evidenced abdominal skin lesions and an isolated inguinal lymphadenopathy. Skin and inguinal lymph node biopsies were performed and revealed intravascular large atypical lymphoid cells, with a moderate amount of cytoplasm and irregular ovoid nuclei within the small vessels of the dermis and of the adipose tissue surrounding the lymph node. The lymph node was not infiltrated. These neoplastic cells were positive for CD3, CD2, CD7, CD56, CD30 (focal), GranzymeB and Perforin. EBV was positive by in situ hybridization, supporting a diagnosis of Intravascular NK/T-cell lymphoma. Further investigations showed no evidence of a NK/T lymphoma, nasal type or an NK/T cell leukemia.

Discussion

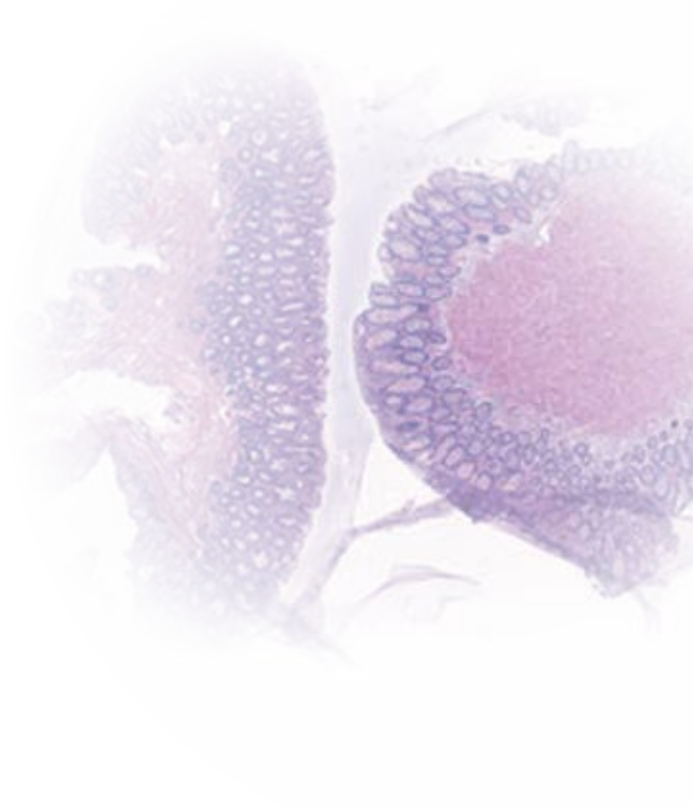
Intravascular NK/T-cell lymphomas are rare and aggressive forms of lymphoma characterized by neoplastic NK/T cells within lumen of small blood vessels. They can involve any organ, with, however, a clear predominance for the skin and the central nervous system.

So far, this type of lymphoma is not recognized as a specific entity by the last 2017 World Health Organization (WHO) classification of lymphoid neoplasms, probably due to its rarity. Indeed, to our knowledge, only 30 cases of intravascular natural killer/T-cell lymphoma have been reported in the literature.

Because of its rarity and the non-specific manifestations of this entity, the diagnosis and treatment of patients are often delayed resulting in a poor outcome despite an aggressive therapeutic management.

Conclusions

IVNKTL is a rare form of non-Hodgkin's lymphoma still little-known today and it must be kept in mind in the differential diagnosis of intravascular lymphoproliferation with aspecific symptoms to avoid delayed diagnosis.



P 11
SYNCHRONOUS THYROID CARCINOMAS IN A 13 YEAR OLD GIRL

H. Van Beveren / UZ Gent

Background

The presence of synchronous differentiated, medullary and/or anaplastic thyroid carcinoma has been reported in various presentations, however it is considered very rare. Synchronous thyroid carcinoma in children have never been reported so far.

Case Report

We herein report a case of a 13 year old girl presenting with a large, painless, non-tender firm nodule in the left thyroid lobe. There was no palpable lymphadenopathy. Slight tachycardia, intermittent sore throat, increasing nervousness and a 2 kg weight loss since several months were reported. Thyroid function tests showed an elevated FT4 (51 pmol/l) and thyroglobulin (435 µg/l) and a decreased TSH (< 0.005 mU/L). Doppler ultrasound showed a normal right lobe and a sharp hypervascular solid multilobular mass (longest diameter 5.3 cm) with cystic components in the left lobe, whereas scintigraphy showed a global but heterogeneous hyperfunctioning thyroid gland with excessive uptake at the upper left lobe and upper right lobe. A left tracheal deviation by the left thyroid mass and no cervical lymphnodes or thoracal mass were seen at CT. Fine needle biopsy was refused by the patient. Diagnosis of large (benign) toxic adenoma crossing the midline was made. Patient underwent a left lobectomy after 2 months of methimazole therapy.
Histological examination however showed two clear morphologically distinct neoplastic lesions in the left lobe arising in what appears to be a multinodular goiter. The first neoplastic lesion, measuring 2.9 cm, showed a follicular growth pattern with endocrine nuclear atypia, multiple foci of intracapsular vascular invasion and some foci of capsular invasion. Separated from this lesion by a couple of millimeters is a second neoplastic papillary lesion with a prominent follicular architecture and oncocytic changes with nuclear features of a papillary carcinoma (nuclear clearing and grooves). The papillary mass showed apical staining for HBME1, whereas the adjacent follicular mass was complete negative. Therefore diagnosis of a synchronous follicular carcinoma (with multifocal capsular and angioinvasion) and a papillary carcinoma, classical type (with follicular and oncocytic) was made. The findings of two distinct carcinomas in a child are unusual. Further testing was performed to exclude genetic syndromic causes. PTEN staining (in the context of PTEN hamartoma syndrome)was retained and beta catenin (in the context of Familial Adenomatous Polyposis) showed membranous staining, discounting involvement by either of these two syndromes. BRAF mutation analysis showed no mutations. Results of TSHR gen and GNAS gen analysis are pending.

Conclusions

This case report illustrates some important messages one needs to keep in mind when examining a (hemi)thyroidectomy specimen originating from a child. Although clinical records showed no clear features raising suspicion regarding malignancy, this case turned out to be malignant. Therefore always be aware of potential malignancy, including when performing a gross examination.
Although thyroid carcinoma and especially synchronous thyroid carcinoma are very rare in children, always consider the diagnosis when you have two morphologically different neoplastic lesions.
When diagnosing a thyroid carcinoma in children, always consider underlying genetic syndromes. Therefore further immunostaining and genetic testing is recommended.

P 12

LIPOBLASTOMA-LIKE TUMOR OF THE VULVA IN A 33 YEAR OLD WOMAN

H. Van Beveren / UZ Gent

Lipoblastoma-like tumors of the vulva are very rare with only 19 cases reported in literature so far.
A lipoblastoma-like tumor of the vulva is a benign myxoid adipocytic tumor of the vulva predominantly occuring in young adults in which conservative complete excision is curative. They present as well circumscribed, multilobulated lesions composed of mature adipocytes, lipoblasts and spindle cells located in a myxoid background with prominent chicken-wire branching vessels. We herein report a case of a 33 year old women presenting with a mass of the right labia majora.
The objective of this case report is to summarize its main characteristics and to highlight the important differential diagnosis which needs to be made with other (malignant) mesenchymal tumors of the vulva.

P 13

PRIMARY CUTANEOUS ADENOID CYSTIC CARCINOMA OF THE UPPER LIMB: COMMON TUMOR, RARE LOCATION

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Introduction

Adenoid cystic carcinoma is a malignant tumor that accounts for 22% of all salivary gland malignancies. However, there are fewer than 70 confirmed cases of primary cutaneous adenoid cystic carcinoma (PCACC) in the English literature. The scalp is the most commonly affected region. The tumor has been shown to have a high local recurrence rate, however distant metastases are rare.

Materials and methods

We report a unique case of a 59-year old male presenting with a subcutaneous nodular lesion on the right upper limb, showing a slow growth, rather indolent behavior. Diagnosis followed incomplete removal of the lesion, after which thorough radiological examination was performed to confirm its primary cutaneous origin. Considering there were no enlarged lymph nodes and distant metastasis was excluded, wide local excision was carried out.

