Quoi de neuf??

….. En tumeurs des tissus mous
..... En tumeurs osseuses

C. GALANT
Avec la participation de J.M. Coindre et G. de Pinieux

Cliniques universitaires
SAINT-LUC
UCL BRUXELLES

Plan de l'exposé

- TISSUS MOUS
- TISSUS OSSEUX
- Nouveautés en immunohistochimie/ biologie moléculaire

Diagnostic des MPNST

- 1. Le Guellec (Coindre 2016)

- Revue de 160 diagnostics primaires de MPNST
- Après réévaluation et analyses cliniques et biologiques complémentaires: changement de diagnostic dans 18,1% des cas
  - Confusion possible avec le mélanome à cellules fusiformes
  - Autres tumeurs
- Association avec NF

TABLE 1. Excluded Cases (N = 29) After Pathology Review, IHC Analysis, and Molecular Analysis

Histologic Type	N (29) (% of Total)
Undifferentiated sarcoma	9 (31)
Malignant melanoma	5 (17.2)
Synovial sarcoma, spindle cell	4 (13.6)
Pleomorphic rhabdomyosarcoma	2 (6.9)
Epithelioid sarcoma	1 (3.5)
Sinonasal sarcoma with PAX3-MAML3 fusion	1 (3.5)
Myxofibrosarcoma	1 (3.5)
Dedifferentiated liposarcoma	1 (3.5)
Myoepithelial carcinoma	1 (3.5)
Dermatofibrosarcoma protuberans	1 (3.5)
Benign nerve sheath tumor	10.3
Neurofibroma	2
Perineurioma	1

Am J Surg Pathol • Volume 00, Number 00, ■■ 2016

Diagnostic des MPNST

TABLE 4. Univariate and Multivariate Analysis of Predictors of Local Recurrence and Distant Metastasis at 5 Years

	Local Recurrence				Distant Metastasis			
	Univariate		Multivariate		Univariate		Multivariate	
	CI (5 y) (%)	*P*	sHR (95% CI)	*P*	CI (5 y) (%)	*P*	sHR (95% CI)	*P*
NF1 disease								
No	26.9	0.4710	1.33 (0.51-3.48)	0.563	14.9	**0.0217**	2.50 (0.77-8.15)	0.129
Yes	28.7				38.3			
Sex								
Male	20.5	**0.0217**	1.90 (0.78-4.66)	0.160	26.4	0.3792	2.22 (0.92-5.36)	0.075
Female	40.9				33.6			
Tumor location								
Extremities	22.9	0.3639			28.2	0.7622		
Trunk wall	34.7				28.2			
Head/neck	29.5				36.3			
Depth								
Superficial	6.7	0.0753			0	**0.0206**		
Deep	31				32.5			
Tumor size (cm)								
≤ 10	26.7	0.4510			26.8	0.3760		
> 10	30.9				32.6			
Margin status								
R0 (negative)	17.4	**0.0329**	2.39 (0.98-5.83)	0.055	29.8	0.9007	0.94 (0.40-2.24)	0.896
R1/R2 (positive)	36				27.9			
Adjuvant chemotherapy								
No	31.5	0.3246			32.6	0.1221		
Yes	20				21.1			
Adjuvant radiation therapy								
No	44.8	**< 0.001**	4.50 (1.67-12.12)	**0.003**	32.1	0.7448	0.49 (0.19-1.27)	0.143
Yes	13.3				26.5			
Tumor grade (FNCLCC)								
1/2	32.1	0.9892	1.06 (0.43-2.61)	0.898	10.9	**0.0080**	3.55 (1.19-10.63)	**0.023**
3	26.9				37.6			

Récidive locale: Marges positives , absence d'irradiation

Facteurs pronostiques principaux : existence d'un contexte de NF1 et le grade

Survie à 5 ans: 34,8% qd NF1 , 68,5% sans contexte de NF1

Am J Surg Pathol • Volume 00, Number 00, ■■ 2016

Diagnostic des MPNST

- 2. Schaefer (Fletcher 2016)

Peu de marqueurs IHC pour le MPNST, difficulté diagnostique (sporadique)

Perte de la triméthylation de l' histone H3K27 (H3K27me3) => évaluée par IHC ds 100 MPNST

- 70 sporadiques, 10 radioinduits, 10 épithélioïdes, 10 neurofibromatose

Ac polyclonal de lapin : » *trimethylated lysine 27 residue of the N-terminal portion of histone H3* (1:500 dilution; 07-449· Millipore, Billerica, USA »

Loss of H3K27 trimethylation distinguishes malignant peripheral nerve sheath tumors from histologic mimics

Inga-Marie Schaefer, Christopher DM Fletcher and Jason L Hornick

Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

MODERN PATHOLOGY (2015), 1–10

Diagnostic des MPNST

- 2. Schaffer (Fletcher 2016)

Table 1 Summary of immunohistochemical staining for H3K27me3 in 100 malignant peripheral nerve sheath tumors

Tumor type	*Total cases*	*H3K27me3 negative*	*H3K27me3 heterogeneous*
Malignant peripheral nerve sheath tumor (total)	100	51 (51%)	6 (6%)
Sporadic	70	34 (49%)	3 (4%)
Tier 1	47	22 (47%)	3 (6%)
Tier 2	23	12 (52%)	0 (0%)
NF1-associated	10	7 (70%)	3 (30%)
Radiation-associated	10	10 (100%)	0 (0%)
Low grade	31	9 (29%)	3 (10%)
Intermediate grade	29	17 (59%)	2 (7%)
High grade	30	25 (83%)	1 (3%)
Epithelioid	10	0 (0%)	0 (0%)

Abbreviation: H3K27me3, histone H3 lysine 27 trimethylation.

Diagnostic des MPNST

2. Schaffer (Fletcher 2016)

- **Perte d'expression de H3K27me3:**
  - radioinduits: 100%
  - MPNST sur NF: 70%
  - sporadiques: 49% (mieux que PS100)
- **Relation significative avec le grade: absence complète H3K27me3 :**
  - 29% des tumeurs low-grade,
  - 59% des tumeurs de grade intermédiaire,
  - 83% des tumeurs high-grade

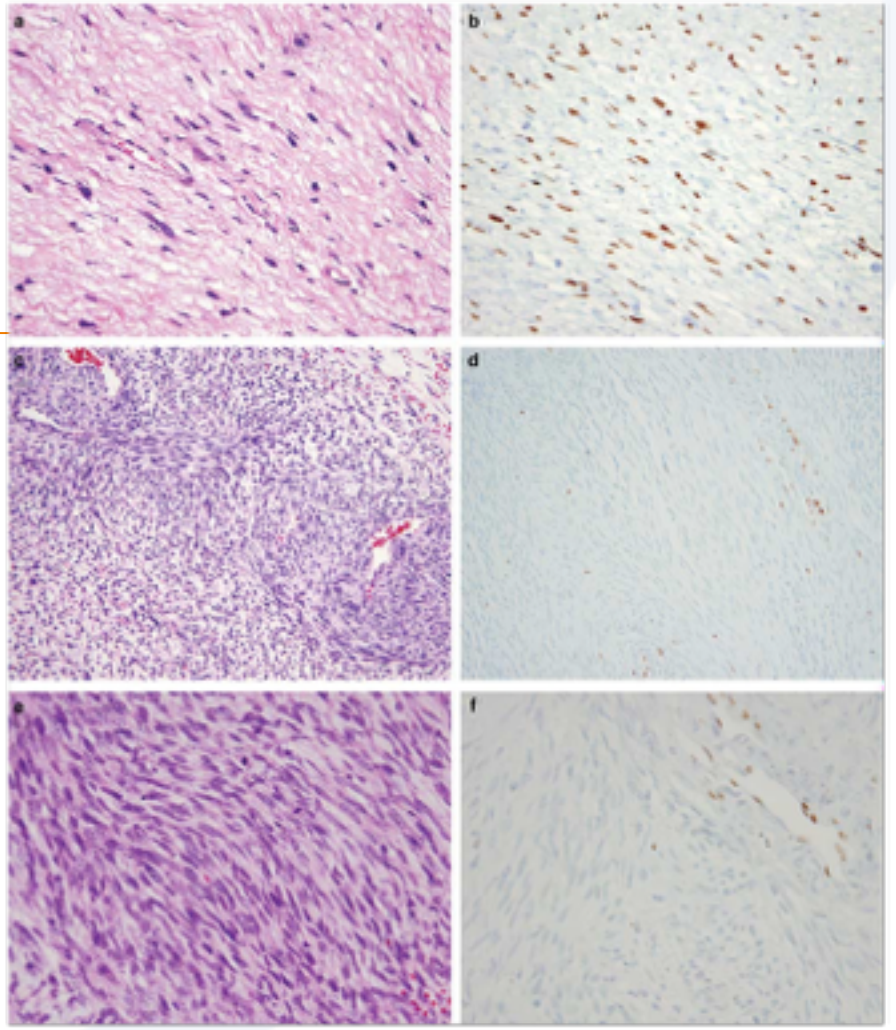


Figure 1 The majority of low-grade malignant peripheral nerve sheath tumors (a: hematoxylin and eosin (H&E)) show positive staining for histone H3 lysine 27 trimethylation (H3K27me3) (b). In contrast, more than half of all high-grade malignant peripheral nerve sheath tumors (c and e: H&E) exhibit loss of H3K27me3 expression (d and f); vascular endothelial cells and scattered inflammatory cells serve as positive internal controls.

