Cutaneous Soft Tissue Tumors

By Konstantinos Linos MD, FASDP
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I have no financial disclosures

Fibroblastic/myofibroblastic tumors

Superficial desmoplastic fibroma

Acceptable: collagenous fibroma

The American Journal of Surgical Pathology 19(9): 1077–1081, 1995

Desmoplastic Fibroblastoma

A Report of Seven Cases

Harry L. Evans, M.D.

Collagenous Fibroma (Desmoplastic Fibroblastoma): A Clinicopathologic Analysis of 63 Cases of a Distinctive Soft Tissue Lesion With Stellate-Shaped Fibroblasts

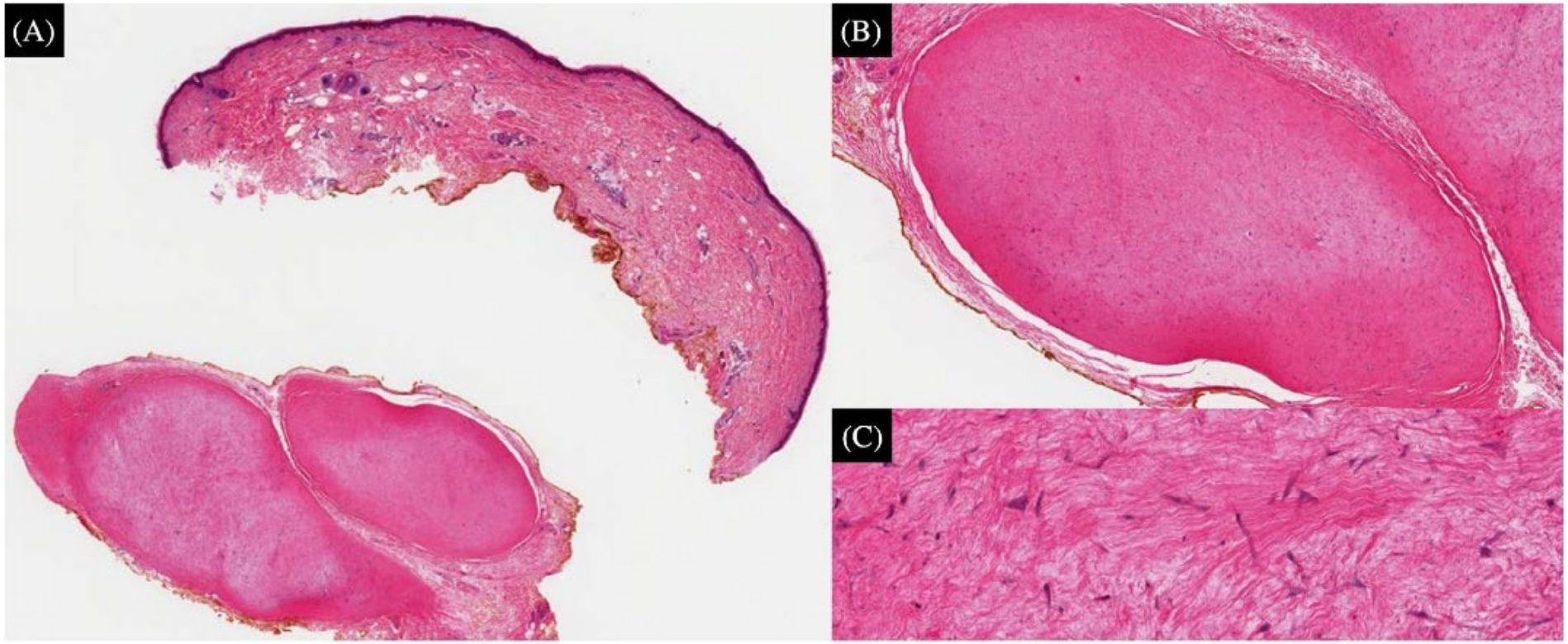
MARKKU MIETTINEN, MD AND JOHN F. FETSCH, MD

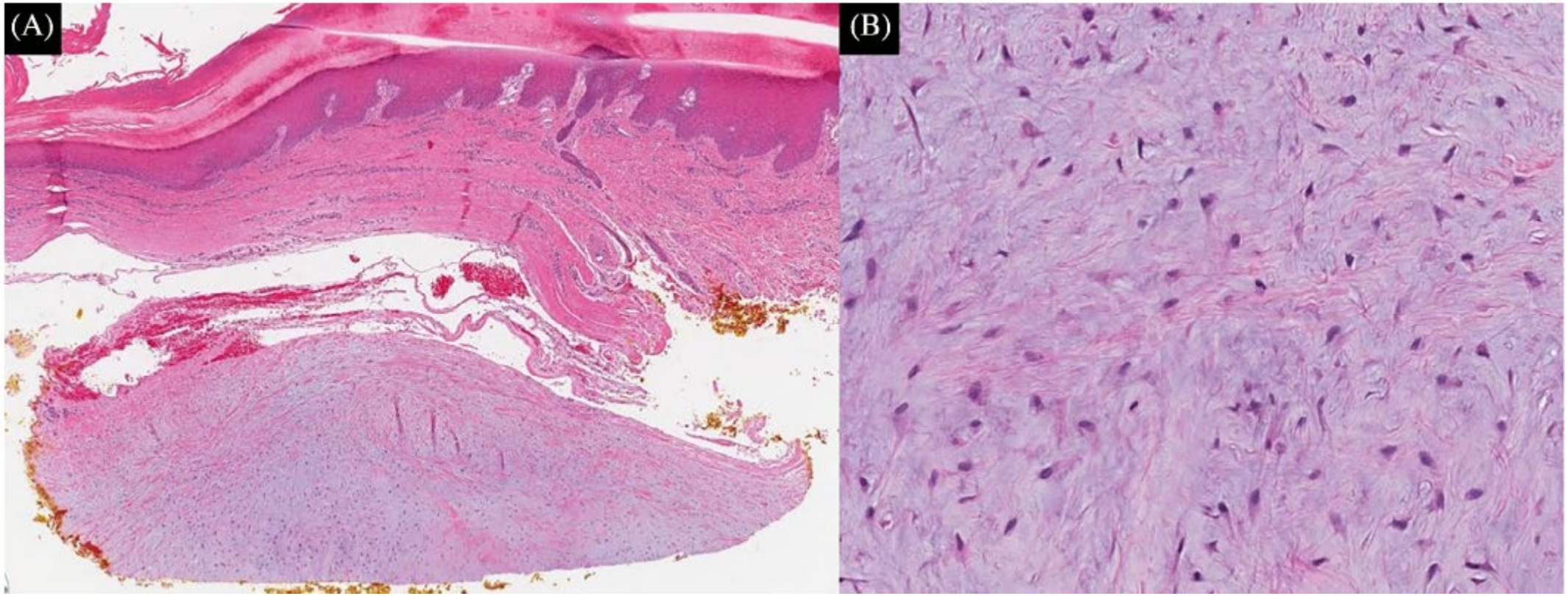
HUMAN PATHOLOGY Volume 29, No. 7 (July 1998)