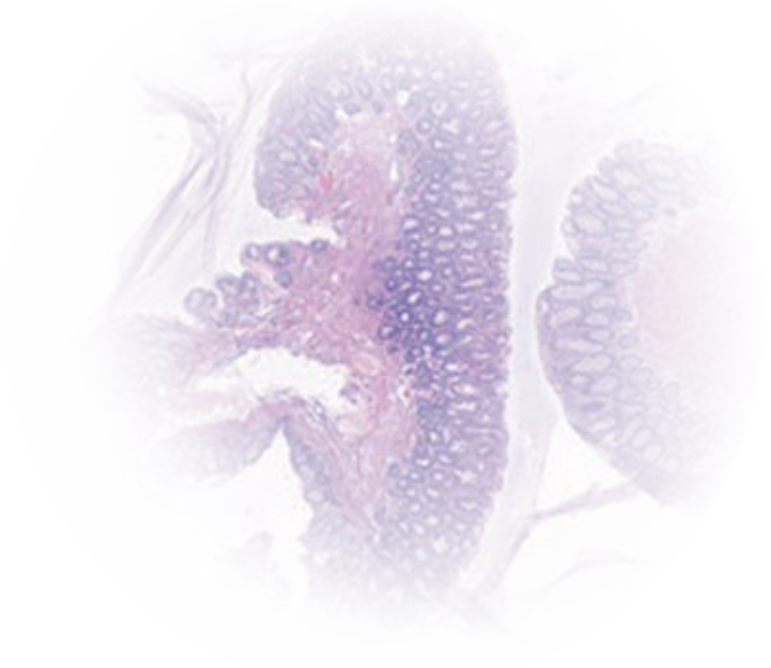
Results

Histologic examination showed a well-circumscribed nodular lesion, composed of small, monomorphic basaloid cells with small, round to oval nuclei and scant cytoplasm. Tumor cells are arranged into a few solid islands and numerous cribriform structures, surrounding multiple, variably sized pseudo-cystic spaces forming a “Swiss cheese”-like pattern. The pseudo-cystic spaces are surrounded by PAS+ basement membrane material. There is perineural invasion. Immunohistochemical examination revealed CD117 positivity in a large part of the tumor cells. Next generation sequencing did not show any significant mutations.

The differential diagnosis included PCACC, dermal cylindroma, adenoid basal cell carcinoma and primary cutaneous cribriform apocrine carcinoma. However, given the morphology, the tendency to perineural invasion and the CD117-positivity, PCACC was diagnosed.
The patient is doing well with no local recurrences up to now.

Conclusion

PCACC is an uncommon neoplasm. There are no large series of studies to significantly evaluate treatment or prognosis of these tumors. Local wide excision with negative margins and close follow-up is the most commonly used therapy with seemingly good outcome.



P 14

THE MILAN SYSTEM FOR REPORTING SALIVARY GLAND CYTOPATHOLOGY: SINGLE CENTRE EXPERIENCE WITH CELL BLOCKS

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Background and objective

Salivary gland fine needle aspiration (SG-FNA) has a well-established role in the evaluation of salivary gland lesions. However, salivary gland cytology is known to be challenging due to tumour diversity and morphological overlap between different lesions. In 2018 Rossi et al. developed the «Milan system for reporting salivary gland cytopathology» (MSRSGC) to accomplish a more standardized reporting across institutions. This classification is predominantly based on the use of direct smears. In this study we aim to evaluate and further validate the MSRSGC based on the sole use of cell blocks and carry out a risk assessment based on follow up histopathology.

Materials and methods

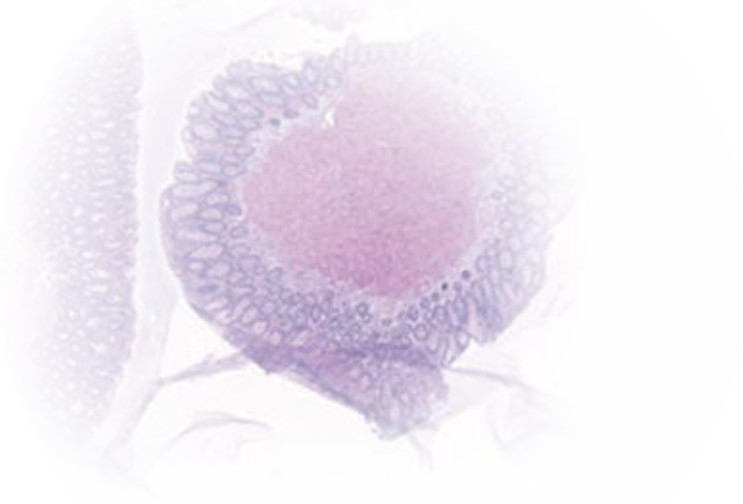
A retrospective collection of all reported SG-FNA processed as cell blocks between 2012 and 2018 was made. The cytological diagnosis were categorized according to the Milan System. The use of ancillary immunohistochemistry or molecular testing was recorded. Correlation with follow up histopathology was made and ROM was calculated for each diagnostic category.

Results

A total of 359 salivary gland aspirates were evaluated: 117 samples (32,5 %) were non-diagnostic, 12 samples (3,3%) were categorized as non-neoplastic, 37 cases (10,3%) showed atypia of undetermined significance (AUS), 127 cases (35,4%) were categorized as benign neoplasms, 26 cases (7.2%) showed salivary gland neoplasms of uncertain malignant potential (SUMP), 5 cases (1,4%) were suspicious for malignancy and 35 cases (9,7%) were classified as malignant neoplasms. Follow-up resection was available in 235 cases (65,5%).
With exception of AUS and SUMP categories, the risk of malignancy (ROM) was in accordance with those of the Milan System.

Conclusions

This large retrospective series indicates that the use of cell blocks has an advantage in the classification of salivary gland cytopathology and the corresponding risk for malignancy (ROM) for each diagnostic category.



P 15

NEUROPATHOLOGICAL FINDINGS IN LEIGH SYNDROME A REPORT OF NEONATAL CASE

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Introduction

Leigh syndrome (LS) is a progressive neurological disease defined by specific neuropathological features involving brainstem and basal ganglia. It has multiple causes, resulting in a deficit in aerobic energy production. Neonatal presentation of LS is very rare.

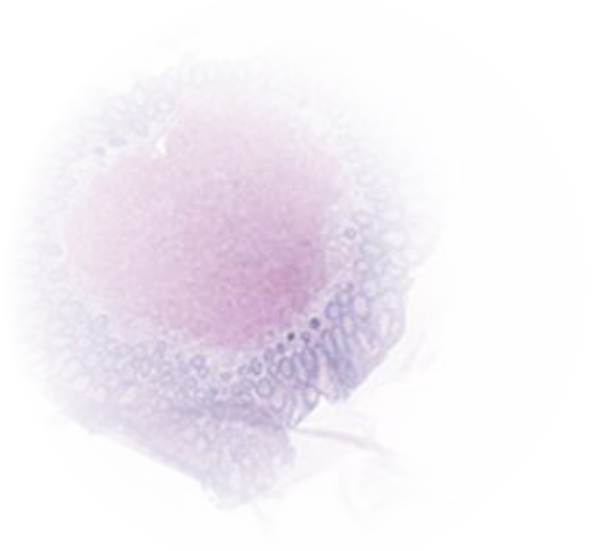
We report the case of a neonate presenting with neurologic disturbances in which neuropathological examination suggested the diagnosis of LS.

Case report

A term boy born from a primipara mother was admitted at birth for hypotonia and convulsions. Parents were consanguineous. Antenatal ultrasonography showed nuchal translucency. Karyotype was normal. Caesarean section was performed for breech presentation and macrosomia. Apgar score was 6 and 7. The baby weight was 3970 g. The patient presented with hypotonia, seizures, macrocrania, facial dysmorphy and hirsutism. The major frequent causes of neonatal neurologic distress were ruled out. An inborn error of metabolism was highly suspected. CNS MRI with spectroscopy couldn't be performed. The infant died at 15th day. Autopsy findings with neuropathological examination revealed diffuse necrotic lesions of the neocortex, basal ganglia, thalami and brainstem suggesting LS associated with lesions similar to those seen in MELAS syndrome.

Conclusions

LS encompasses a spectrum of diseases with highly variable clinical, imaging, and pathological presentations. It manifests typically in the first two years of life saving the neonatal period, so that our cases was somewhat atypical in clinical presentation. Neuropathological examination is of great contribution in assessing the origin of unexplained neurological manifestations.



P 16

HYDROCEPHALUS IN FETUSES REVEALING A SPECTRUM OF WALKER-WARBURG SYNDROME (TYPE II LISSENCEPHALY): A FETAL NEUROPATHOLOGICAL STUDY OF 5 CASES

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Introduction

Walker Warburg Syndrome (WWS) is a lethal, genetically heterogeneous autosomal recessive disorder characterized by a spectrum of lesions including, a type II lissencephaly (Cobblestone lissencephaly), retinal malformation, cerebellar malformation, and congenital muscular dystrophy.