Diagnostic des MPNST

- 3. Cleven 2016 (Bovee& Hoogendoorn)

- Anticorps H3K27-trimethyl (Millipore, Billerica, USA)
- Perte d'expression de H3K27me3:
  - 34% des MPNST sporadiques
  - 0% des neurofibromes
  - 60% des sarcomes synoviaux
  - 38% des DFSP fibrosarcomateux

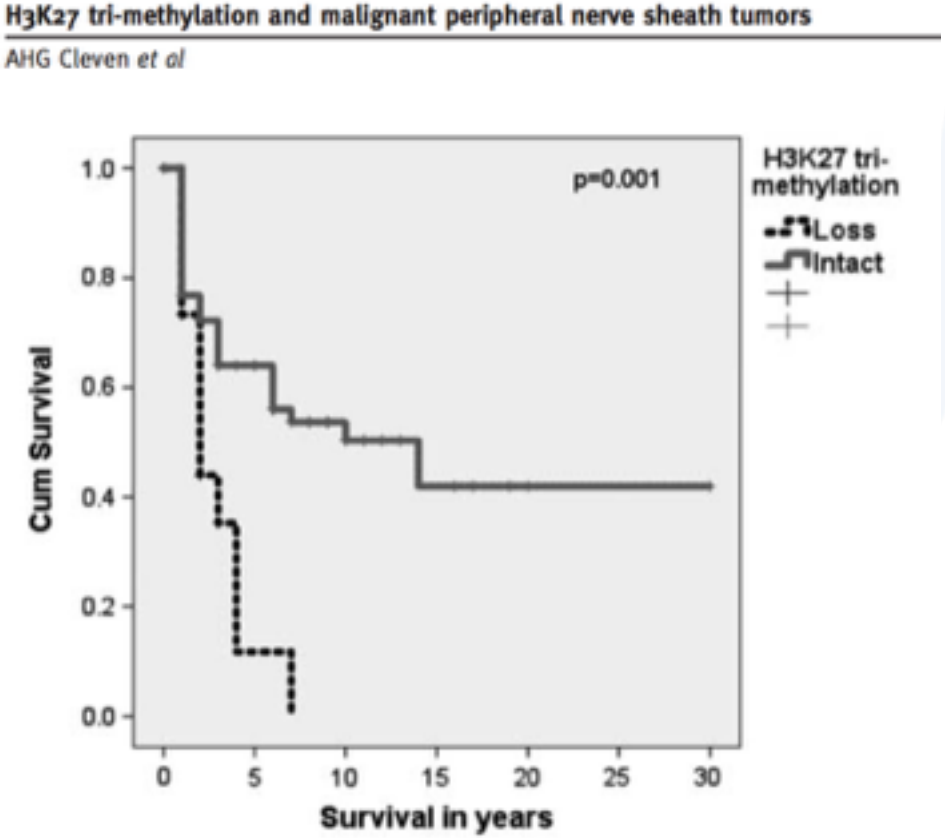


Figure 2 Loss of H3K27me3 is associated with poor outcome: poorer disease specific survival (in years) of MPNSTs with loss of H3K27 tri-methylation ($n=14$) compared with MPNSTs with intact H3K27 tri-methylation ($n=48$), $P=0.001$.

Utilité pour la distinction de lésion nerveuse bénigne/ MPNST
Différence de pronostic

Diagnostic des MPNST

4. Prieto-Granada (Antonescu 2015)

Loss of H3K27me3 Expression Is a Highly Sensitive Marker for Sporadic and Radiation-induced MPNST

Carlos N. Prieto-Granada, MD,† Thomas Wiesner, PhD,‡ Jane L. Messina, MD,† Achim A. Jungbluth, MD,* Ping Chi, MD, PhD,‡§‖ and Cristina R. Antonescu, MD**

(*Am J Surg Pathol* 2015

TABLE 1. Summary of the Results of H3K27me3 IHC of the Different MPNST Groups

MPNST Groups	H3K27me3 IHC Loss (n [%]) Complete	Partial	H3K27me3 IHC Retained
NF1-associated MPNSTs (N = 33)	15 (45)	4 (12)	14 (42)
Sporadic MPNSTs (N = 18)	16 (90)	1 (5)	1 (5)
RT-associated MPNSTs (N = 12)	11 (91)	—	1 (9)
Epithelioid MPNSTs (N = 5)	—	—	5 (100)
Total MPNST cases (N = 68)	47 (69)		21 (31)

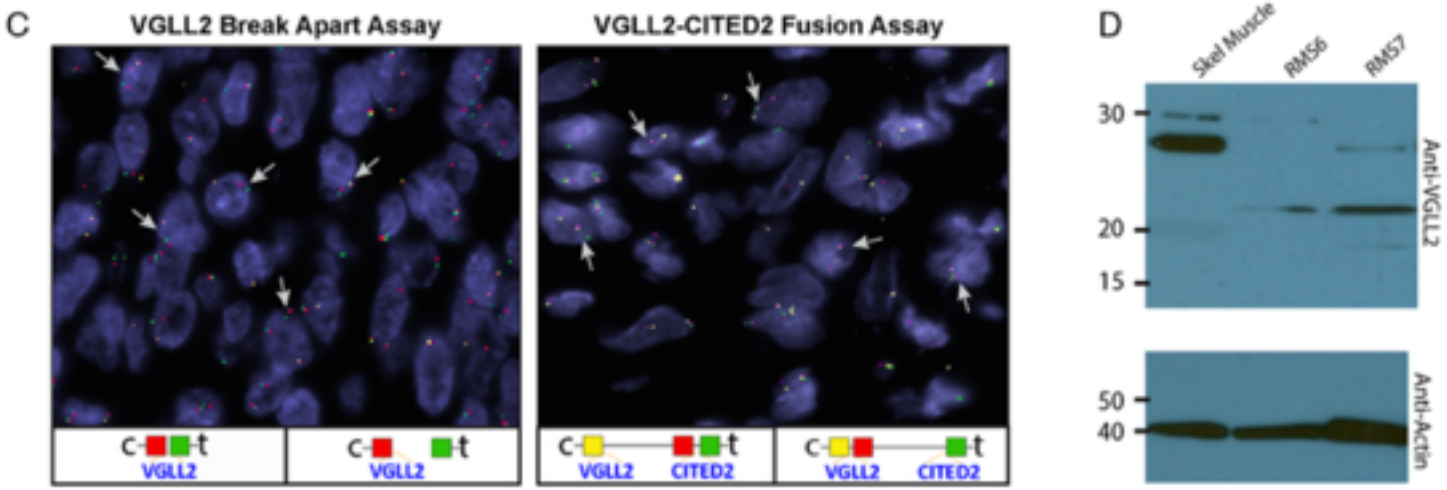
Pas de perte d'IHC dans d'autres tumeurs (sarcome synovial…)

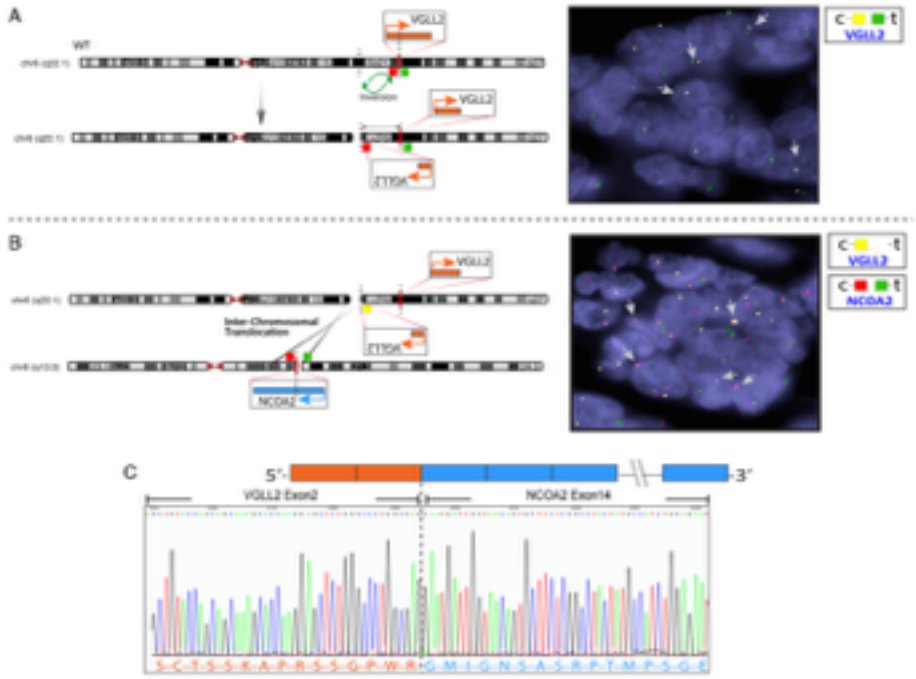
Classification des rhabdomyosarcomes

- Alaggio et al (Anthonescu 2016)

- 10/11 SRMS congénital/infantile avec gène de fusion :
  - Nouveau réarrangement impliquant VGLL2 ds 7 cas (63%),
    - VGLL2-CITED2 fusion ds 4 cas
    - VGLL2-NCOA2 ds 2 cas.
  - gène de fusion NCOA2: 3/11 (27%)
    - Impliquant TEAD1-NCOA2 dans 2 cas
    - Impliquant SRF-NCOA2 dans 1 cas
- Bonne évolution sans métastases
- « Démembrement » des RMS: Rhabdomyosarcome sclérosant (ScRMS) et rhabdomyosarcome à cellules fusiformes (SRMS)

Am J Surg Pathol Volume 40, Number 2, Feb 2016


C
VGLL2 Break Apart Assay
VGLL2-CITED2 Fusion Assay
c t
VGLL2
c t
VGLL2
c t
VGLL2
CITED2
c t
VGLL2
CITED2
D
Skel Muscle
RMS6
RMS7
30
20
15
Anti-VGLL2
50
40
Anti-Actin


A
VGLL2
WT
Inversion
VGLL2
ETV6
c t
VGLL2
B
VGLL2
Inter-Chromosomal Translocation
ETV6
NCOA2
c t
VGLL2
c t
NCOA3
C
5'
3'
VGLL2 Exon2
NCOA2 Exon14