Superficial desmoplastic fibroblastoma (collagenous fibroma): Clinicopathologic study of 11 cases

Ahmed Bakhshwin MD[1,2] | Gabriel Oaxaca MD[2] | Susan Armstrong MD, PhD[2] | Jennifer Ko MD, PhD[2] | Steven Billings MD[2]

J Cutan Pathol. 2024;51:70–75.





J Cutan Pathol. 2024;51:70–75.

Collagenous fibroma (desmoplastic fibroblastoma) with a new translocation involving 11q12: a case report

Amin Maghari[a,*], Naili Ma[a], Seena Aisner[a], Joseph Benevenia[b], Meera Hameed[a]

Cancer Genetics and Cytogenetics 192 (2009) 73–75

Translocation (2;11)(q31;q12) is recurrent in collagenous fibroma (desmoplastic fibroblastoma)

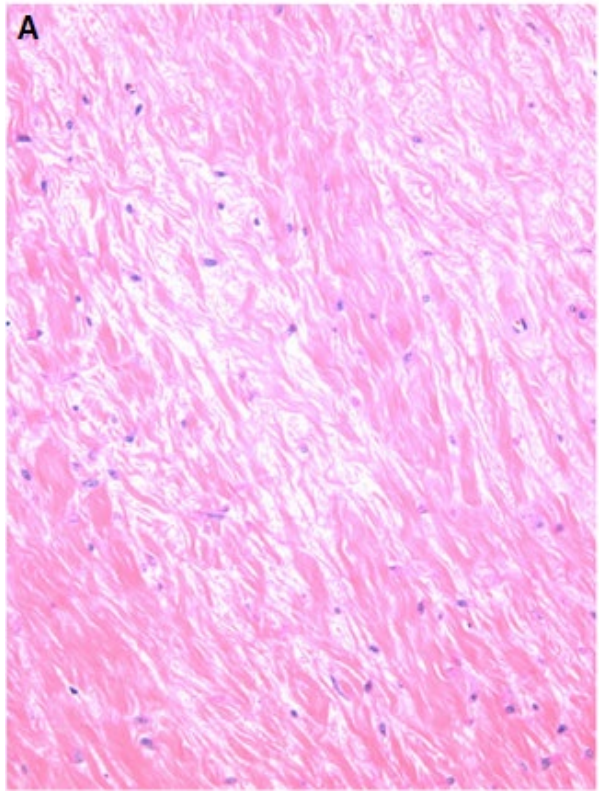
Kerry Bernal[a], Marilu Nelson[b], James R. Neff[a,c], Stephen M. Nielsen[a,d], Julia A. Bridge[a,b,c,*]

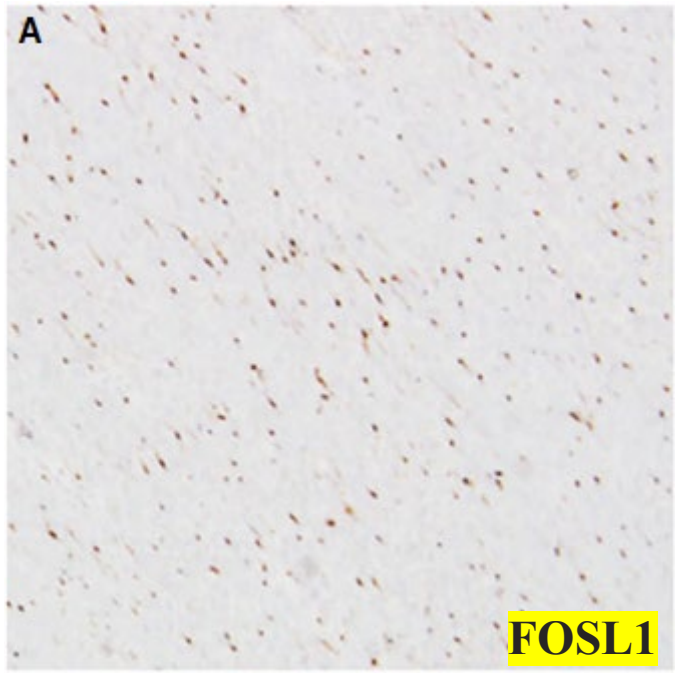
Cancer Genetics and Cytogenetics 149 (2004) 161–163