The neuropathological findings at the fetal autopsies in five cases of type II lissencephaly are hereby presented.

Material and methods

We report the autopsy findings of 5 cases, two of them are a siblings referred to pathology department for major hydrocephalus discovered on ultrasound between 20 and 22 gestational weeks in 3 cases and at 37 Weeks for the two others. Hydrocephalus was associated with occipital encephalocele in one case and with 4th ventricle cyst suggesting a Dandy-Walker malformation in the other case. Medical termination of pregnancy was performed at 22 Weeks in 3 cases. For the two others, one was stillborn at term and the other died few hours after birth. Pathology findings in all cases showed lissencephaly, hydrocephalus, diffuse and severe cerebral and cerebellar cortical dysplasia with glial and neuronal displacement into the leptomeninges, consistent with diagnosis of Walker Warburg syndrome.

Conclusions

Fetal hydrocephalus was the major manifestation leading to the prenatal detection of this syndrome. Our cases are highlighting the necessity to look for associated anomalies in fetuses or newborn infants with hydrocephalus in order to establish a better prenatal diagnosis and an effective family genetic counselling.

P 17

MENINGEAL HEMANGIOPERICYTOMA A PATHOLOGICAL DILEMMA: IMMUNOHISTOCHEMICAL AND GENETIC STUDY

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Background

Meningeal Hemangiopericytoma (MHPC) is vascular tumor arising from pericytes. Most intracranial hemangiopericytomas apparently arise from the meninges, and often misdiagnosed as meningiomas.

Methods

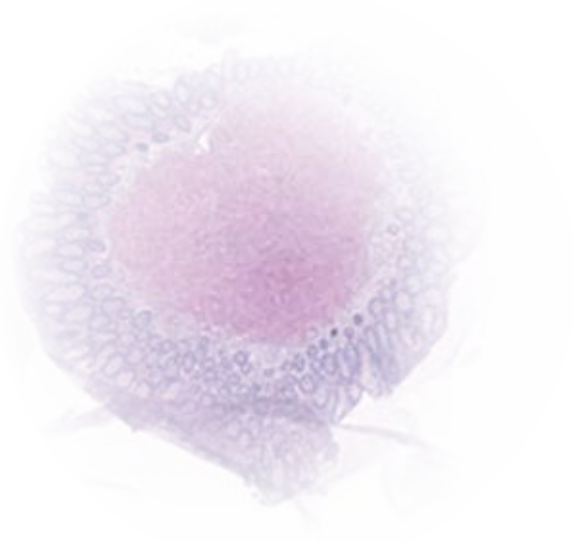
We report 8 cases of MHPS in comparison with 5 cases of meningiomas collected from Department of anatomic pathology in University Hospital of Sousse (Tunisia) in the period from 2007 to 2011. Immunohistochemistry (IHC) was performed by using EMA, Vimentin, CD99, Bcl-2, CD56, S100, Synaptophysin, P21, CD34, NSE, ACE, FVIII, Desmin, GFAP, P16 antibodies. Additionally, we focused on the analysis of a large panel of genetic markers using molecular technique: Multiplex Ligation Probe Amplification (MLPA).

Result

Both MHPC and meningioma showed 100% Vimentin positivity. The four useful IHC markers (Bcl2, EMA, CD34 and CD99) were 87%, 37%, 62% and 62% respectively in MHPC. However, the P21 antibody was seen positive in 62% of HPC and less than 1% in all meninigiomas.

Conclusions

Meningiomas and MHPC seems to be as spectrum of tumor that IHC can not absolutely differentiate between them because of their unspecific IHC profile. Despite of the help given by genetic investigations to characterize these two tumors; their prognosis still depends on histological grade.



P 18

IMMUNOHISTOCHEMISTRY ACCURACY IN THE DIAGNOSIS AND HISTOLOGICAL CLASSIFICATION OF OVARIAN CARCINOMA

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Introduction

Epithelial ovarian malignant tumor (ovarian carcinoma) is the main cause of death by gynecologic cancer, occupying the 6 th rank of female cancer mortality in Tunisia. 5 major histological subtypes are identified, High Grade serous carcinoma, endometroïd carcinoma, mucinous carcinoma, clear cell carcinoma and Low-Grade Serous Carcinoma, However the reproducibility of this morphologic classification is moderate.

Aim of the study

we will assess in this study the accuracy of the immunohistochemistry in the diagnosis and classification of ovarian carcinomas.

Material and methods

A retrospective study of 74 cases of ovarian carcinomas diagnosed in the department of pathology and listed in the register of cancer of Farhat Hached university hospital of Sousse (Tunisia), during a 5 year period. Initial diagnoses were morphologically reviewed by two observers. Then, the histological type of ovarian carcinoma was determined after immunohistochemical study using panel of antibodies, specific to each type. An assessment of reproducibility was made for each step.

Results

A reassessment of the histological diagnosis gave a degree of agreement of 86% and Kappa index of 0.80.The study of the immunohistochemical expression of a panel of 7 antibodies including p53, WT1, p16INK4a, CK7, CK20, estrogen and progesterone receptors has led to a significant increase of the reproducibility with a degree of agreement of 91% and a Kappa index of 0.86.

Conclusions

The results of our study indicate that ovarian carcinoma type can be reliably diagnosed by pathologists, and also demonstrate that immunohistochemistry has an important role in improving diagnostic accuracy and agreement between pathologists.

P 19

PROGNOSTIC IMPACT OF GLIOBLASTOMA STEM CELL MARKERS OLIG2 AND CCND2

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Background and objective

Glioblastoma (GBM) is the most common and lethal malignant brain tumour in adults. Glioma stem cells (GSCs) are implicated in this poor prognosis and in radio(chemo-) resistance. We have previously demonstrated that among potentially highly specific GSCs markers oligodendrocyte lineage transcription factor 2 (*OLIG2*) appears to be the most specific and cyclin D2 (*CCND2*) the only one related to cell cycle regulation. The purpose of this work is to investigate the clinical significance and the evolution of *OLIG2* and *CCND2* protein expression in GBM.

Materials and methods

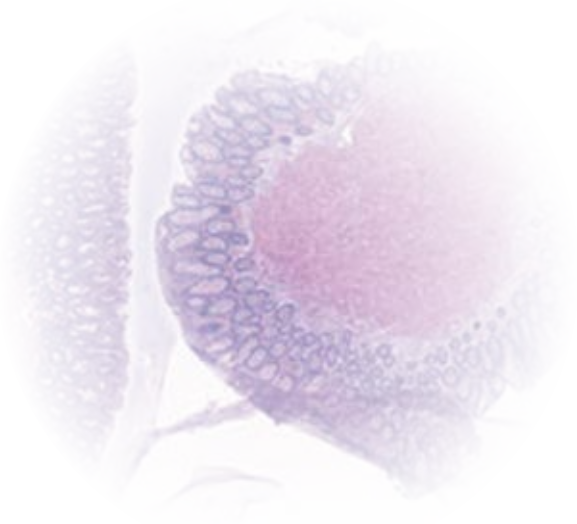
Immunohistochemical expression analysis of Olig2 and Ccnd2 was carried out on a cohort of 72 human paired GBM samples comparing initial resections with local recurrent tumours after radiation therapy (RT) alone (n=37) or radio-chemotherapy with temozolomide (RT-TMZ) (n=35). Semi-quantitative analysis of nuclear staining was performed by two independent observers. Every tumor was scored according to the number of stained cells (low nuclear expression <30% and high nuclear expression ≥30%).

Result

Multivariate logistic regression analysis revealed that significant risk factors predicting early mortality (<12 months) are: subtotal surgery for recurrence [OR 16.54(CI 95% 2.21 to 124.23)], time to recurrence <6 months [OR 16.85(CI 95% 2.78 to 102.24)], Ccnd2 nuclear expression at initial surgery ≥30% [OR 14.33(CI 95% 1.80 to 114.27)], and Olig2 nuclear expression <30% at second surgery after RT alone and RT-TMZ [OR 7.14(CI 95% 1.31 to 38.94)].

Conclusions

We demonstrated that patients for whom nuclear expression of Olig2 becomes low (<30%) after adjuvant treatments have a significantly shorter time to recurrence and survival reflecting most probably a proneural to mesenchymal transition of the GSCs population. We also highlighted the fact that at initial surgery, high nuclear expression (≥30%) of Cyclin D2, a G1/S regulator specific of GSCs, has a prognostic value and is associated with early mortality (<12 months).