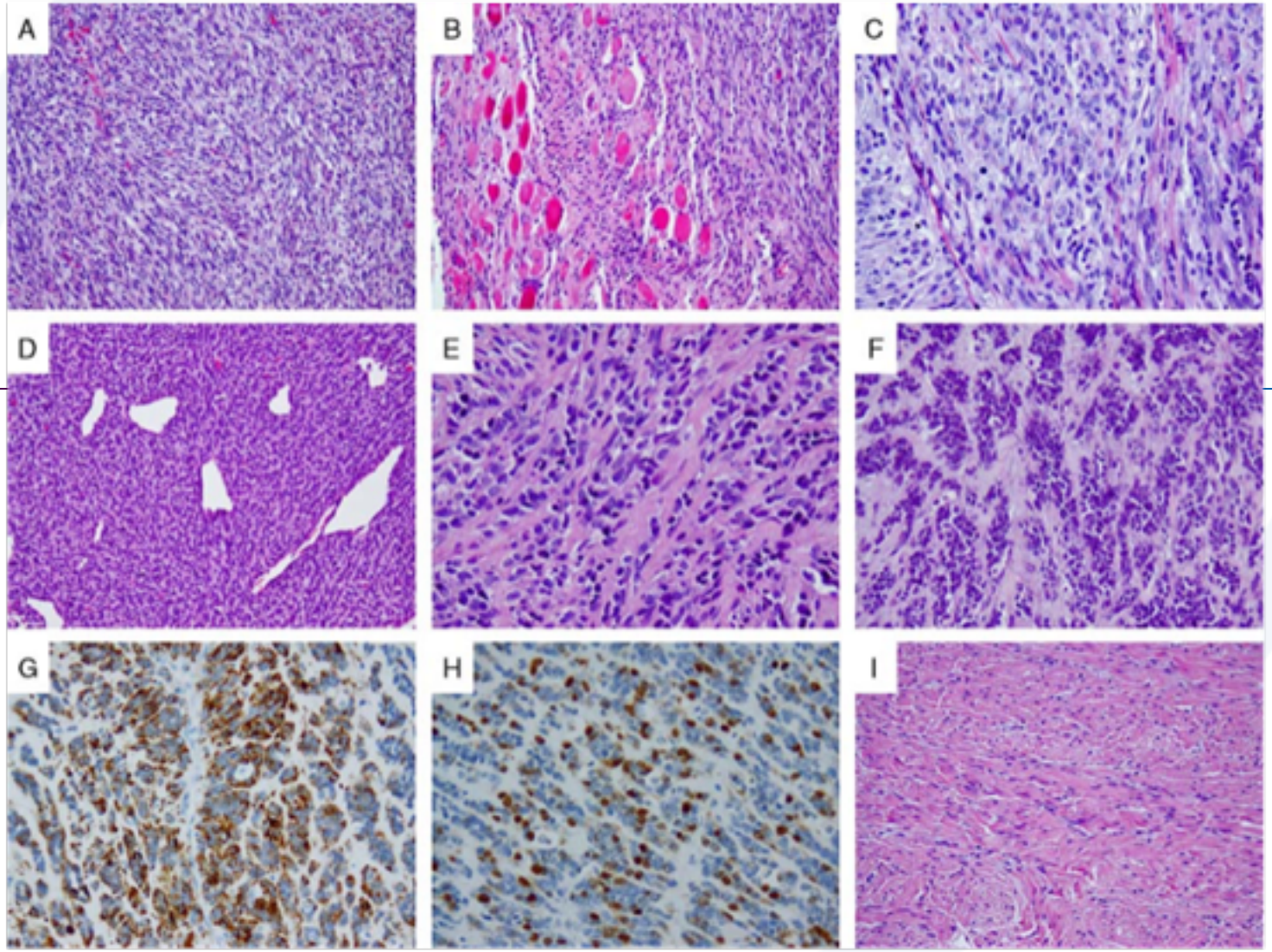
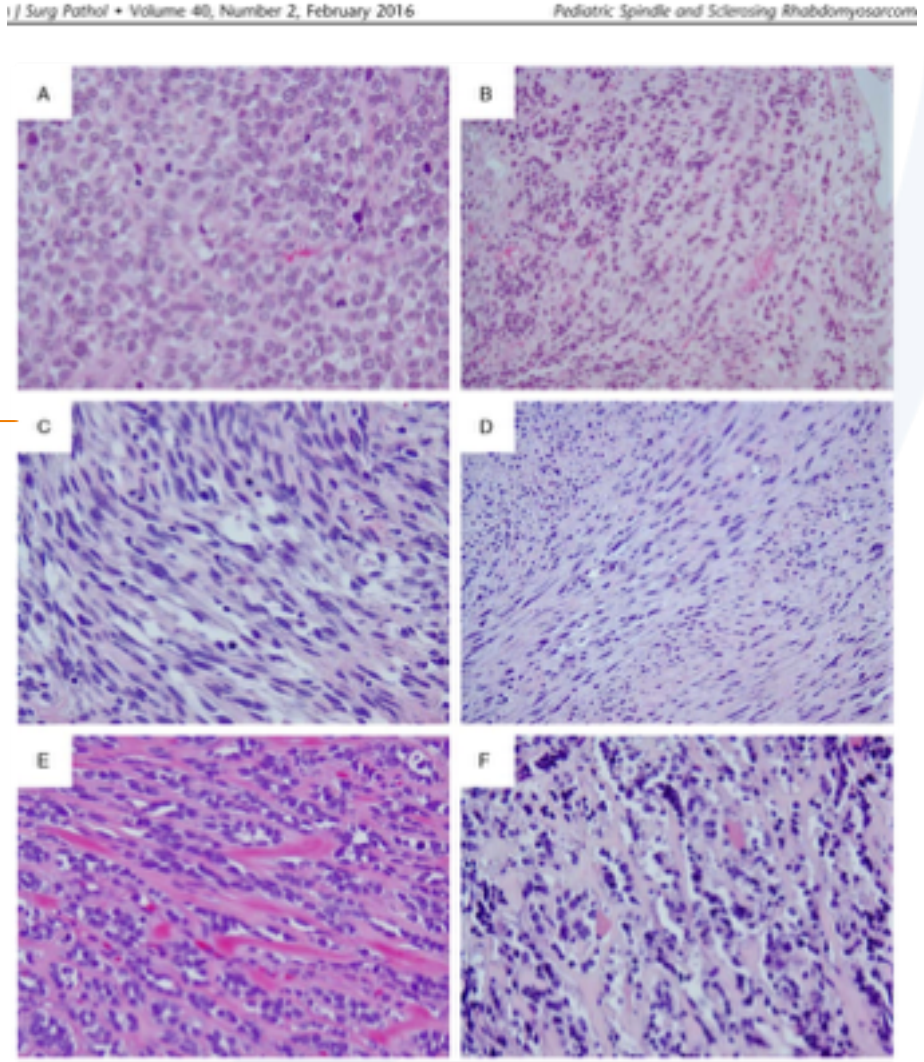


FIGURE 3. Pathologic features of congenital/infantile fusion-positive SRMS. *VGLL2-CITED2* fusion-positive tumors shared similar morphology (A–C) with monomorphic spindle cells arranged in short intersecting fascicles (A, SRMS6), infiltrating within skeletal muscle (B, SRMS6) and showing a more plump oval cells with pale eosinophilic to clear cytoplasm, fine chromatin, and scattered mitotic figures (C, SRMS7). *VGLL2-NCOA2* fusion-positive tumor (SRMS3) showed a highly cellular and hyperchromatic appearance reminiscent of infantile fibrosarcoma with a distinctive hemangiopericytoma-like vascular pattern in the primary tumor (D); in the subsequent 2 local recurrences, 2 years (E) and 5 years (F) later, it had a more sclerosing appearance; latter recurrence showed reactivity for desmin (G) and myogenin (H). In contrast, a *VGLL2* rearranged tumor with no identifiable partner showed a more sclerotic background mimicking fibromatosis (SRMS16, I).

Rhabdomyosarcome

- 15 SRMS patients >1 an: mutation MYOD1+/-PIK3CA
  - Topographie: tronc, Tête/cou
  - 10 cas (67%) mutation MYOD1 L122R sans PIK3CA: évolution défavorable
  - 4 cas avec mutation MYOD1/ PIK3CA : **RMS sclérosant.**
- 5 cas RMS: fusion/mutation-négatifs : présentation sous forme de masse intra-abdominale ou para-testiculaire



URE 5. Wide morphologic spectrum of *MYOD1*-mutant pediatric SRMS. Coexisting *MYOD1*, *PIK3CA*, and *FGFR4* mutation re associated with a highly primitive and solid growth of undifferentiated round cells with high mitotic activity and necrosis (A 517). Focal areas of dense sclerosis were noted in keeping with a cellular variant of ScRMS (B). *MYOD1*-mutant SRMSs from th ad and neck area showing monomorphic spindle cells with fibrillary pale eosinophilic cytoplasm, fine chromatin, and scattere totic figures, in a loose edematous stroma (C, RMS20) or in a more sclerotic background and arranged in long sweepin cicles (D, RMS21). Coexisting *MYOD1* and *PIK3CA* helical mutations in 2 ScRMSs showing a distinctive microalveolar growt ttern and alternating refractile collagen bundles (E, RMS15; F, RMS16).

Mélanome indifférencié

- Mélanome métastatique: propriété de diversité phénotypique et perte de différenciation des marqueurs IHCs
- Différenciation « hétérologue » possible: grande plasticité phénotypique et hétérogénéité moléculaire

---

- **Utilité du testing moléculaire : BRAF/NRAS/KIT**

Metastatic Malignant Melanoma With Complete Loss of Differentiation Markers (Undifferentiated/Dedifferentiated Melanoma)

Analysis of 14 Patients Emphasizing Phenotypic Plasticity and the Value of Molecular Testing as Surrogate Diagnostic Marker

Abbas Agaimy, MD, Katja Specht, MD,† Robert Stoehr, PhD,* Thomas Lorey, MD,‡ Bruno Märkl, MD,§ Gerald Niedobitek, MD,‖ Melanie Straub, MD,† Thomas Hager, MD,¶ Anna-Carinna Reis, MD,¶ Bastian Schilling, MD,# Regine Schneider-Stock, PhD,* Arndt Hartmann, MD,* and Thomas Mentzel, MD***