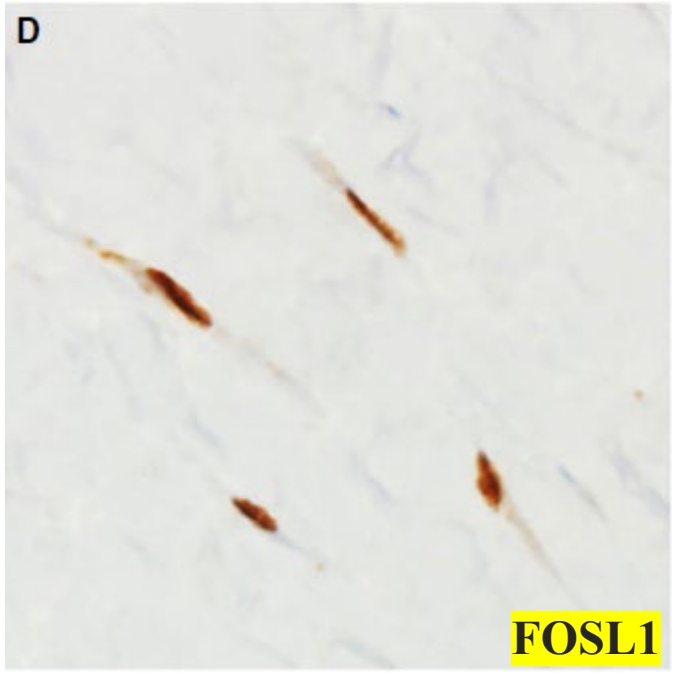
FOSL1 immunohistochemistry clarifies the distinction between desmoplastic fibroblastoma and fibroma of tendon sheath

Ikuma Kato,[1,2] Akihiko Yoshida,[3,4] Masachika Ikegami,[5] Tomotake Okuma,[5] Akiko Tonooka,[1] Shinichiro Horiguchi,[1] Nobuaki Funata,[1] Akira Kawai,[4,6] Takahiro Goto,[5] Tsunekazu Hishima,[1] Ichiro Aoki[2] & Toru Motoi[1]

Histopathology 2016, **69**, 1012–1020. DOI: 10.1111/his.13042







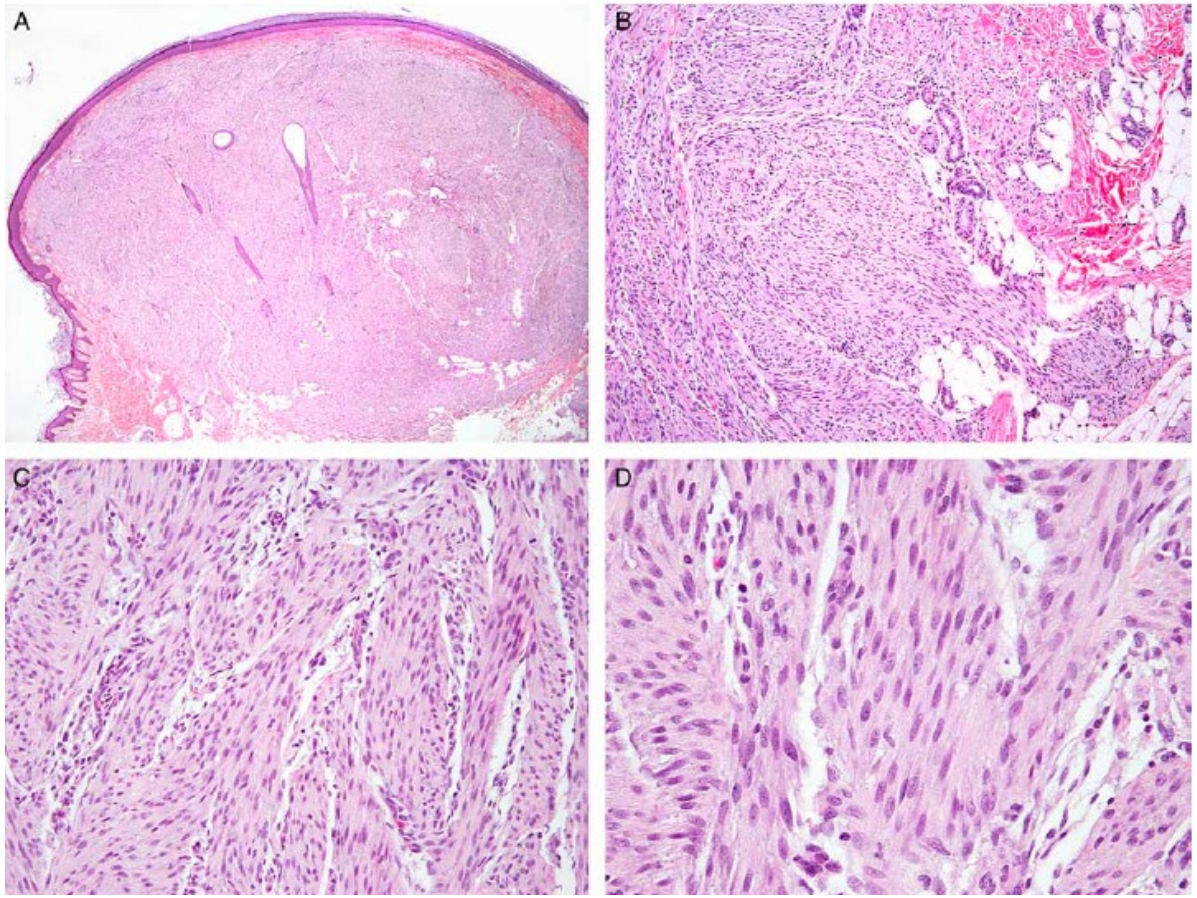
EWSR1::SMAD3-rearranged fibroblastic tumor