P 20

HIGHLIGHT OF MISMATCH REPAIR (MMR) EXPRESSION ON BIOPSY OR SURGICAL SPECIMEN IN CRC : SIMILARITY OR DIFFERENCE IN RESULTS ?

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Introduction

Belgian guidelines recommend to analyse the expression of mismatch repair protein (MMR) by immunohistochemistry (IHC) and /or the microsatellite instability (MSI) status by PCR in all new diagnosed colorectal cancer (CRC) because the clinical prognosis and treatment response are closely related to the molecular mechanism (1). Still, several open questions remain 1. Is there a match between MMR expression results and MSI ? 2. Is there a difference between MMR expression results obtained from biopsies and those obtained from surgical specimens?

Methods

We retrospectively analysed 142 patients suffured from CRC for which biopsy and surgical specimen were available from january 2017 to december 2018. IHC analysis of the MMR proteins (MLH1, MSH2, MSH6, PMS2) was conducted on both diagnostic biopsy and surgical sample. Specimens were also subjected to a PCR panel of 5 microsatellites markers (BAT25, BAT26, NR21, NR22, NR24).

Results

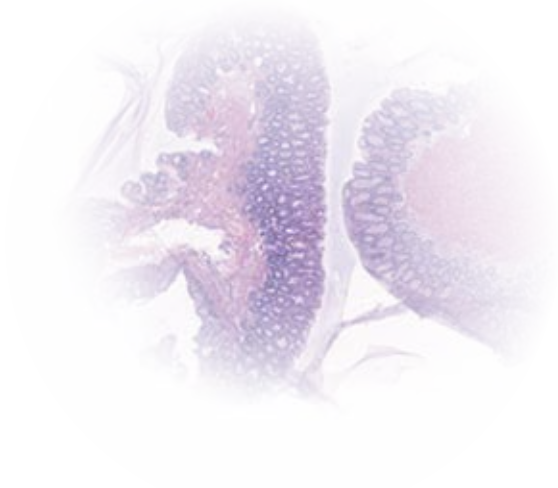
In our series, IHC and PCR show MMR-déficient (MMR-d) and MSI for 26/142 (18%) patients with a majority of loss of function of MLH1 and PMS2 proteins (24/26 cases).

MMR-d/MSI is statistically associated with female gender, right colon location, colloid type and poorly differentiated adenocarcinomas, as described in the literature.

The results of MMR expression and MSI are consistent in 141 cases if samples from surgical specimen are used. In 1 case (0,7%), PCR detected instability while IHC revealed MMR-proficient.
Discrepancies results were observed in 7 cases (4,9%) if we compare the IHC results obtained on biopsies with those obtained on surgical specimens. We observed technical problems for two cases, a lack of tissue material for two cases and interpretation problems for three cases.

Conclusions

MMR expression appeared to be more difficult to analyse on biopsy samples than on surgical specimens which are consistent with PCR results. PCR is more sensitive. These preliminary results must be confirmed by a larger series of cases.



(1) A. Hebrant et al. Molecular test algorithms for digestive tumours, BJMO 2019;13(1):4-10

P 21

CLINICOPATHOLOGIC IDENTIFICATION & RISK GRADATION OF NAEVUS SUB-TYPES BASED ON INTERDISCIPLINARY DATA

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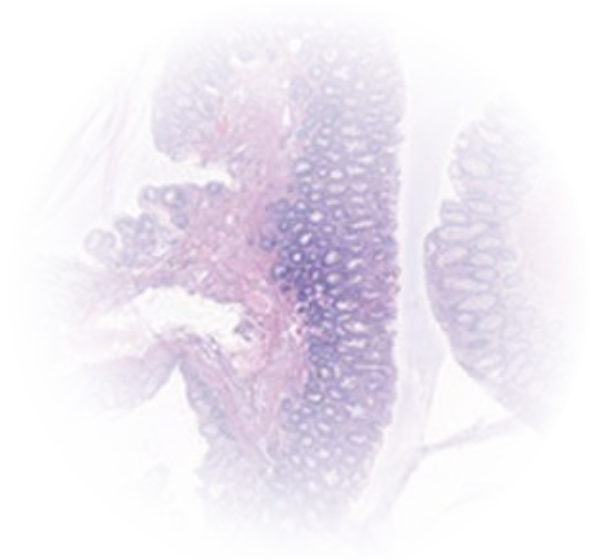
In daily practice, most pathology labs process skin biopsies using the standard random sectioning technique - which examines less than 2% of the tissue - and without access to clinical or dermoscopical images. The limitations of this approach can be addressed by using the newly described and scientifically validated method to process skin biopsies: ex vivo dermoscopy with derm dotting, which allows the identification and marking of focal, superficial zones for targeted sectioning and evaluation under the microscope. As such, it mitigates a more precise delineation of naevus subtypes and gives rise to a new proposal for the dermoscopical-pathological classification of pigmented moles, especially within the subgroup of flat, so-called dysplastic naevi.

A retrospective analysis on 1989 excised naevi showed that the dermoscopical-pathological differences between these putative subtypes are also reflected in clinical/epidemiological differences. For instance, some of these subtypes appear to be associated with elevated dysplasia levels and increased melanoma risk for the patient.

We hypothesize that some of these subtypes can be considered melanocytomas, i.e. naevi with more than one genomic abnormality, potentially operating as a precursor of melanoma. Moreover, we consider the possibility that these subtypes are linked to a specific pigmentation phenotype. In this regard, we will compare the underlying geno- and phenotype of these naevus subtypes to discover polymorphisms or mutations linked to melanomatous degeneration. Additionally, we will examine whether these subtypes are distinguishable not only for dermatologists and pathologists, but also through artificial intelligence, to facilitate the identification of these lesions in clinical settings.



P 22

THE ASSESSMENT OF STROMAL TUMOR INFILTRATING LYMPHOCYTES (STILS) IN INVASIVE MICROPAPILLARY CARCINOMA OF THE BREAST AND CORRELATION WITH PROGNOSIS AND CLINICO-PATHOLOGICAL FEATURES

F. Deman[1,2], K. Punie[3,4], A. Laenen[5], T. Faes[1,2], H. Wildiers[3,4], P. Neven[3,6], A. Smeets[3,7], I. Nevelsteen[3,7], C. Van Ongeval[1,8], A. Baten[3,9], M. Christiaens3, 9, E. Oldenburger[3,9], H. Janssen[3,9], C. Weltens[3,9], C. Desmedt[10], G. Floris[1,2]

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Background and objective

Invasive micropapillary carcinoma (IMPC) of the breast is a special variant of breast carcinoma with a unique morphology. The role of sTILs is not fully understood in IMPC. We aimed to assess sTILs and clinico-pathological features in pure and non-pure IMPC.

Materials and methods

Consecutive patients with stage I-III IMPC who underwent upfront surgery at our institution between 2000 and 2016 were included. Standard clinico-pathological features and follow-up data were obtained from clinical records. Pathologic review of representative H&E-slides of the resection specimens included evaluation of sTILs, tertiary lymphoid structures (TLS) and assessment of the micropapillary component. Surrogate molecular subtypes were based on receptor-status and histological grade. Using tissue microarrays we assessed by immunohistochemistry the pattern of staining of P53, and scored semi-qualitatively the expression of Bcl2, PAX8 and WT1.

Results

We included 111 patients (median age 61,5 years; range 33-88). Of all cases 59% were pure IMPC. sTILs where classified as low (<30%), intermediate (30-50%) and high (>50%) in 78%, 14% and 8% of specimens respectively. Luminal surrogate subtype was most prevalent with 51 luminal A-like, 41 luminal B-like, 12 luminal HER2+, 5 HER2+ and 2 triple negative. Standard clinico-pathological features were comparable between pure and non-pure IMPC. Comparison between surrogate subtypes showed higher sTILs ($p=0.025$) and a higher likelihood of TLS ($p=0.026$) and aberrant P53 expression ($p<0.001$) in HER2+ compared to luminal A-like subtype. Bcl-2 expression was strongly related to all luminal subtypes ($p<0.03$). After a median follow-up of 100 months, we observed 8 distant relapses (7,2%) and 3 breast cancer-related deaths (2,7%). All events occurred in non-pure IMPC. Higher sTILs was correlated with worse distant relapse-free interval (HR=1.55; $p=0.0172$) and breast cancer-specific survival (HR=2.10; $p<0.001$).

Conclusions

Standard clinico-pathological features do not differ in pure and non-pure IMPC. Higher sTILs was associated with worse outcome in this IMPC cohort, confirming previously published observations.