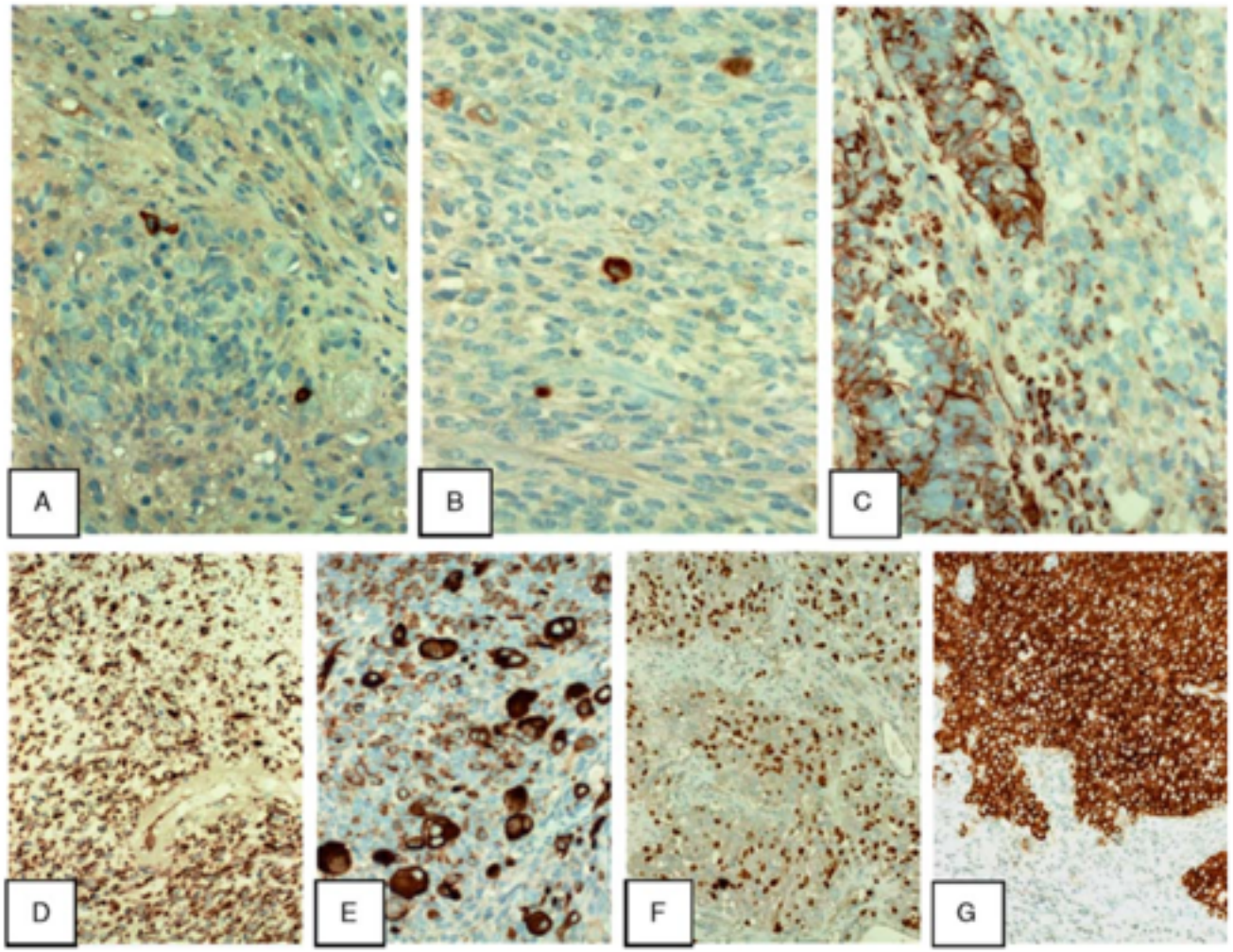


FIGURE 4. Examples of immunohistochemical findings in undifferentiated metastatic melanoma. A, Very rare isolated cells stained for HMB45 in case 10. B, Isolated desmin-positive cells were seen in 2 cases (image: case 3). C, Prominent pancytokeratin expression in the epithelial glands and in a few primitive cells in case 10. D, Prominent perinuclear expression of pancytokeratin in case 6. This finding together with strong expression of CD56 was misinterpreted as metastatic small cell carcinoma on pre-operative biopsy. E, Desmin was strongly positive in large rhabdomyoblasts as well as in small primitive cells in case 10. F, Myogenin from the same case. G, Case 7 showed strong expression of synaptophysin in the primitive component but not in the rhabdomyoblastic area (same as Fig. 3F).

Am J Surg Pathol; 2016: 40,(2), February

TABLE 2. Immunohistochemical Findings in Undifferentiated/Dedifferentiated Melanomas (n = 14)

No	S100	HMB45	Melan A	Pan-Melanoma	SOX10	P16	ASMA	Desmin	PanCK	TP53	Other Markers
1	–	–	–	–	–	–	–	–	+ + +	+ + +	Negative: CK7, CK20, TTF1, CDX2
2	–	–	–	–	–	–	–	+	–	–	Positive in primary tumor: desmin, S100, pan-Melanoma, HMB45 & pancytokeratin
3	–	–	–	–	–	–	–	+	+ (< 5%)	NA	Negative: MDM2, CDK4 & caldesmon. INI1 intact
4	–	–	–	–	–	–	–	–	–	+ + +	Negative: CD31, D2-40. INI1 intact
5	–	–	–	–	–	–	–	–	–	5%	INI1 intact
6	–	–	–	–	–	–	–	+	+ + +	NA	Negative: MDM2, CDK4, ERG, CD34, EMA, synaptophysin, caldesmon, CK20, GFAP. INI1 intact
7	–	–	–	–	–	–	–	+ +	–	–	Positive: myogenin & myoglobin. negative: CD117, h-caldesmon, OCT3/4, CDK4, MDM2. INI1 intact
8	–	–	–	–	–	–	–	–	–	–	CD31 + / –. INI1 intact
9	–	–	–	–	–	–	–	–	–	–	Negative: MDM2, CDK4, caldesmon. INI1 intact
10	i +	i +	–	i +	–	–	F +	+ +	+	+ (20%)	Positive: myogenin & myoglobin. Negative: CD117, h-caldesmon, CDK4 & MDM2. INI1 intact
11	–	–	–	–	–	–	–	–	–	–	CD34 negative
12	–	–	–	–	–	–	–	–	–	–	CD34 negative
13	–	–	–	–	–	–	–	–	–	–	CD34 strongly positive
14	–	–	–	–	–	+	–	–	–	–	–

ASMA indicates alpha smooth muscle actin; F, focal; i +, isolated cells positive; NA, not available; PanCK, pancytokeratin.

Myofibroblastome

- Lésion mésenchymateuse décrite initialement dans le sein: MTMF
- Cellules fibroblastiques, collagène et tissu adipeux
- CD34, desmine
- Famille « 13q/Rb »: réarrangement de 13q=> **perte d'expression de rB par IHC**

Mammary-type Myofibroblastoma

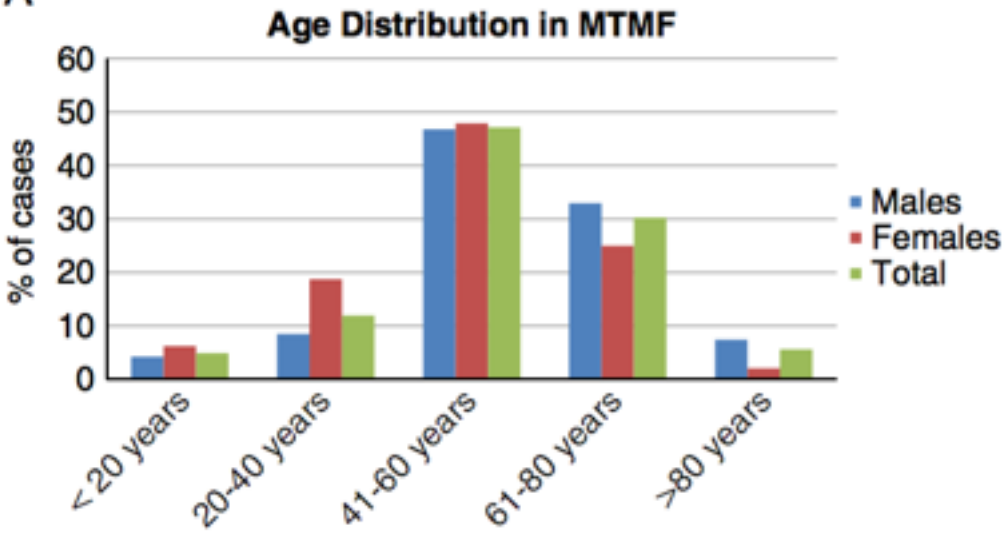
Clinicopathologic Characterization in a Series of 143 Cases

Brooke E. Howitt, MD and Christopher D.M. Fletcher, MD, FRCPath

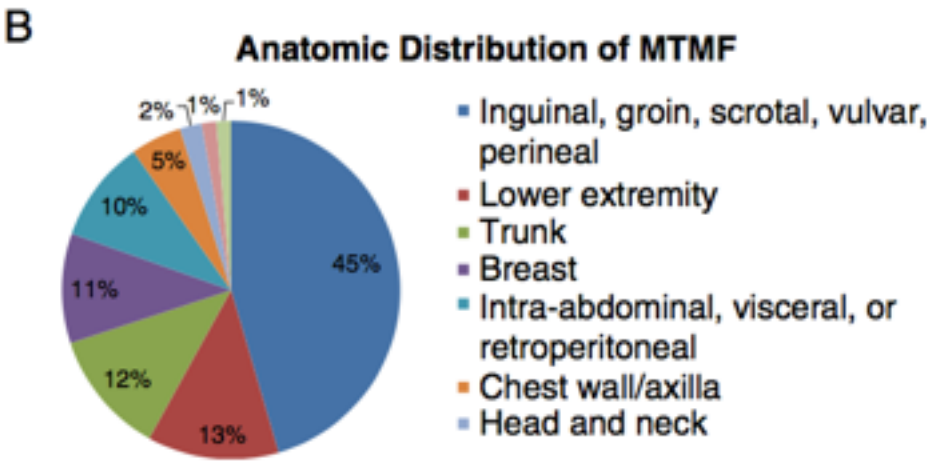
(*Am J Surg Pathol* 2016;40:361–367)