Novel *EWSR1-SMAD3* Gene Fusions in a Group of Acral Fibroblastic Spindle Cell Neoplasms

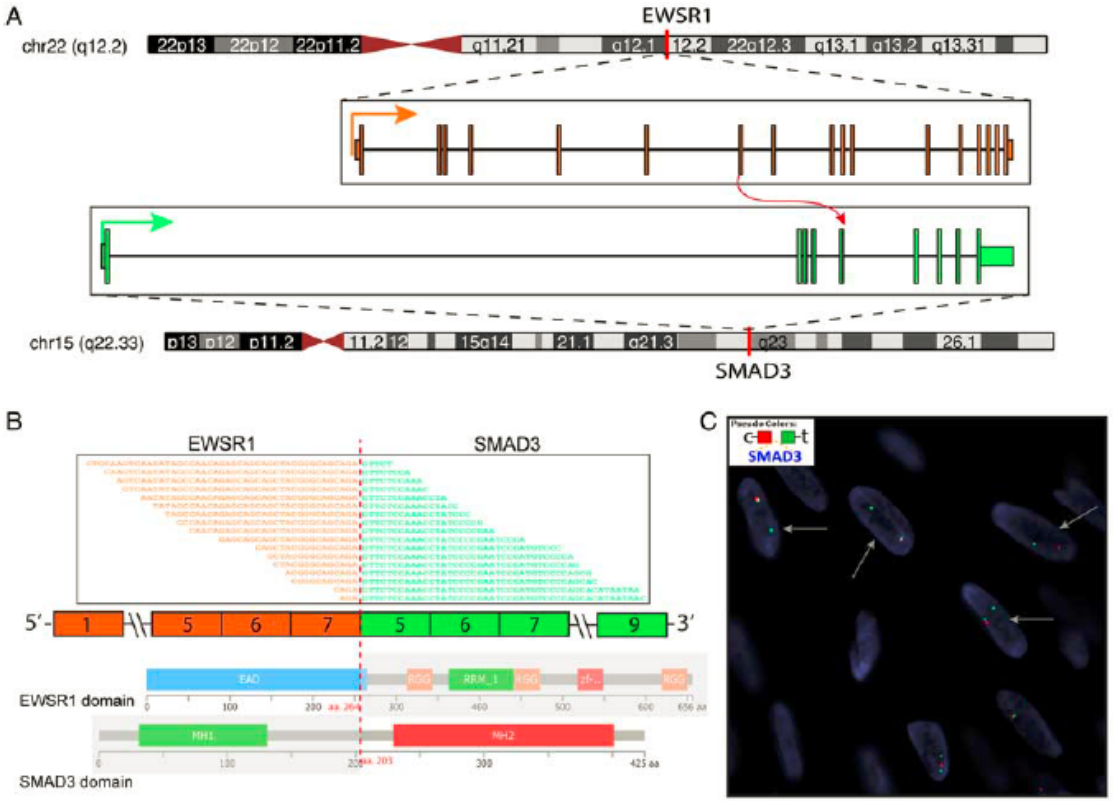
Yu-Chien Kao, MD, Uta Flucke, MD, PhD,† Astrid Eijkelenboom, PhD,† Lei Zhang, MD,‡ Yun-Shao Sung, MSc,‡ Albert J.H. Suurmeijer, MD, PhD,§ and Cristina R. Antonescu, MD‡*

(*Am J Surg Pathol* 2018;00:000–000)

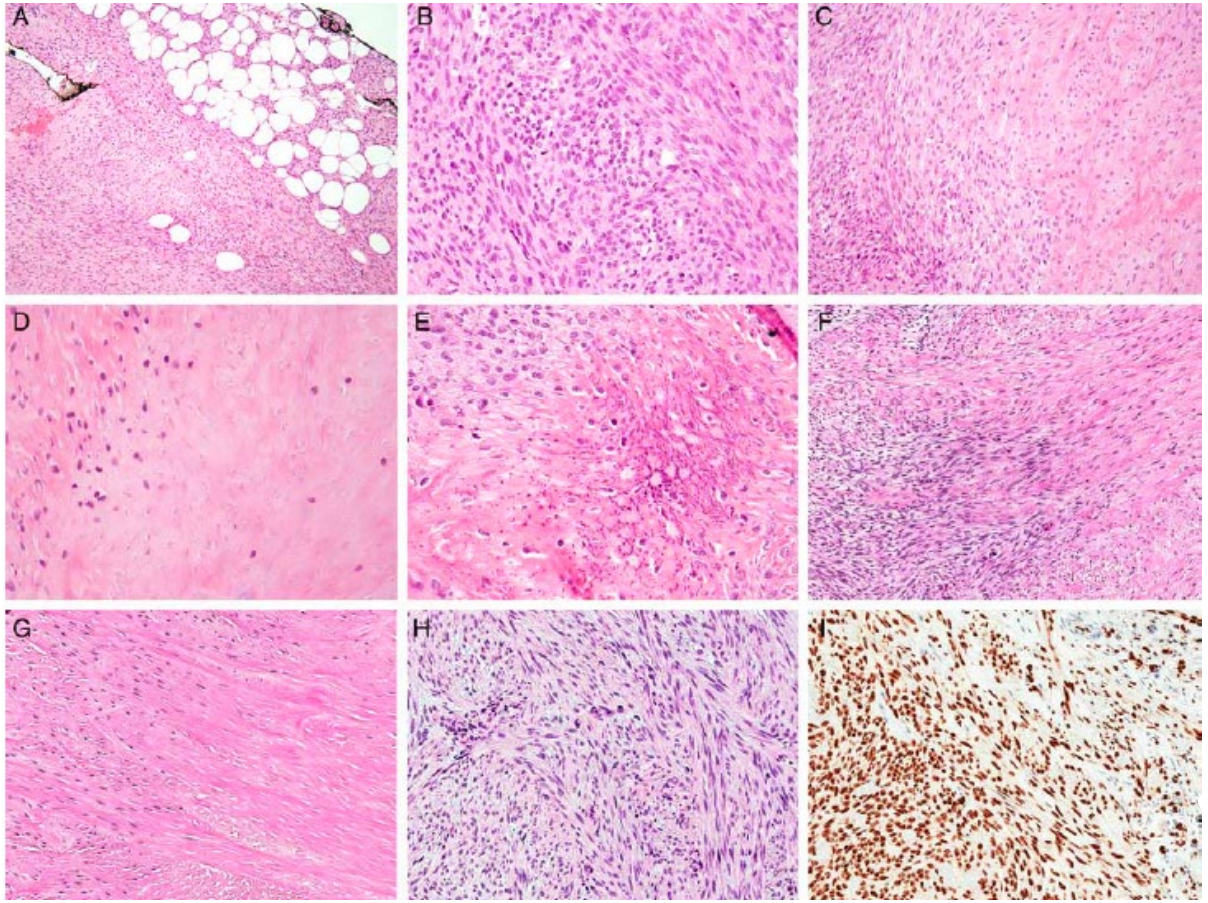
Case #	Age (y)/Sex	Location	Depth	Size (cm)	Immunohistochemistry				Follow-up
					ERG	CD34	SMA	S100	
1	1/M	Heel	Dermis and subcutis	1.0	+	−	−	−	LR (14 mo)
2	61/F	Foot	Subcutis	2.0	+	−	−	−	NA
3	58/F	Toe	Dermis and subcutis	1.1	+	−	−	−	LR (5 mo)