P 23

PROGNOSTIC VALUE ASSOCIATED WITH THE PRESENCE OF HYBRID EMT STATES IN UROTHELIAL CARCINOMA

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Background and objective

In cancer Epithelial-to-Mesenchymal Transition (EMT) is associated with tumorigenesis, stemness, invasion, metastasis, and resistance to therapy. Recent data suggest that EMT should be a stepwise process with distinct intermediate hybrid states characterized by co-expression of epithelial and mesenchymal markers. These data come mainly from in vitro cell cultures and some animal models. In contrast, the present study aims to evaluate the prognostic value of hybrid EMT states for patients with urothelial carcinomas.

Materials and method

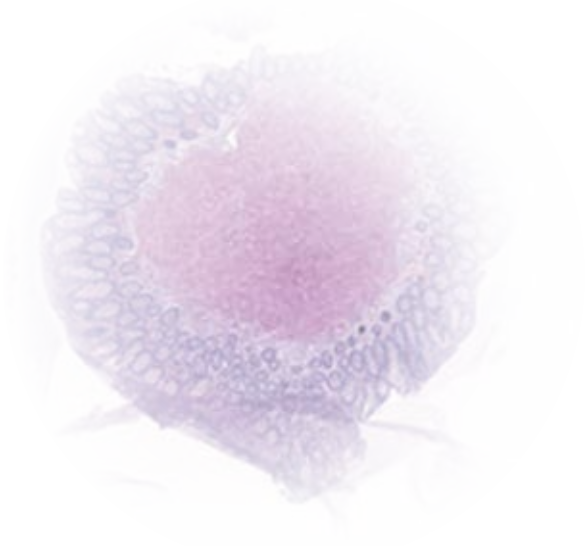
The hybrid EMT cell status was assessed on 113 carcinomas using an original methodology to highlight pan-cytokeratin (CK) and vimentin (VIM) co-expression. It involves sequential immunostaining on the same tissue slide, whole slide imaging and image registration. A semi-quantitatif hybrid EMT score was assessed from 0 (absence of hybrid EMT state) to 3 (1 = isolated CK+++/VIM+ tumor cells, 2 = numerous CK+++/VIM+ tumor cells, 3 = numerous CK+/VIM+++ tumor cells). The prognostic value of this score was evaluated using univariate and multivariate statistical analyses.

Results

In our series 68 tumors scored 0, 37 tumors 1, 7 tumors 2 and 1 tumor 3. After binarization of the hybrid EMT score (0 versus 1-3), univariate survival analyses showed that the hybrid EMT state presence has a bad prognostic value regarding both disease-free (p=0.0001) and overall survival (p=0.006). Multivariate analyses confirmed the independent prognostic value of the binary score for recurrence and overall survival (considering prognostic clinical features). We also refined our analysis by quantifying a hybrid EMT score using image analysis and confirmed that a binary score (absence/presence) is more contributive than a quantitative one.

Conclusions

The present study is one of the first on the hybrid EMT status assessed in a series of human cancers. It evidences a negative prognostic impact of this status in urothelial carcinoma.



P 24

IMPACT OF NEXT GENERATION SEQUENCING ANALYSIS FOR PATIENTS WITH AN INDETERMINATE CYTOLOGICAL DIAGNOSIS

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Background and objective

Thyroid nodules are very common in the general population. The biggest challenge is to identify the cancerous ones through fine needle aspiration and cytological analysis. 20-30% of the patients have an indeterminate cytological diagnosis, which can not affirm the benignity or the malignity. To improve the management of these patients, molecular profiling has been proposed through next generation sequencing (NGS). The aim of this work is to investigate the impact of this analysis for thyroid nodules with an indeterminate cytological diagnosis.

Materials and methods

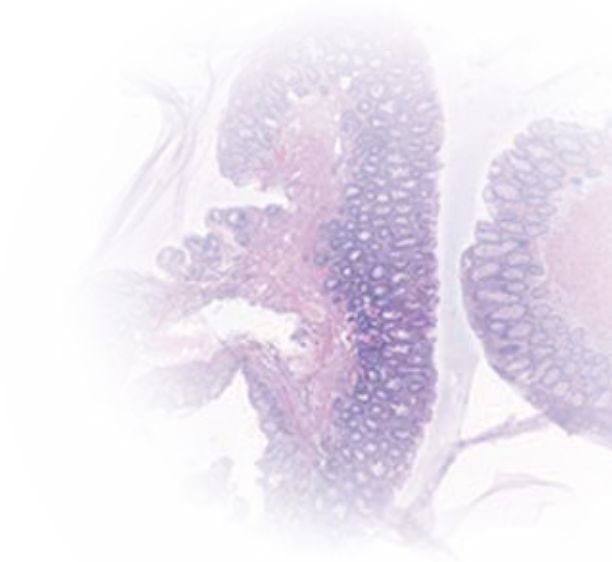
We conducted a retrospective study of patients with an indeterminate cytological diagnosis of a thyroid nodule for which an NGS analysis was performed using a panel specific for the thyroid pathology targeting mutations in 26 genes and 93 gene fusions. All the patients had a surgical resection afterwards. The histological diagnosis was considered as the Gold-standard. Clinical, pathological and molecular data were collected to study the association with the histological diagnosis.

Results

The risk of malignancy (ROM) for an indeterminate cytological diagnosis (follicular proliferation grade 1 and 2, N=59) was 11 and 29% respectively. None clinical data showed a statistical significant association with an increased ROM. 22/59 patients had a positive molecular test, which means they presented at least 1 mutation or gene fusion. The ROM for the patients with a positive molecular test was 50% and, at the opposite, the ROM was 13,5% in the case of negative molecular test (p=0,003).

Conclusion

This study showed that the analysis of a gene panel could add elements that help to discriminate between benign and malignant thyroid nodules. However, considering the small size of the cohort further studies are needed to appreciate the contribution of the clinical data.



P 25

PROLIFERATION INDEX AND EXPRESSION OF PD-L1 : PDXS OF HEAD AND NECK, SKIN, ESOPHAGUS AND LUNG

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Background

Patient-derived xenografts (PDX) models generated from surgically implanted tumour fragments from patients into immunodeficient mice and passed from generation to generation, represent an in oncologic research.
The majority of studies showes correlations between histopathological characteristics and expression of biomarkers of the original patient samples and PDX. Nevertheless, some studies showes mismatches between the primary tumor and the associated PDXs.
The objective of this work is to characterize a PDX model and evaluate the preservation of the initial characteristics of the tumor. To do this, we evaluated the time required for tumor growth in mice, tumor proliferation and expression of the PD-L1 biomarker in the passages and compared these data with those of the primary tumor.

Method

We consented 33 new patients with primary tumours of the esophagus, lung, skin or ENT sphere and calculated the tumor growth rate time. Immunohistochemistry was performed in tumoral tissue sample of tumors PDXs and their subsequent passages: with a quantitative method for Ki67 and Ku80, and semi-quantitative for PD-L1. We established a proliferation index defined as the ratio between Ki67 and Ku80 labelling index.

Results

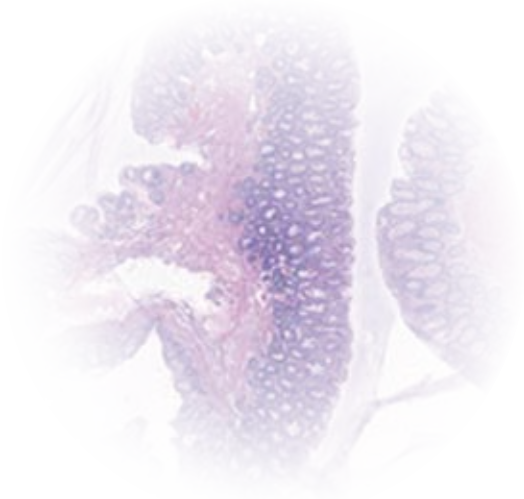
We observe a decrease in tumor growth time associated with an increase of the proliferation index over the passages, these changes being statistically significant from the third and fourth passages respectively.

PD-L1 expression between primary tumor and PDX has 3 profiles: expression preserved for 15 cases, decreased for 13 cases and increased for 5 cases.

We observe a statistically significant overall decrease in PD-L1 expression over time.

Conclusions

The stability of proliferation index across the first 2 PDX passages will hopefully allow greater investiation of predictive biomarkers in order to identify ones other than PD-L1 for further pre-clinical and clinical investigation.



P 26

CLINICAL, MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL CHARACTERIZATION OF 58 PHEOCHROMOCYTOMAS AND PARAGANGLIOMAS

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Background

Pheochromocytomas (PHCs) and paragangliomas (PPGLs) are rare neuroendocrine tumors with significant gene inheritance and transmission. The terms of "malignant" and "benign" from the 2004 WHO classification of endocrine tumors have been abandoned in the current WHO classification. Indeed, there is no validated histological system to predict biological aggressiveness of those tumors that all have metastatic potential explaining the lifelong monitoring recommendation.