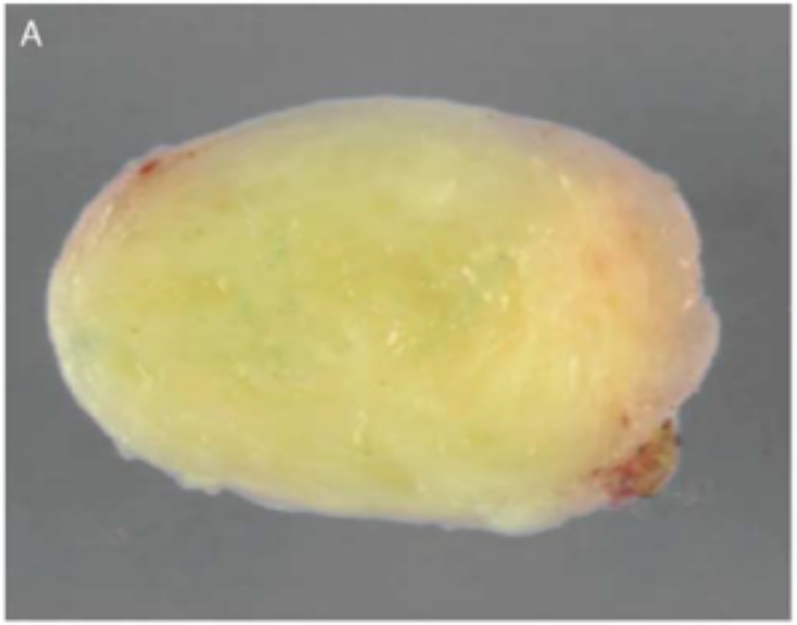
Myofibroblastome

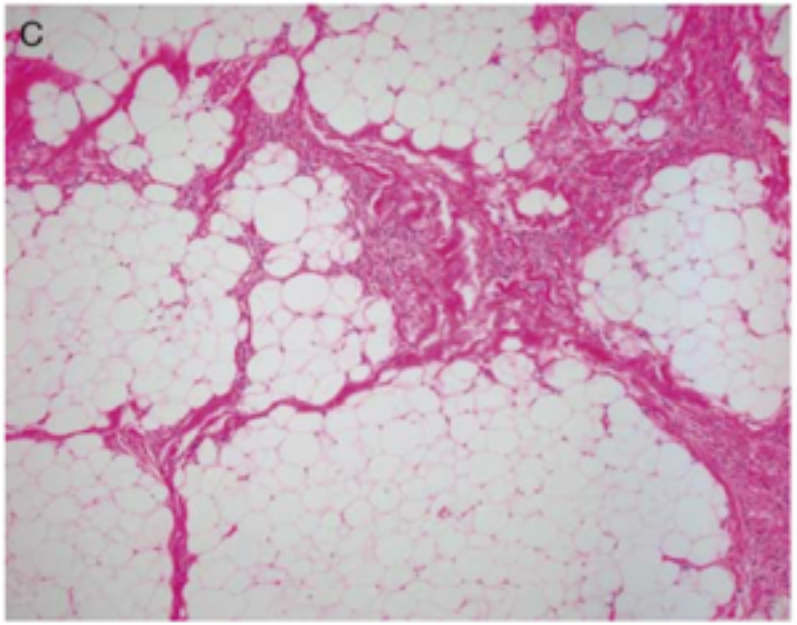
A



B







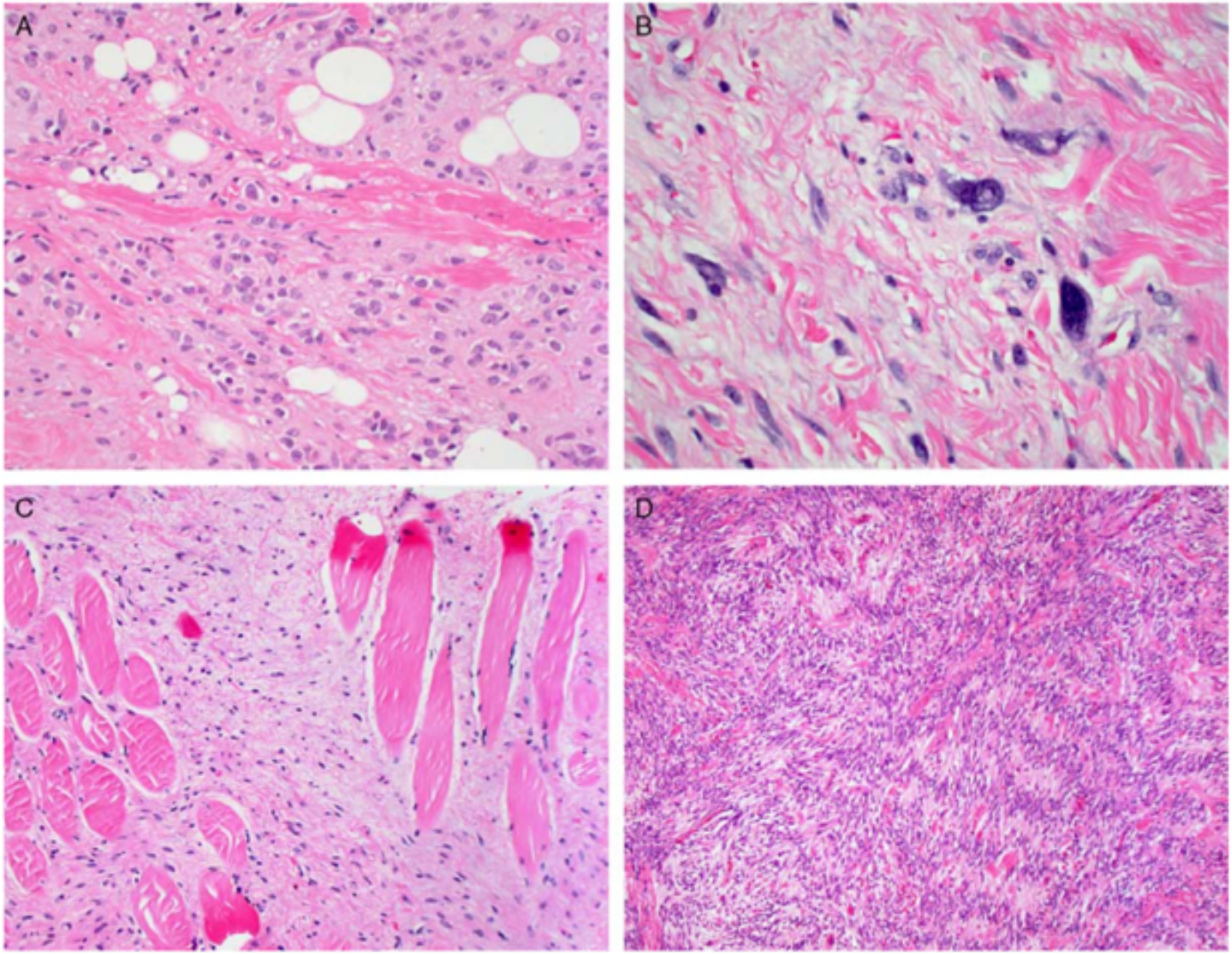


FIGURE 3. Unusual morphologic features of MTMF include epithelioid tumor cell morphology (A), nuclear atypia frequently characterized by "bizarre" likely degenerate nuclei (B), infiltrative growth, which was primarily seen in intramuscular locations (C), and prominent nuclear palisading "neurilemmoma-like" pattern (D).

Myofibroblastome

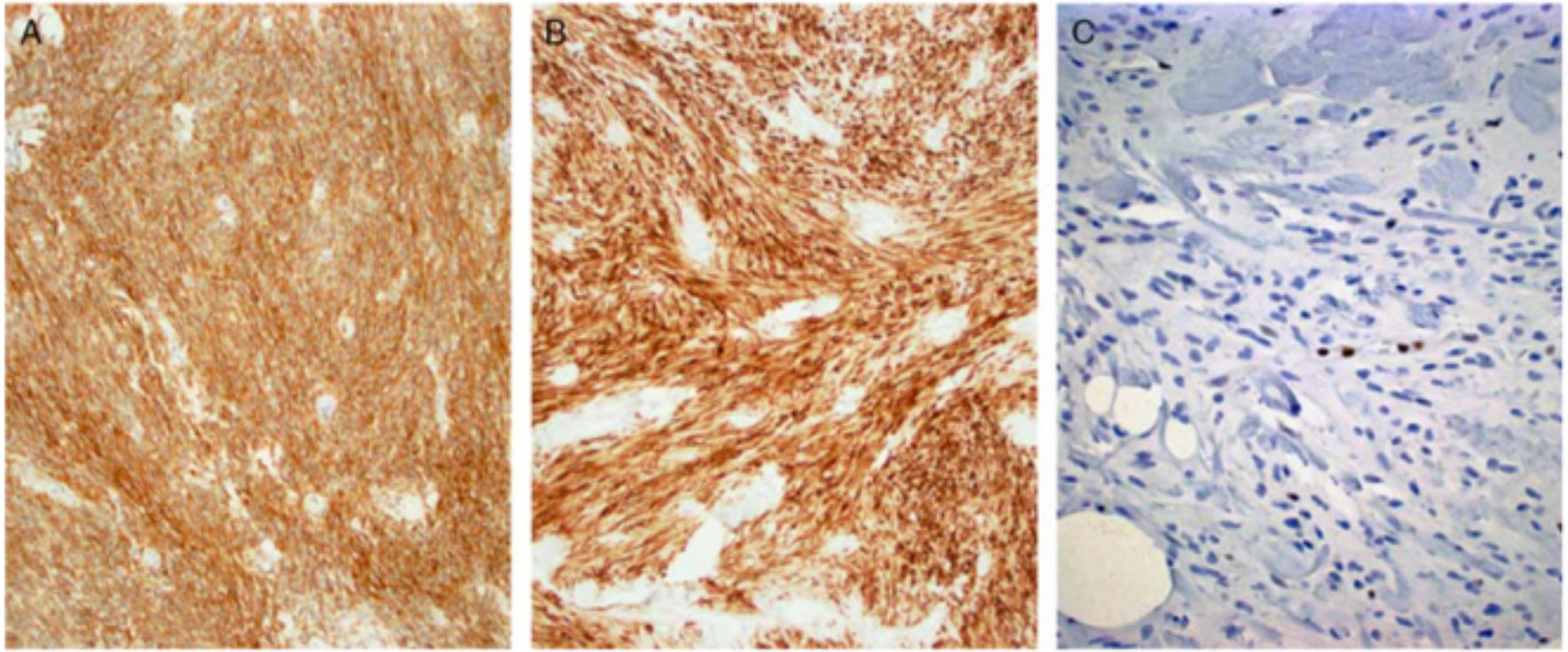


FIGURE 4. IHC features of MTMF. CD34 (A) and desmin (B) are usually strongly and diffusely positive. Rb is frequently lost in tumor cells (C), with positive internal control staining in the endothelial cells.