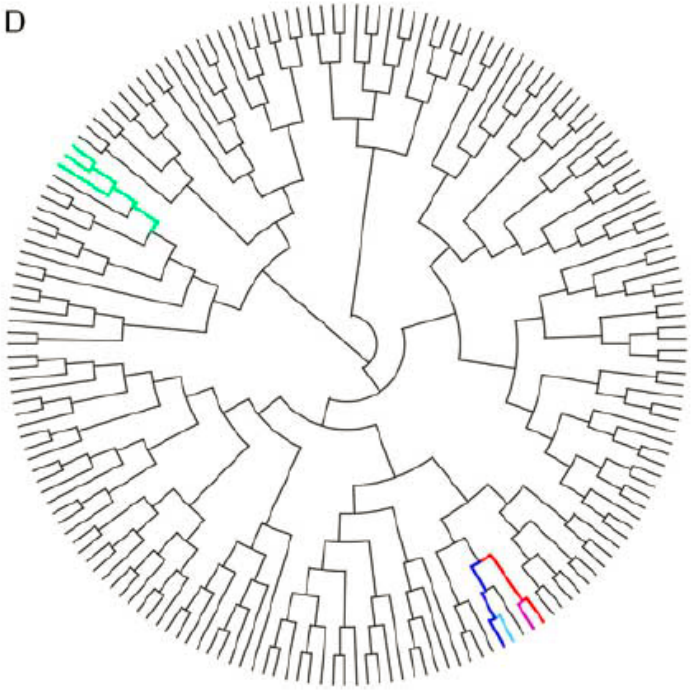
(*Am J Surg Pathol* 2018;00:000–000)

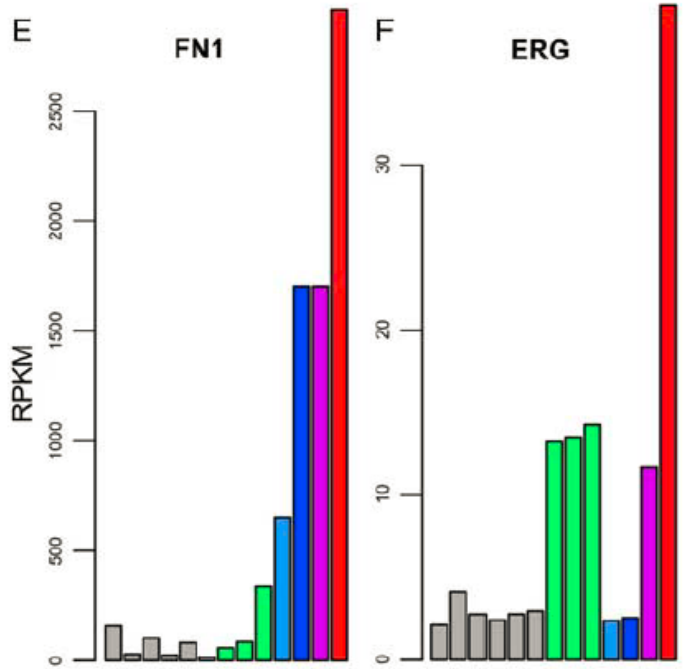


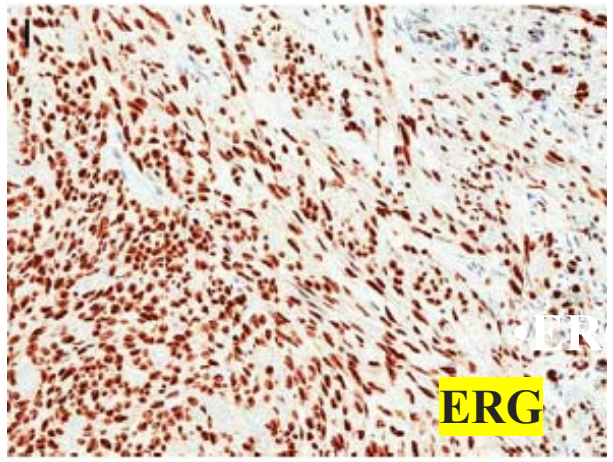
(*Am J Surg Pathol* 2018;00:000–000)