Aim

The aim of this study was to investigate, retrospectively, statistical associations between presence of some clinical, morphological criteria, biomarkers and the advent of metastasis.

Methods

We collected clinical data in a large cohort of 58 patients who underwent a surgery for a pheochromocytoma or a paraganglioma in CUB Hôpital Erasme between 1999 and 2019. Immunohistochemistry was performed in tumoral tissue samples to characterize succinate dehydrogenase B (SDHB), S100 protein and Ki67 expression, as well as computerized quantification of proliferation index and cellularity index.

Results

Our series consists of 34 PHCs and 24 PPGLs among which five were metastatic. Median age was 47 years and median follow-up 34 months. Tumors were secreting in 50% of cases and secretion was positively correlated to tumoral size ($p < 0.01$). In comparison to non-metastatic tumors, metastatic ones were largest (80% vs 44% of pT2 following AJCC), had more often positive margins (80% vs 24%) and were more often of high cellularity [100% vs 74% of > 250 cells/field (high power field)]. We also observed an increased proliferation index in case of diffuse architecture or large nests ($p = 0.040$).

Conclusion

Given the rarity of this disease, it is important to better characterize these tumors and identify biological markers predictive of metastatic behaviour and worse prognosis. In reference centers, histology should be improved by the use of biological markers to determine patient at higher risk of adverse disease course.

P 27

OLFACTOMEDIN 4 (OLFM4) EXPRESSION IS ASSOCIATED WITH NODAL METASTASES IN ESOPHAGEAL ADENOCARCINOMA

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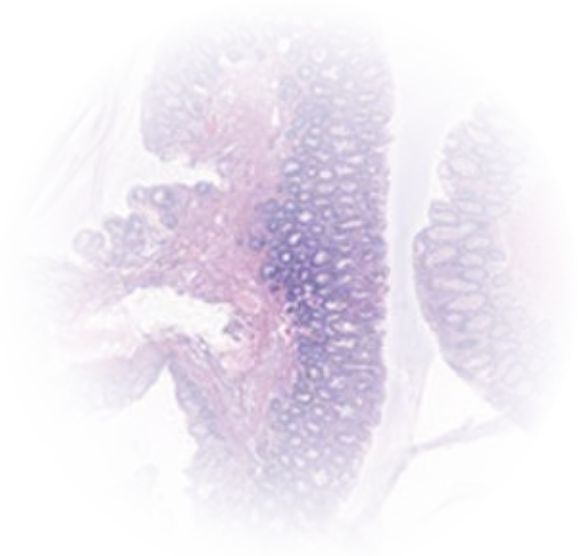
To date no informative biomarkers exist to accurately predict presence of lymph node metastases (LNM) in esophageal adenocarcinoma (EAC). We studied the discriminative value of Olfactomedin 4 (OLFM4), an intestinal stem cell marker, in EAC. Patients who had undergone esophagectomy as single treatment modality for both advanced (pT2-4) and early (pT1b) adenocarcinoma of the esophagus or gastro-esophageal junction were selected for this study from an institutional database (Erasmus MC University Medical Center, Rotterdam, The Netherlands). Surgical resection specimens of 196 advanced and 44 early EAC were examined. OLFM4 expression was studied by immunohistochemistry and categorized as low (<30%) or high (>= 30%) expression. Low OLFM4 was associated with poor differentiation grade in both advanced (60% vs. 34.8%, p= 0.001) and early EAC (39.1% vs. 9.5%, p= 0.023). LNM were present in 161 (82.1%) of advanced and 9 (20.5%) of early EAC respectively. Low OLFM4 was independently associated with the presence of LNM in advanced EAC in multivariable analysis (OR 2.7; 95% CI, 1.16-6.41; p= 0.022), but not in early EAC (OR 2.1; 95% CI, 0.46-9.84; p= 0.338). However, the difference in association with LNM between advanced (OR 2.7; 95% CI, 1.18-6.34; p= 0.019) and early (OR 2.3; 95% CI, 0.47-11.13; p= 0.302) EAC was non-significant (p= 0.844), suggesting that the lack of significance in early EAC is due to the small number of patients in this group. OLFM4 was not of significance for the disease free and overall survival. Overall, low expression of intestinal stem cell marker OLFM4 was associated with the presence of LNM. Our study suggests that OLFM4 could be an informative marker with the potential to improve preoperative assessment in patients with EAC. Further studies are needed to confirm the value of OLFM4 as a biomarker for LNM.



P 28

MICRORNA PROFILES DO NOT PREDICT BARRETT'S ESOPHAGUS PROGRESSION TO ESOPHAGEAL ADENOCARCINOMA

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Identification of patients with Barrett's esophagus (BE) at risk for progression to esophageal adenocarcinoma (EAC) remains challenging with current histology-based surveillance programs. Better risk stratification is essential to rightly identify those at risk but also to avoid overdiagnosis and subsequent overtreatment. So-called microRNAs (miRs) could potentially serve as prognostic biomarkers for improved risk stratification of BE patients. This study aims to identify miRs that could help to detect patients at risk for EAC prior to the development of dysplasia.

Non-dysplastic Barrett's esophagus (NDBE) samples of patients from a Dutch multicenter prospective cohort study (PROBAR) were investigated (n=34), including 16 patients that developed high grade dysplasia (HGD) or EAC (progressors) and 18 patients that not progressed after a long-term follow-up (non-progressors). Patients were divided in a discovery and validation set, with median time to progression 27 (n=9) and 60 months (n=7) respectively, whereas median follow-up of non-progressors (both sets n=9) was 112 and 157 months respectively. Both high throughput miR-profiling (including 381 different miRs) and individual targeted assays were used.

The discovery set revealed eleven miRs with a significantly higher level in NDBE tissues from progressors compared to non-progressors (adjusted p-value <0.05) while no significant differences were found between paired NDBE and HGD/EAC samples. Thirteen miRs showed higher levels in HGD/EAC versus NDBE samples from non-progressors (unpaired). Of these, three were similarly upregulated in paired NDBE and HGD/EAC tissue compared to NDBE samples from non-progressors (i.e. miR-18a, miR-93, and miR-331-5p). The validation set (n=16) however, could not confirm these results, despite using two normalization methods. In addition, our data could not confirm previously described prognostic miRs (miR-192, miR-194 and miR-196b) to be associated with progression.
This study could not identify significant progression related miRs in NDBE samples and illustrates that independent validation is crucial for (molecular) biomarker validation studies.

P 29

THE USE OF IMMUNOHISTOCHEMISTRY IN THE ASSESSMENT OF BRAF V600E AND P53 MUTATIONS IN MELANOMAS

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Background and objective

Metastatic melanoma is a fatal disease with a poor prognosis. Many efforts were made to better understand the molecular pathways, in order to develop new treatment possibilities. Considering the importance of identifying the molecular profile for therapeutic purposes, our main objective is to evaluate if immunohistochemistry (IHC) can be a surrogate marker for BRAF and TP53 gene mutations.

Materials and methods

Formalin-fixed paraffin-embedded samples (FFPE) of 55 melanomas for whom molecular testing was required and performed between 2014 and 2019 were immunostained with BRAF V600E and p53 antibodies. Two pathologists blind evaluated the IHC slides in order to evaluate inter-observer concordance. Discordant cases were evaluated by a third observer. The association between IHC results and molecular testing was evaluated.

Results

Considering the results obtained by next generation sequencing (NGS) technique for BRAF and TP53 mutations to be the reference, IHC had an overall diagnostic accuracy of 78.95% for the TP53 mutation. The sensitivity for IHC was 88.9% and the specificity 74.36% for TP53. We have obtained a statistically significant association between the two diagnostic methods (p=0.013). Regarding BRAF-V600E, IHC had an overall diagnostic accuracy of 95.92%. The sensitivity for IHC was 80% and the specificity was 100%. The unweighted kappa coefficient representing the inter-observer concordance is 0.851 and 0.667 for p53.

Conclusion

Based on the obtained results, IHC staining is a reliable method for identifying the BRAF-V600E mutation, becoming an efficient screening technique before DNA-based analysis.

The "abberant" p53 IHC profile is sometimes associated with rare TP53 gene mutations. Even if we obtained statistically significant results, we recommend with caution the use of IHC to detect TP53 gene mutations. Further investigations are necessary.