Lésion bénigne, pas de récidives (1 cas après 20 ans)
PERTE DE L'EXPRESSSION de Rb

Schwannome épithelioïde

- Tumeur bénigne nerveuse rare
- Tissus mous superficiels
- Amas de cellules de Schawann épithélioïdes
- Atypies possibles
- Relation avec MPNST épithélioïde?? NON

Epithelioid Schwannomas

An Analysis of 58 Cases Including Atypical Variants

Jesse Hart, DO, Jerad M. Gardner, MD,† Mark Edgar, MD,‡ and Sharon W. Weiss, MD‡*

Am J Surg Pathol • Volume 40, Number 5, May 2016

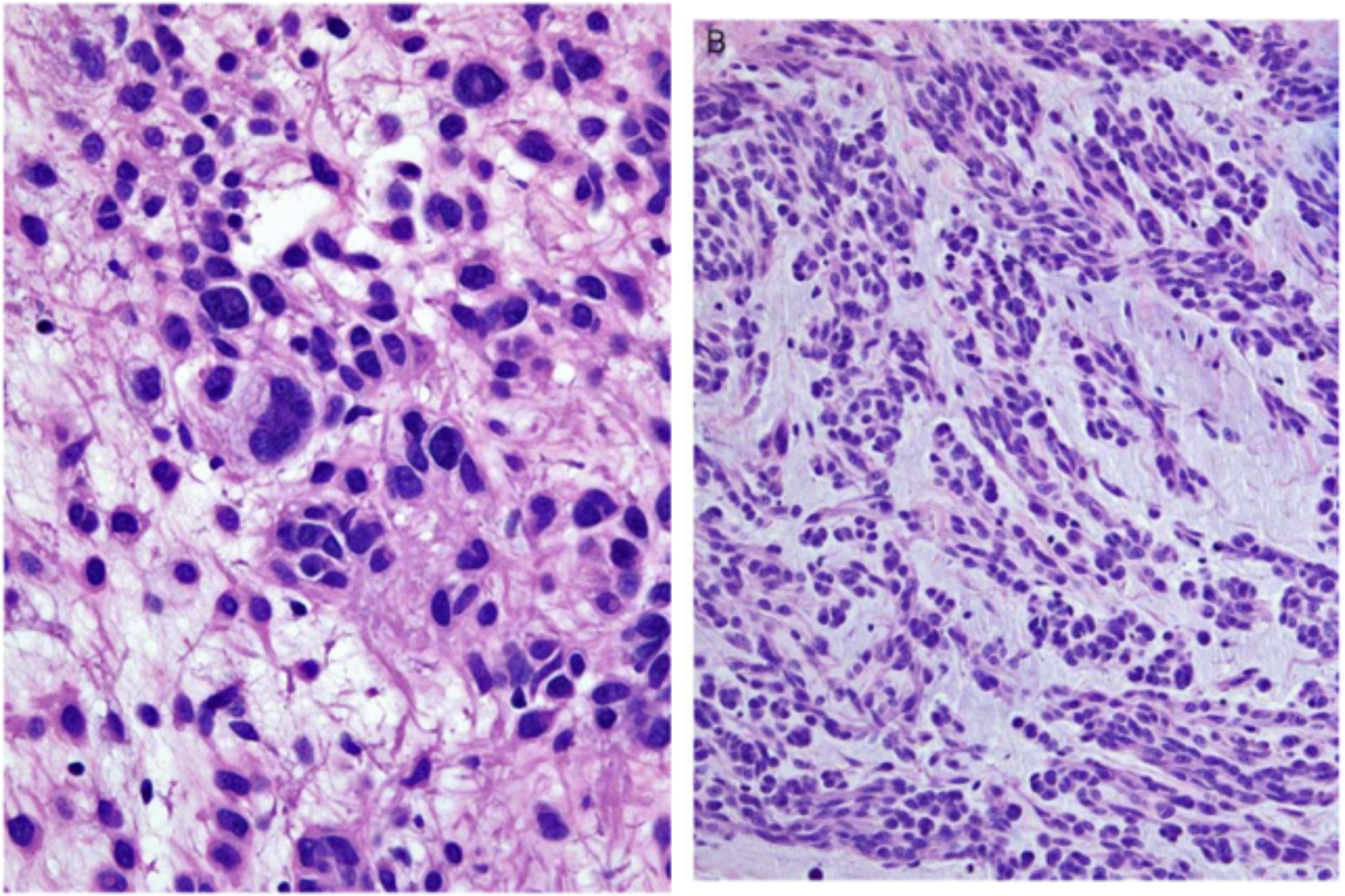


FIGURE 5. Epithelioid schwannomas showing transition from epithelioid (A) to spindled (B) areas within the same case.

Schwannome épithelioïde

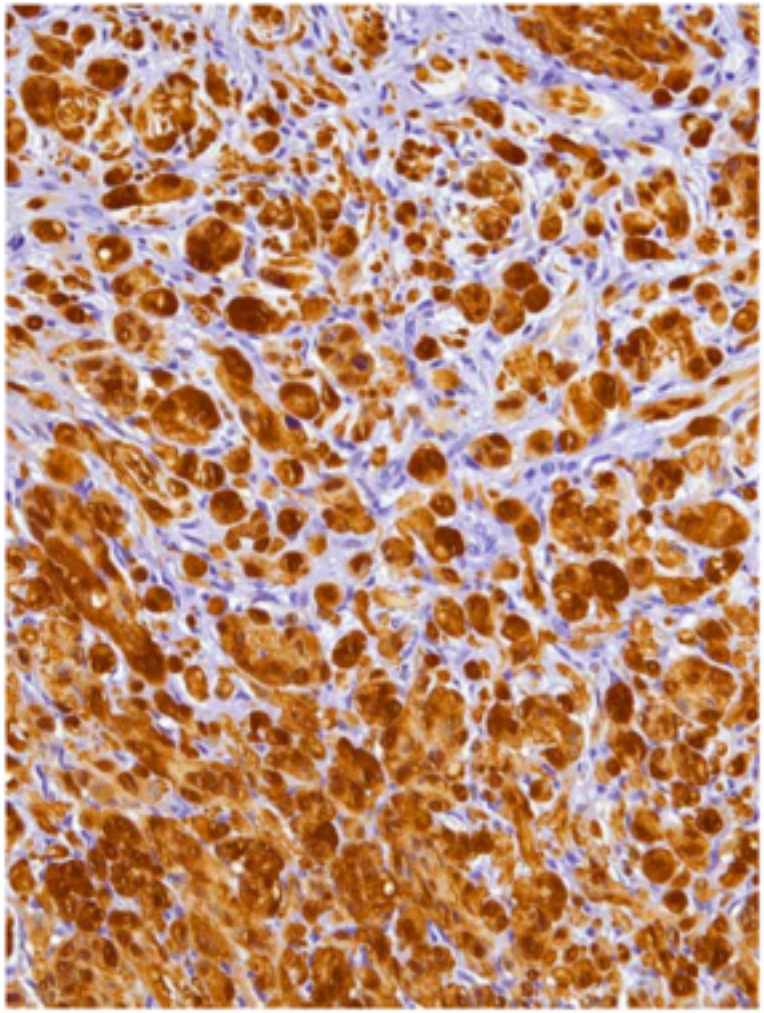


FIGURE 14. Epithelioid schwannomas showing intense diffuse expression of S100 protein.

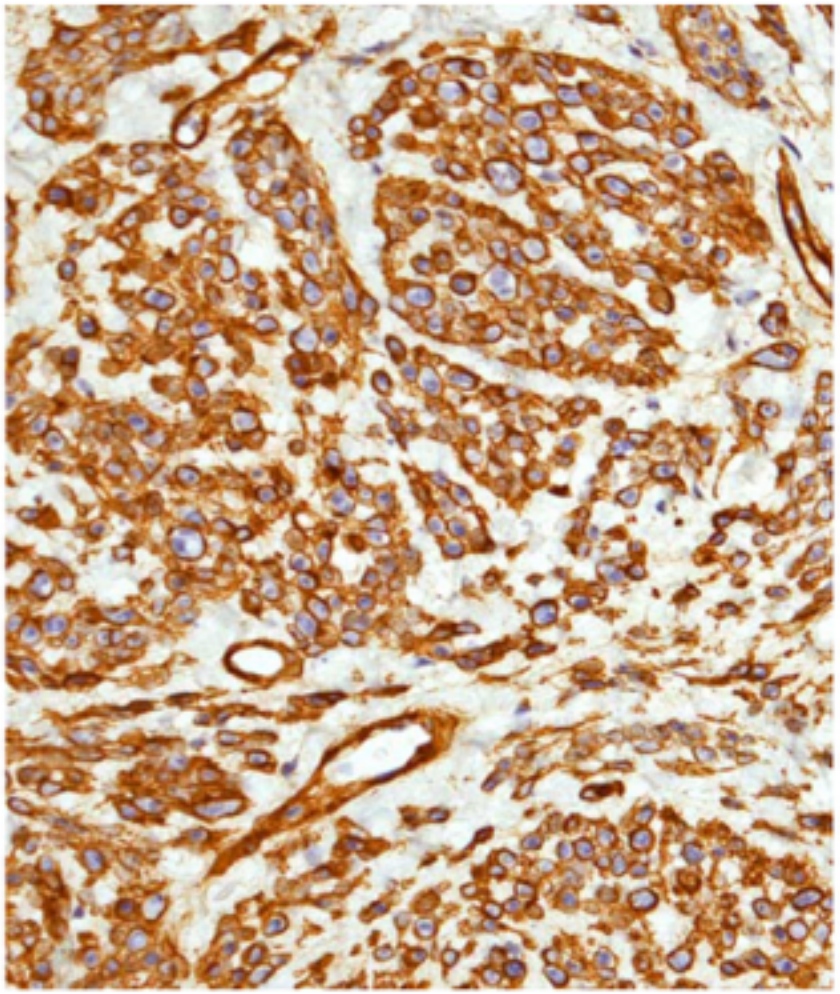


FIGURE 15. Type IV collagen, reflective of basal lamina deposition, invests nests and individual cells in epithelioid schwannomas.

Et dans l'os???