(*Am J Surg Pathol* 2018;00:000–000)







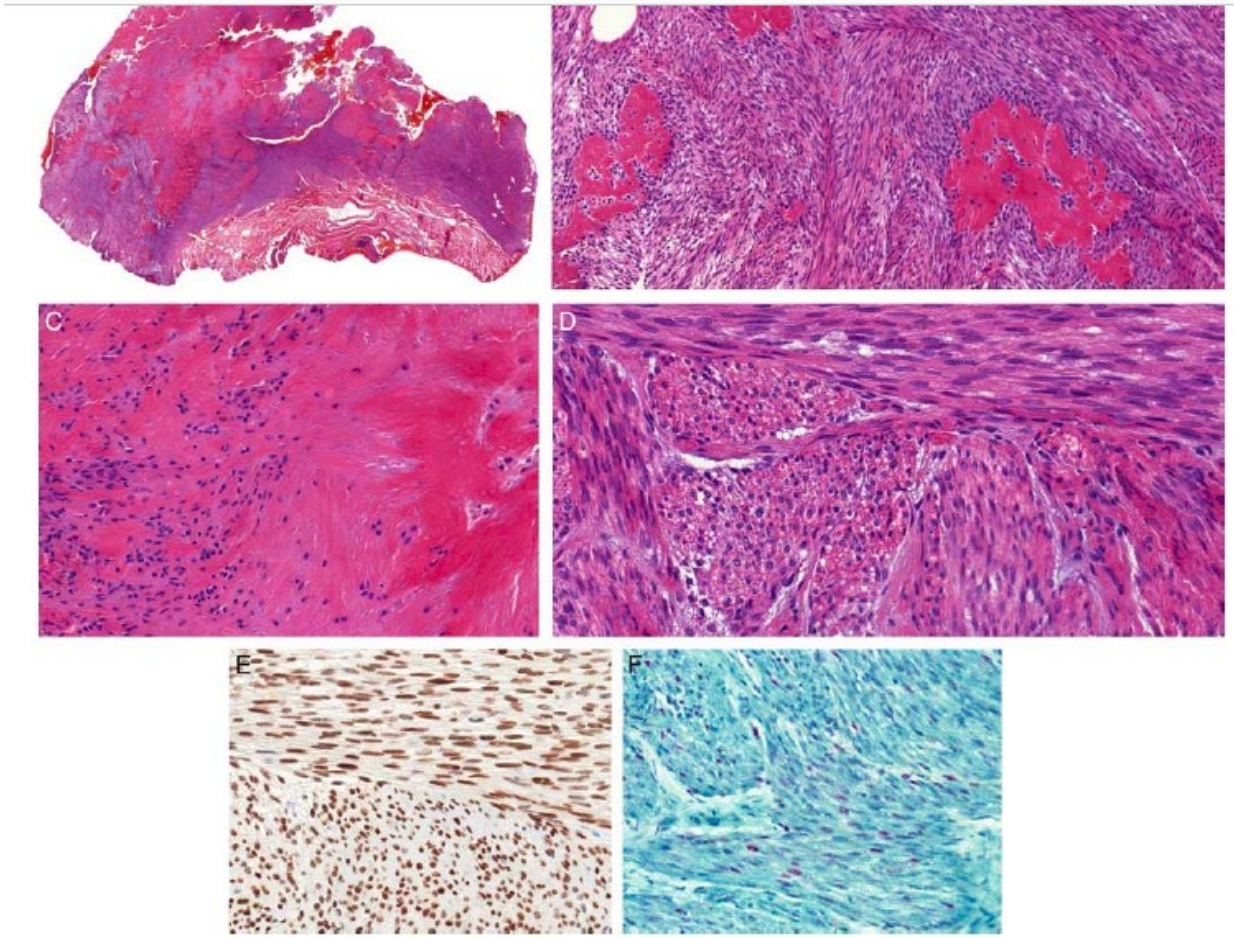
(*Am J Surg Pathol* 2018;00:000–000)