P 30

THE USE OF DEEP LEARNING TO RECOGNIZE INFLAMMATORY BREAST CANCER CELLS IN H-DAB STAINED IMAGES

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Introduction

Deep-learning is a machine learning method based on artificial neural networks. Using a PanCK staining as golden standard, we wanted to examine if artificial intelligence (AI) using deep-learning is able to recognize Inflammatory breast cancer (IBC) cells on a slide that is immunostained for CD8 (H-DAB, Hematoxylin-DAB).

Methodology

For this research we used a training set of 18 images and a test set of 12 images. First, we aligned two consecutive slides: one PanCK stained slide and one slide stained for CD8 (H-DAB). Using virtual multiplexing, we determined the tumor regions on the H-DAB stained slide. Subsequently we used 15 images to train the algorithm (in Deeplabv3+) with more than 150 000 iterations. After a first visual control the algorithm was improved by training the algorithm with 3 additional images. Finally, this algorithm was evaluated in the test set.

Results

We trained an algorithm using deep-learning that detects tumor cells on H-DAB immunostained (CD8) slides. For accuracy metrics we used the Dice coefficient. If the tumor regions picked up by AI are the same as the original labels this coefficient is 1. The mean coefficient in the test set was 0.83, indicating a good overlap between the tumor area on the PanCK stained slides and the tumor area determined by the AI on the H-DAB slides.

The relative marker area of CD8 in the tumor area and stroma was also determined. There was a strong linear correlation between the manually annotated tumor regions compared to the regions annotated by the AI: in the tumor area the R2 was 0.85 and in the stroma 0.9.

Conclusion

Using 18 training images we were able to create a deep learning algorithm that adequately detects IBC tumor cells on H-DAB images.

P 31

INFILTRATING IMMUNE CELLS IN THE TUMOR EMBOLI OF INFLAMMATORY BREAST CANCER

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Introduction

Inflammatory breast cancer (IBC) is a rare, aggressive type of breast cancer characterized by cohesive tumor emboli within lymphatic vessels, thought to be responsible for the clinical presentation, the typical diffuse growth pattern and the fast local spread. In this study we wanted to investigate infiltrating immune cells in the tumor emboli in IBC.

Methodology

Four FFPE tissue sections of the pretreatment biopsies of 24 IBC patients were immunostained and evaluated using VISIOPHARM® software making virtual multiplexing possible after alignment of the different slides. We used four validated antibodies: CD79a (B-cell lineage), CD8 (cytotoxic T-cells), FOXP3 (Tregs) and CD163 (TAMs).

Results

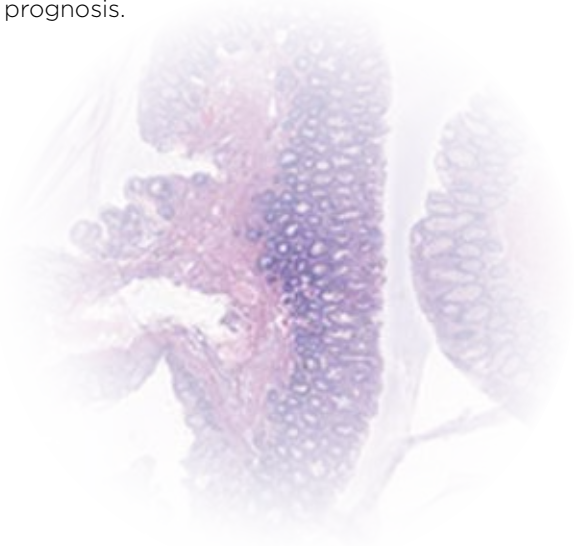
For every staining we report the number of patients that have infiltrated emboli, the median density in the invasive carcinoma (IC), the median density in the emboli (E) and the ratio between the invasive tumor and emboli in the table.

	# patients	Density (IC) #/um2	Density (E) #/um2	Ratio Density E/IC	P-value
CD8	12/24 (50 %)	19.6	2.4	0.11	< .001
CD163	19/23 (83 %)	35.4	12.8	0.43	.02
CD79a	11/24 (46 %)	18.2	3.5	0.31	.01
FOXP3	4/23 (17 %)	5.1	0.3	0.04	.003

Patients with more immune cells in the invasive carcinoma (IC) also had more immune cells in the emboli (E). This correlation was significant for all stainings (P-Value in table). CD163+ macrophages are the most abundant immune cells in emboli, especially when compared to the invasive carcinoma. CD8+ cells were uncommon in emboli. Interestingly, patients with a higher CD8 IC/E density ratio achieved more often a complete pathological response (P = 0.03). Only 20.8% (n= 5/24) had invasive carcinoma directly surrounding the intravascular emboli; median overall survival in these patents was significantly shorter (P= 0.003)

Conclusion

This is the first study looking at infiltrating immune cells in IBC tumor emboli. We demonstrated that TAMs are the predominant immune cell type in IBC tumor emboli and cytotoxic T cells are less common. Patients with invasive carcinoma nearby the emboli had a worse prognosis.



P 32

HIGH-THROUGHPUT ANALYSIS OF AN AETIOLOGY DRIVEN DUCTULAR REACTION AND ITS NICHE IN THE HUMAN LIVER DISEASE SPECTRUM

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Background

Ductular reaction (DR) is observed in virtually all liver injuries. This reaction with a ductular phenotype harbours the liver progenitor cells (LPCs) when normal liver regeneration by hepatocytes or biliary cells is impaired. In this study, we aim to unravel the aetiology driven microenvironment in acute and chronic liver diseases.

Methods

We extracted the ductular reaction and its niche from snap frozen tissue of human explant livers (n=34) by laser capture microdissection. We studied the spectrum of liver diseases: non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), autoimmune hepatitis (AIH), hepatitis C virus (HCV), primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), acetaminophen intoxication (TOX) and normal livers. Whole transcriptome sequencing and pathway analysis were performed.

Results

Transcriptomic analysis shows that the DR and the interacting niche are clustered by disease. We compared the expression profiles of the control group (a non-proliferating LPC state) with the separate disease groups to illustrate the differential expressed genes involved in the disease-specific LPC activation. We found 835, 463, 1048, 1567, 989, 1103 and 870 differentially expressed genes between the non-proliferative niche and the ductular reaction of AIH, ASH, HCV, NASH, PBC, PSC and TOX, respectively. Pathway analysis revealed a significant common upregulation of the IL-17 pathway in all included diseases with exception of the PBC group. Furthermore, disease-specific differences in the extracellular matrix are observed. For example, COL1A1 and COL4A2 are upregulated in NASH compared to ASH, while COL1A2 and COL3A1 are increased in the TOX group compared to all chronic injuries. In addition, disease-specific differences of the immune regulatory microenvironment (e.g. increased B cell signalling in NASH compared to ASH) are detected.

Conclusion

Our data suggest that the ductular reaction and their interactive niche are disease-specific. Pathway analysis suggests that the IL-17 pathway is a common denominator in LPC activation and/or maintenance.

P 33

HISTOPATHOLOGIC ASSESSMENT OF UNUSED DONOR LUNGS: WHEN TO DECLINE OR NOT?

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Background and objective

Donor organ shortage, in combination with a 70% decline rate of offered donor lungs, results in significant waiting list mortality. Assessing donor lungs for transplant suitability is currently based on donor's history, gas exchange, chest X-ray, bronchoscopy findings, and ultimately in situ visual inspection and palpation; but donor lung acceptance remains subjective. We performed an in depth histopathologic assessment of retrieved but unused donor lungs.

Materials and methods

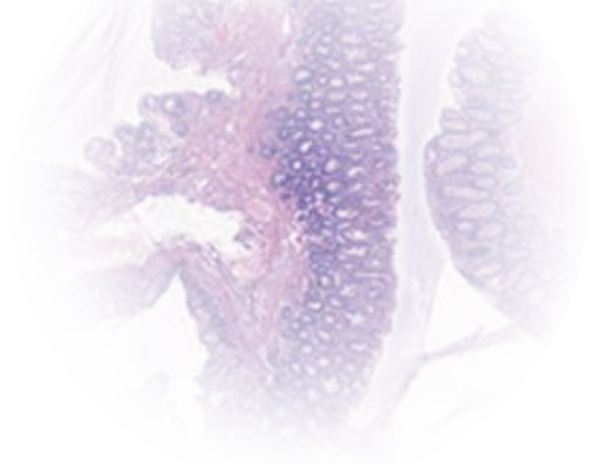
We assessed 62 donor lungs declined for transplantation (2010-2019). These lungs were air-inflated, frozen, scanned with computed tomography, systematically sampled on 4 different locations, and assessed macroscopically and microscopically by two experienced lung pathologists (BW, EV), blinded for the reason of decline.