TCG:

- Mutations de H3F3A :
  - Chromosome 1
  - Mutation « driver »: G34W,
  - Mutation « driver »: G34R/V

=>IHC H3.K36 triméthylée
=>IHC H3.K36 mutée

- Mutations du gène ATRX
  - =>responsable de l'incorporation de H3.3

=>IHC ATRX

Chondroblastome:

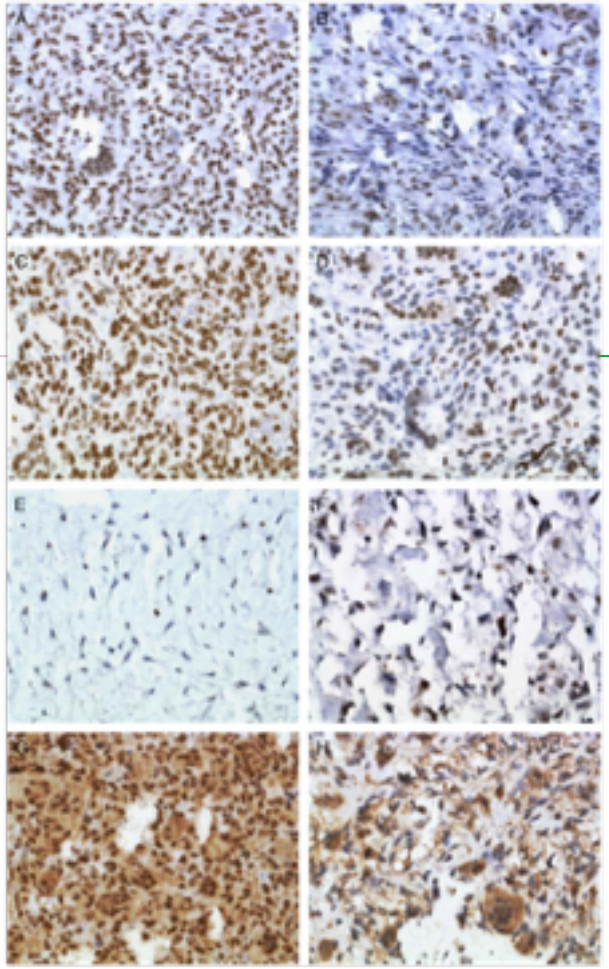
- Mutations de H3F3B :
  - Chromosome 17
  - Mutation K36M

=>IHC H3.K36M

Chondrome/chondrosarcome:

- Mutations de IDH1/IDH2, miRNA

Cleven 2015: H3F3 ds TCG & chondroblastome



H3.36K triméthylation

H3K36me3 (ab9050, Abcam, 1:4000)

ATRX

FIGURE 3. H3K36 trimethylation and ATRX staining patterns. A, "Diffuse type" of staining pattern for H3K36 trimethylation in GCTB. B, "Mosaic type" of staining pattern for H3K36 trimethylation in GCTB. C, "Diffuse type" of staining pattern for H3K36 trimethylation in chondroblastoma. D, "Mosaic type" of staining pattern for H3K36 trimethylation in chondroblastoma. E, "Mosaic type" of staining pattern for H3K36 trimethylation in chondromyxoid fibroma. F, "Diffuse type" of staining pattern for H3K36 trimethylation in telangiectatic osteosarcoma. G, Positive expression of ATRX in GCTB. H, Loss of nuclear expression of ATRX in GCTB.

TABLE 2. Numbers Mutated of *H3F3A*, *H3F3B*, and H3K36 Trimethylation in GCTB, Chondroblastoma, Aneurysmal Bone Cysts, Chondromyxoid Fibroma, and Telangiectatic Osteosarcoma

	No. Mutated		No. Positive	
	H3F3A (G34W/V)	*H3F3B* (K36M)	H3K36 (Diffuse)	H3K36 (Mosaic)
GCTB	41/59 (69)	0/46 (0)	41/59 (69)	18/59 (31)
Chondroblastoma	0/9 (0)	7/10 (70)	4/10 (40)	6/10 (60)
Aneurysmal bone cyst	0/6 (0)	0/6 (0)	5/6 (83)	1/6 (17)
Chondromyxoid fibroma	0/11 (0)	0/10 (0)	4/12 (33)	8/12 (67)
Telangiectatic osteosarcoma	0/5 (0)	0/2 (0)	2/4 (50)	2/4 (50)

- IHC de H3K36 triméthylée et de ATRX ne peuvent pas être utilisés comme marqueurs de mutations H3F3A
- A l'inverse, détection IHC de H3K36 triméthylée plus diffuse en cas de mutation
- Pas de corrélation avec l'immunomarquage ATRX

IHC H3K36M dans le chondroblastome (Amary 2016)

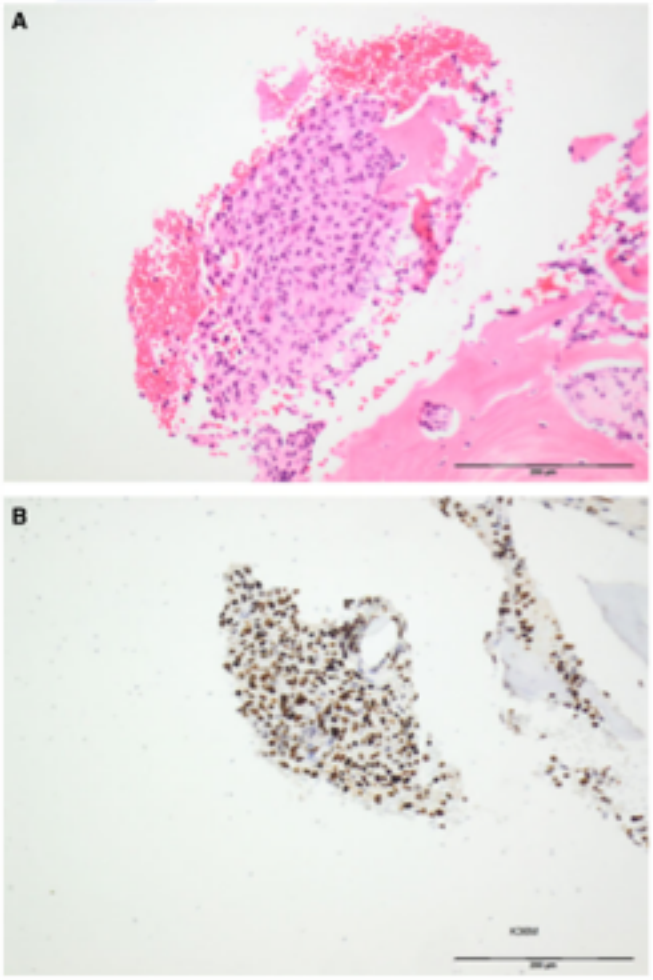


Figure 1. Photomicrographs of a needle biopsy showing small fragments of a chondroblastoma (A). Tumour cells are crisply decorated by the H3F3 K36M mutant antibody (B).

- Ac H3F3 muté
- Ac lapin H3F3 K36M clone M193
- 85 chondroblastomes:
  - 82 mutés=> IHC+
  - 3 wild type=> IHC
- 1047 tumeurs osseuses primitives négatives (y compris les 76 TCG)
- 507 tumeurs des tissus mous
  - 0/4 MPNST négatives
  - 1/10 chondrosarcome à cellules claires
  - 0/83 granulomes à cellules géantes de la mâchoire

IHC H3K36M dans le chondroblastome

The H3F3 K36M mutant antibody is a sensitive and specific marker for the diagnosis of chondroblastoma

M Fernanda Amary,[1,2] Fitim Berisha,[1] Rafael Mozela,[1,3] Rebecca Gibbons,[1] Alice Guttridge,[2] Paul O'Donnell,[4] Daniel Baumhoer,[5] Roberto Tirabosco[1] & Adrienne M Flanagan[1,2]

[1]*Department of Histopathology, Royal National Orthopaedic Hospital NHS Trust, Stanmore, UK,* [2]*UCL Cancer Institute, Huntley Street, London, UK,* [3]*Department of Anatomical Pathology, A. C. Camargo Cancer Centre, Sao Paulo, Brazil,* [4]*Department of Radiology, Royal National Orthopaedic Hospital NHS Trust, Stanmore, UK, and* [5]*Bone Tumour Reference Centre at the Institute of Pathology, University Hospital Basel, Basel, Switzerland*

Date of submission 17 November 2015
Accepted for publication 31 January 2016
Published online *Article Accepted* 4 February 2016

Amary M F, Berisha F, Mozela R, Gibbons R, Guttridge A, O'Donnell P, Baumhoer D, Tirabosco R & Flanagan A M (2016) *Histopathology* **69**, 121–127. DOI: 10.1111/his.12945

Chondrome/chondrosarcome: Zhang miRNA

Connect Tissue Res. 2016 Jun 7. [Epub ahead of print]

The Use of MicroRNA Biomarkers to Distinguish Enchondroma from Low Grade Chondrosarcoma.

Zhang L[1], Yang M[1], Mayer T[2], Johnstone B[3], Les C[1], Frisch N[4], Parsons T[4], Mi QS[5], Gibson G[1].

Author information

Open/close author information list

Abstract

Establishing a definitive diagnosis between benign enchondroma versus low grade chondrosarcoma presents a potential challenge to both clinicians and pathologists. microRNAs (small non-coding RNAs) have proven to be effective biomarkers for the identification of tumors and tumor progression. We present analysis, both array and quantitative PCR, that shows consistently and substantially increased expression of two microRNAs, miRs-181a and -138, in low grade chondrosarcomas compared with enchondromas. The data suggest these microRNAs would provide an analytical distinction between the chondrosarcoma and benign neoplasms that can be performed in formalin fixed paraffin embedded specimens. Together with recent publications, these data indicate that miRs-181a and -138 also play a role in tumor development and homeostasis and may provide new targets for the development of much needed therapeutic intervention.