EWSR1-SMAD3–rearranged Fibroblastic Tumor

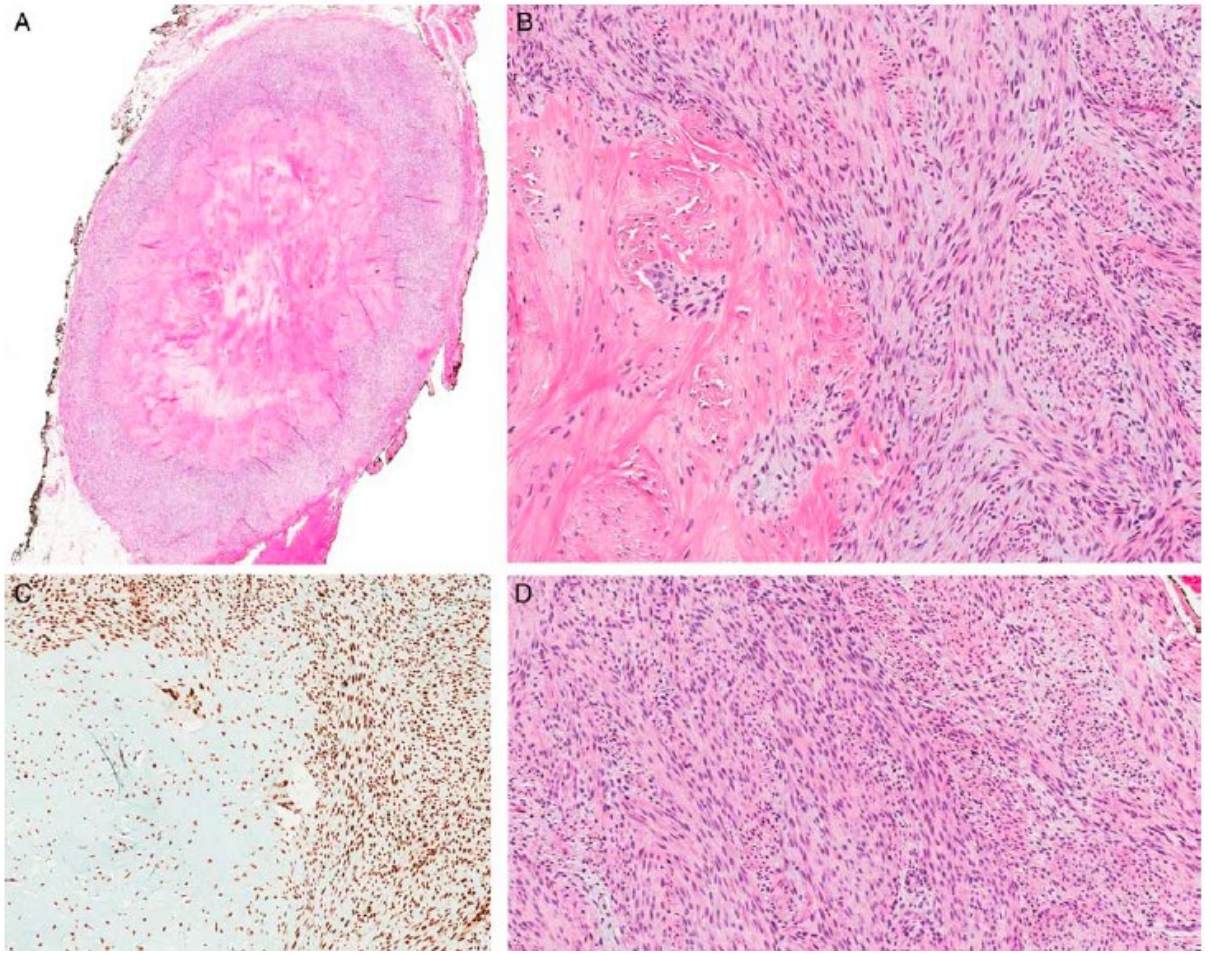
An Emerging Entity in an Increasingly More Complex Group of Fibroblastic/Myofibroblastic Neoplasms

Michael Michal, MD,†‡ Ryan S. Berry, MD,§ Brian P. Rubin, MD,§ Scott E. Kilpatrick, MD,§ Abbas Agaimy, MD,‖ Dmitry V. Kazakov, MD,*‡ Petr Steiner, MD,*‡ Nikola Ptakova, MSc,*‡ Petr Martinek, PhD,*‡ Ladislav Hadravsky, PhD,¶ Kvetoslava Michalova, PhD,*‡ Zoltan Szep, PhD,# and Michal Michal, MD*‡*

Case	Sex/ Age (y)	Location	Duration	Size (cm)	FISH	NGS	IHC +	IHC −	Recurrence	Length of FU (y)	Original Diagnosis	Comment
1	F/5 and 15	Hand—palm	3 y	1.2 and 0.3	NA	*EWSR1-SMAD3*	ERG in both; focal SAT-B2 staining in the 2nd tumor, negative in the first tumor	SOX-10; S100; EMA; CD34; SMA; Actin E; Desmin; SAT-B2; OSCAR; Pan-TRK; SAT-B2	Yes in 10 y	18	Unusual lipofibroma-tosis	Incomplete excision in both the original tumor and the reexcision
2	F/68	Interphalangeal joint of the thumb	10 months	1.5×0.7×0.5	NA	*EWSR1-SMAD3*	ERG, focal SAT-B2 staining	SOX-10; S100; CD34; EMA; Desmin; OSCAR; HMB45	No	10	Unusual fibromatosis	Incomplete excision but no recurrence
3	F/39	Calf	NA	1×0.5×0,5	NA	NA	ERG	S100; EMA; CD34; SMA; Desmin; OSCAR; AE1/3 Synaptophysin; Chromogranin; CD117; DOG-1	No	7	Benign plexiform spindle cell tumor	Early reexcision —no additional tumor tissue
4	F/34	Left foot—dorsal metatarsal aspect	NA	1.1×0.8×0.5	Positive	*EWSR1-SMAD3*	ERG	SOX-10; S100; EMA; CD34; SMA; Desmin; Caldesmon; AE1/3; Beta	Recent case	Recent	Unusual myofibroma	Slowly enlarging, painful, no history of trauma



(*Am J Surg Pathol* 2018;42:1325–1333)



(*Am J Surg Pathol* 2018;42:1325–1333)