Results

Twenty-two lungs (35%) were declined for non-allograft related reasons (single/lobar lung transplant, n=8; logistics, n=6; non-pulmonary malignancy, n=4; other, n=4). Three of these (14%) lungs displayed severe histologic abnormalities (emphysema, n=1; pneumonia, n=2), in addition to mild emphysema in 8 patients. Forty lungs (65%) were clinically declined for allograft-related reasons (pneumonia, n=14; emphysema, n=9; emboli, n=7; contusion, n=4; other, n=6). In 15/40 (38%) allograft-related declined lungs, the clinical abnormality for decline could not be confirmed by histologic assessment (no histologic abnormalities, n=13; moderate emphysema, n=1; minor focus of bronchopneumonia, n=1). In 25/40 (63%) allograft-related declined lungs, histologic assessment confirmed the clinical abnormality for decline (pneumonia, n=10; emphysema, n=8; contusion, n=2; pulmonary vascular disease, n=1; sarcoidosis, n=1; fibrosis, n=1; amyloidosis, n=1, asthma, n=1). However, in 9/25 (36%) lungs, histologic abnormalities were only considered focal and mild (mild emphysema, n=5; minor focus of bronchopneumonia, n=4).

Conclusions

Histopathologic assessment of unused donor lungs revealed discrepancy between the macroscopic reason for decline and histologic findings. Improved strategies with prior chest CT imaging combined with on-site assessment of potential donor lungs by an experienced transplant surgeon might augment current yield.



P 34

INTRA-ALVEOLAR FIBRIN AND ORGANIZING PNEUMONIA IN LUNG ALLOGRAFT BIOPSIES

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Background and objective

Acute fibrinous organizing pneumonia was first described as a distinct histologic pattern associated with acute lung injury and is characterized by prominent intra-alveolar fibrin deposition and organizing pneumonia (OP). After lung transplantation, acute fibrinous organizing pneumonia can be histologically diagnosed on a transbronchial biopsy. However, its association with chronic lung allograft dysfunction (CLAD) remains unclear.

Materials and methods

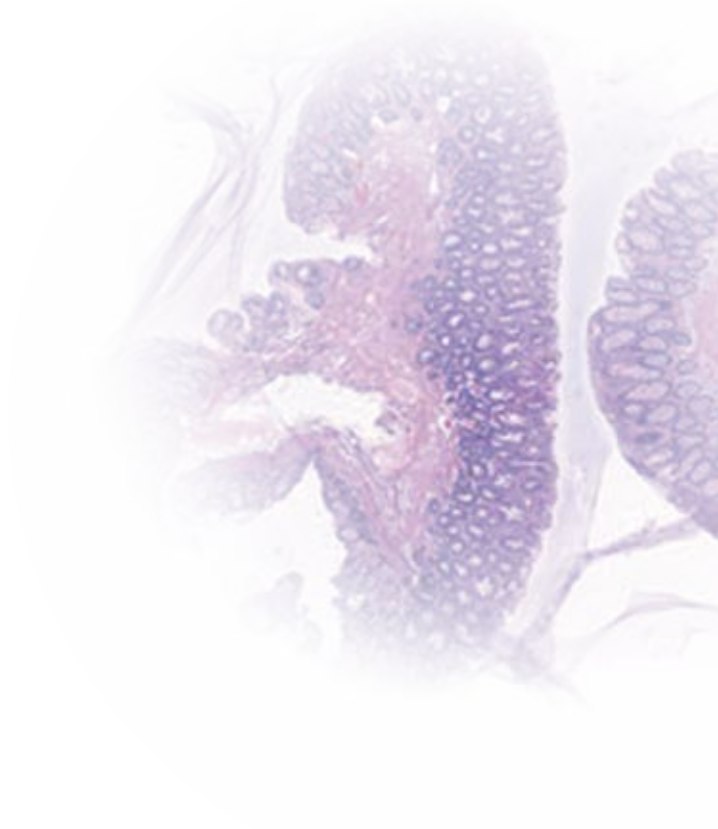
We reviewed lung allograft biopsies from 468 patients who underwent lung transplantation at the University Hospitals Leuven between 2011 and 2017. The presence of fibrin/OP was assessed and defined as early (≤ 90 days post-transplant) or late new-onset (> 90 days post-transplant) fibrin/OP; and associated with CLAD-free survival, graft survival, presence of donor-specific antibodies, airway and blood eosinophilia.

Results

Early and late fibrin/OP was detected in 24 (5%) and 30 (6%) patients, respectively. CLAD-free survival was lower in patients with late fibrin/OP (median survival 2.42y, $p<0.0001$), with specifically an increased incidence of restrictive allograft syndrome (OR:19.02; CI[5.81 – 56.52], $p<0.0001$), compared to patients with early or no fibrin/OP. Similarly, graft survival was lower in patients with late fibrin/OP (median survival 4.39y, $p<0.0001$) compared to patients with early fibrin/OP or without fibrin/OP. Detection of late fibrin/OP was furthermore related to the presence of circulating donor-specific antibodies (OR:4.75, CI[2.17-10.60], $p=0.0004$) and elevated airway and blood eosinophilia ($p=0.043$ and $p=0.045$, respectively).

Conclusion

The pathologist should actively search for intra-alveolar fibrin and OP in transbronchial biopsies, as presence of late new-onset fibrin/OP is associated with a worse prognosis and high risk of CLAD development, specifically restrictive allograft syndrome. Our findings indicate that late new-onset fibrin/OP might play a role in the early pathogenesis of restrictive allograft syndrome. In addition, we demonstrate that the lung displays a different response to identical histologic patterns (i.e. early and late fibrin/OP), based on the time-of-onset of the injury.



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THE DAILY PRACTICE REALITY OF PD-L1 EVALUATION IN NON-SMALL CELL LUNG CANCER: A RETROSPECTIVE STUDY

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Background and objective

The use of pembrolizumab, an anti-Programmed Death-1 monoclonal antibody for the treatment of non-small cell lung cancers (NSCLCs), is conditioned by immunohistochemical (IHC) evaluation of the expression of Programmed Death Ligand 1 (PD-L1), a heterogeneous and complex marker. As well-designed phase III studies with optimistic data have been published, we decided to investigate how pathological and technical factors affect the daily practice of PD-L1 evaluation for NSCLCs.

Materials and methods

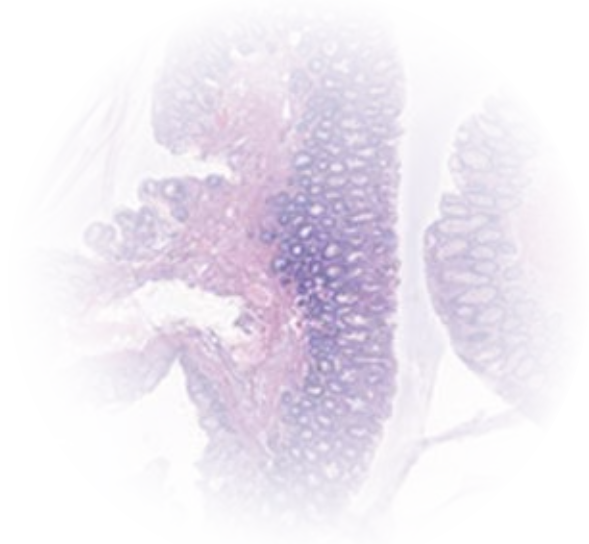
A retrospective study of PD-L1 expression was conducted in 454 NSCLC patients, for whom anti-PD-L1 IHC analysis was prospectively requested, from November 2016 to January 2018. The associations between PD-L1 expression and clinicopathological variables were statistically investigated. The heterogeneity of PD-L1 expression according to the type of sample (cytology, biopsy or surgical specimen) and its location, defined as primary tumour, lymph node or distant metastasis, were assessed, as well as intra- and inter-observer discrepancies.

Results

A statistically significant association was observed between PD-L1 expression and sample location (p=0.005), histological type (p=0.026), total number of mutations (p=0.004), and KRAS mutations (p=0.024). The type of specimen did not influence PD-L1 expression evaluation. The intra- and inter-observer discrepancies were 17% and 15%, respectively.

Conclusion

Based on a routine series, the present study confirms that PD-L1 expression evaluation by IHC can be performed on all types of samples. Moreover, it highlights the heterogeneity of PD-L1 expression in relation to the different tumour locations. For challenging cases, a second PD-L1 IHC evaluation would be envisaged due to intra- and inter-observer discrepancies.



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