KEYWORDS: chondrosarcoma; enchondroma; miR-138; miR-181a; microRNA

Chondrome/chondrosarcome: IDH1/IDH2

- 102 Tumeurs chez 37 patients
- Altérations moléculaires:
  - Substitutions R132 de IDH1
  - Substitutions R172 et R140 IDH2
- Mêmes altérations dans les récidives
- Quand mutation IDH1=> variations du nombre de copies de p16/CDKN2A
  - Dans 75% des chondrosarcomes high grade
  - Absent dans les chondrosarcomes de bas grade

***Isocitrate dehydrogenase 1* mutations *(IDH1)* and *p16/CDKN2A* copy number change in conventional chondrosarcomas**

M. Fernanda Amary · Hongtao Ye · Georgina Forbes · Stephen Damato · Francesca Maggiani · Robin Pollock · Roberto Tirabosco · Adrienne M. Flanagan

Nouveautés dans les marqueurs IHCs

SOX-10

- Facteur de transcription factor exprimé dans les lignées schwanniennes et mélanocytaires
- Marqueurs IHC dans les tumeurs correspondantes
- Evaluation de l'expression dans 5134 néoplasmes
- Clone EP268

⇒ Expression dans les Schwannomes, tumeurs des tissus mous du TD, mélanomes métastatiques (95%) et variablement présent dans les MPNST

⇒ Myoépithéliomes/tumeurs mixtes

⇒ Carcinomes embryonnaires

⇒ (carcinomes rares)

George Lin, MD, PhD; Leona A. Doyle, MD

(*Am J Surg Pathol* 2015;39:826–835)

Nouveautés dans les marqueurs IHCs

Myc

- Types d'angiosarcomes
  - Primaire: exposition au soleil, sporadique
  - Secondaire: lymphoedème, irradiation
- Expression nucléaire de MYC dans la plupart des angiosarcomes secondaires et rarement dans les angiosarcomes primaires
- Absence de détection Myc dans les lésions vasculaires bénignes et les lésions vasculaires atypiques en peau irradiée

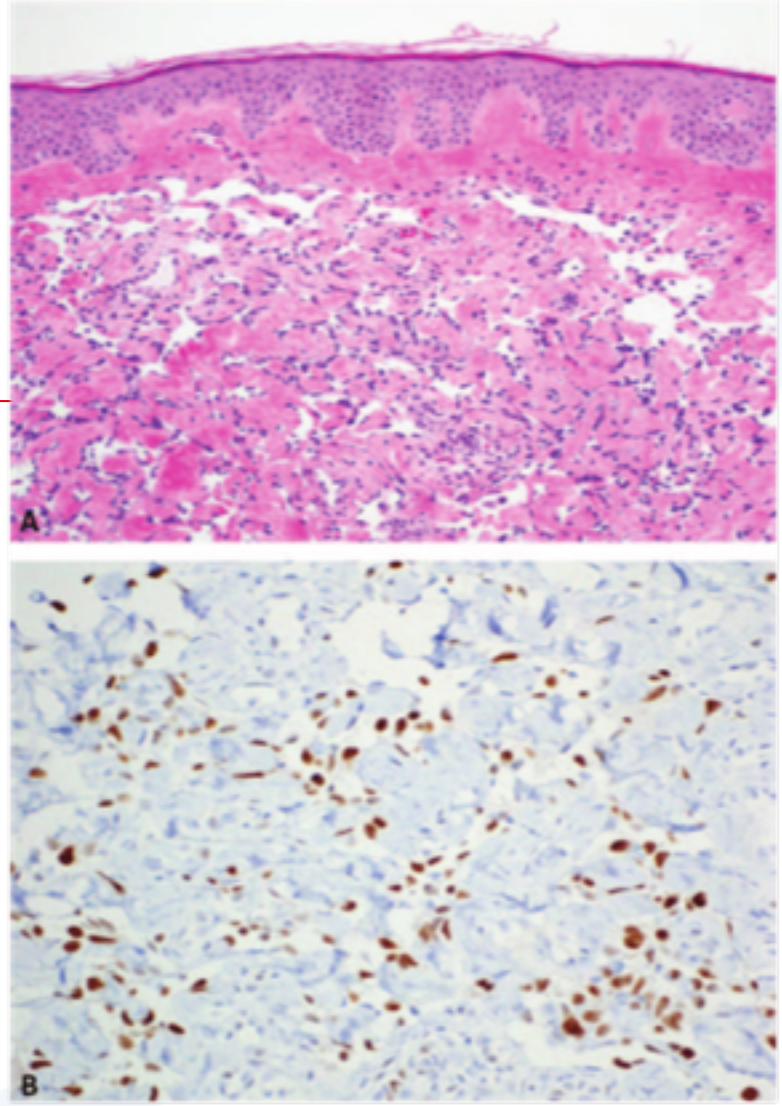


Figure 2. *Postradiation angiosarcoma with a vasoformative growth pattern (A). The tumor cells show diffuse strong nuclear positivity for MYC (B) (hematoxylin-eosin, original magnification ×200 [A]; original magnification ×400 [B]).*

Nouveautés dans les marqueurs IHCs

TFE-3

- Protéine détectée quand gène de fusion impliquantTFE-3
- Sarcome alvéolaire des parties molles
- Carcinome à cellules rénales avec translocation Xp11
- Certains PEComas
- Certains hémangioendotheliomes épithelioïdes

Nouveautés dans les marqueurs IHCs

NY-ESO-1

- Tissu normal:
  - Expression nucléaire dans les cellules germinales testiculaires
  - Médiation de la réponse immunitaire
- >80% des sarcomes synoviaux: pattern cytoplasmique
- Expression dans les liposarcomes myxoides
  - 36/38 liposarcomes myxoïdes (95%)
  - Autres tumeurs myxoïdes négatives
- => Utilité dans la distinction de liposarcome myxoïde versus autres tumeurs myxoïdes

Nouveautés dans les marqueurs IHCs

MDM2/CDK4

- MDM2: chromosome 12q14.3-q15
- CDK4: chromosome 12q13
- Cas de liposarcomes bien différenciés avec IHC négatives!
- Histiocytes MDM2+
- !Utilité de la FISH MDM2!

- Détection dans les sarcomes intimaux et cardiaques
- Ostéosacomes de bas grade/ostéosarcome dédifférencié

FISH reste « gold standard »

Echos de l'USCAP

ETV4

- Diagnostic des sarcomes d'Ewing-like réarrangés CIC (Abstract 73, Le Guellec S, Toulouse, France)
- ~~Part importante (jusqu'à 60% pour certains) des sarcomes~~ de type Ewing mais sans réarrangement du gène EWSR1.
- Nouveau marqueur est très sensible et spécifique au sein des tumeurs malignes à cellules rondes.

Analyses de biologie moléculaire
Erreurs dans l'interprétation de EWSR1

- Inactivation de SMARCB1/INI1 (chromosome 22)
  - Chordome
  - Tumeur rhabdoïde extrarénale
  - Carcinome myoépithélial
  - Sarcome épithélioïde proximal
- Localisation proche de EWSR1
- Possibilité d'implication du locus EWSR1
  - « Splits » non balancés
  - Délétion hétérozygote

=>mauvaise interprétation de réarrangement EWSR1 par FISH

Genes Chromosomes Cancer. 2016 May 24. doi: 10.1002/gcc.22376. [Epub ahead of print]

Secondary EWSR1 Gene Abnormalities in SMARCB1-Deficient Tumors with 22q11-12 Regional Deletions: Potential Pitfalls in Interpreting EWSR1 FISH Results.

Huang SC[1,2], Zhang L[1], Sung YS[1], Chen CL[1], Kao YC[1,3], Agaram NP[1], Antonescu CR[1].

Recently Described Immunohistochemical Markers of Soft Tissue Tumors

Antibody	Expression Pattern	Main Use(s)	Comments
ERG	Nuclear	Confirm endothelial differentiation	Also stains a subset of epithelioid sarcomas, subset of Ewing sarcoma, and 45% of prostatic carcinomas (117 of 261 cases[17]; 30 of 66 cases[13])
MYC	Nuclear	Differentiate postradiation angiosarcoma from APRVP	Expressed in a small subset of primary angiosarcomas (usually head and neck)
MDM2/CDK4	Nuclear	Coexpressed in most well-differentiated and dedifferentiated liposarcomas Coexpressed in intimal sarcoma and parosteal and low-grade central osteosarcoma	MDM2 is positive in up to 64% of MPNSTs (21 of 33 cases[46]), 42% of myxofibrosarcomas (10 of 24 cases[46]), and 29% of embryonal rhabdomyosarcomas (12 of 41 cases[46]); MDM2 positivity is also seen in histiocytes
STAT6	Nuclear (+/− cytoplasmic)	Positive in >97% of SFTs (59 of 60 cases[60]; 54 of 54 cases[61]; 34 of 35 cases[62]; 49 of 49 cases[63])	Expressed in 15% of dedifferentiated liposarcomas (3 of 21 cases[60])
MUC4	Cytoplasmic	Expressed in vast majority of low-grade fibromyxoid sarcoma (49 of 49 cases[72]) and sclerosing epithelioid fibrosarcoma (32 of 41 cases[82]; 14 of 15 cases[83])	Focal positivity seen in synovial sarcoma, ossifying fibromyxoid tumors, and epithelioid GIST Expressed in many carcinomas
DOG1	Cytoplasmic + membranous	Positive in >87% of GISTs (136 of 139 cases[89]; 986 of 1040 cases[90]; 370 of 425 cases[91]) Useful to confirm a diagnosis of GIST in gastric KIT-negative tumors	Various other tumor types reported to show focal staining
SDHB/A	Cytoplasmic, granular	Loss of SDHB expression confirms diagnosis of SDH-deficient GIST Loss of SDHA expression indicative of *SDHA* mutations	Loss of SDHB staining also seen in pheochromocytoma/paraganglioma and rare renal cell carcinomas associated with SDH complex dysfunction
INI1	Nuclear	Loss of expression in 93% of epithelioid sarcomas (127 of 136 cases[131]) and virtually all malignant rhabdoid tumors	Loss of staining also seen in 50% of epithelioid MPNSTs (12 of 24 cases[131]) and 40% of pediatric myoepithelial carcinomas (9 of 22 cases[133])
TLE1	Nuclear	Expression seen in >90% of synovial sarcomas (91 of 94 cases[150]; 249 of 259 cases[151]; 39 of 43 cases[156]; 35 of 35 cases[157]; 18 of 20 cases[158])	Expression often seen in MPNST and SFT (usually, but not always, less diffuse than in synovial sarcoma)
TFE3	Nuclear	Positive in virtually all ASPS	Also positive in Xp11 translocation–type renal cell carcinomas, subset of epithelioid hemangioendotheliomas (with *YAP1-TFE3* fusion gene), and a subset of PEComas
SOX10	Nuclear	Confirm neural crest differentiation—melanocytic tumors, clear cell sarcoma, most benign nerve sheath tumors and 27%–50% of MPNSTs (21 of 78 cases[179]; 38 of 77 cases[182])	Also stains a subset of myoepithelial and salivary gland tumors, and subset of carcinoid tumors and breast carcinomas
NY-ESO-1	Cytoplasmic and nuclear	Expressed in up to 80% of synovial sarcomas (20 of 25 cases[186]; 38 of 50 cases[189]) and 95% of myxoid liposarcomas (36 of 38 cases[192])	Positivity is also seen in melanoma and a variety of carcinomas

Abbreviations: APRVP, atypical postradiation vascular proliferation; ASPS, alveolar soft part sarcoma; GIST, gastrointestinal stromal tumor; MPNST, malignant peripheral nerve sheath tumor; PEComa, perivascular epithelioid cell tumor; SDH, succinate dehydrogenase; SFT, solitary fibrous tumor.

Merci pour votre attention!!