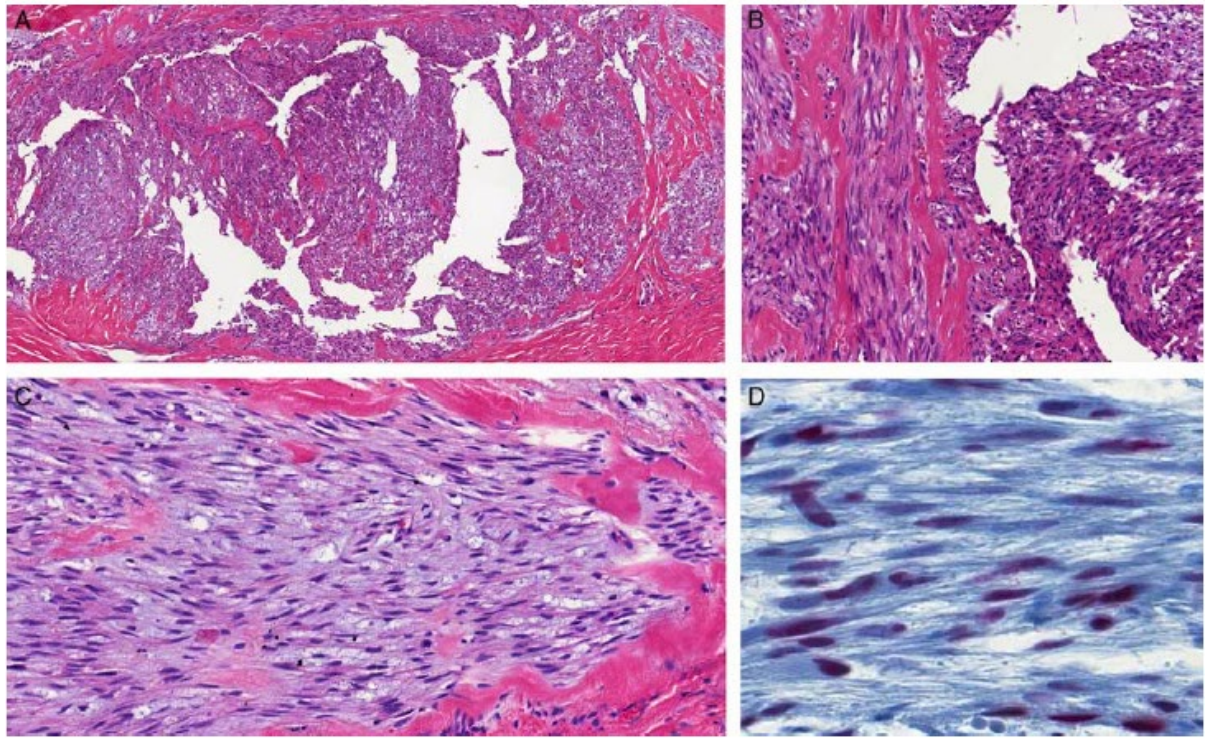


TABLE 2. ERG Immunohistochemical Staining Characteristics of ESFT Mimics

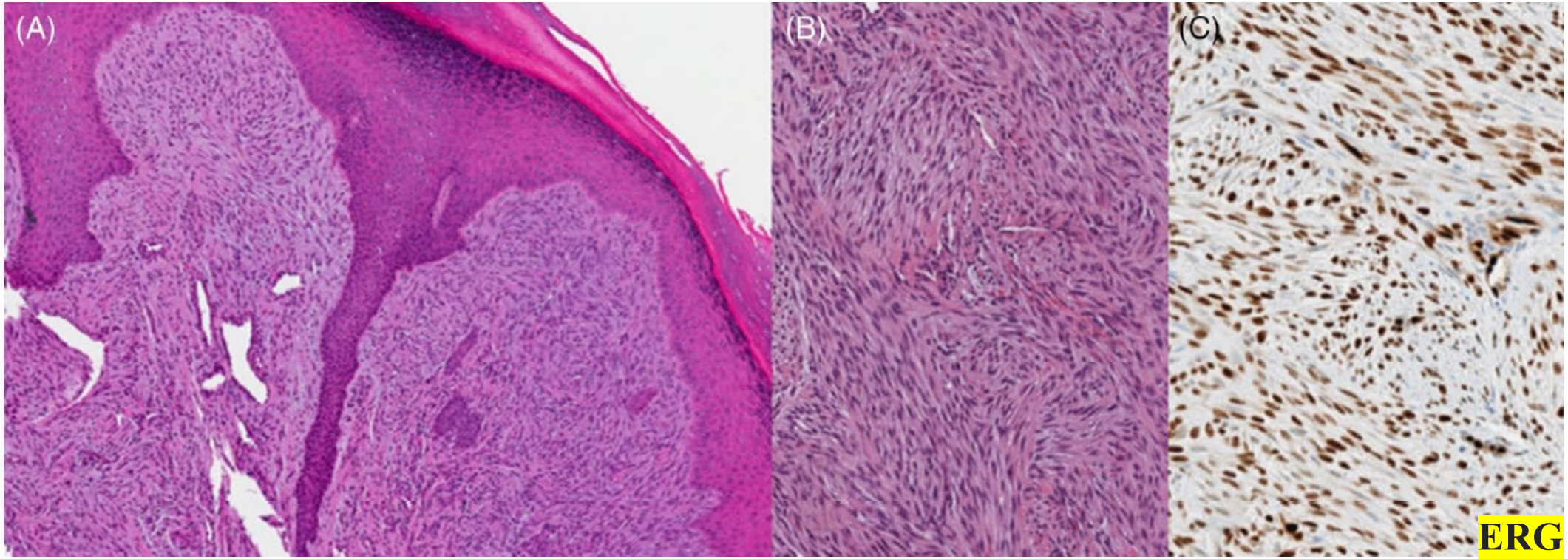
Tumor (Acronym Used in the Text)	ERG Staining: Positive/ Tested Cases (Literature Data)
Lipofibromatosis (LPF)	0/3
Calcifying aponeurotic fibroma (CAF)	9/10 weak to moderate expression*
Lipofibromatosis-like neural tumor (LFLNT)	NA
Myofibroma/myofibromatosis (MF)	0/8 (ref. 3—0/9)
Infantile digital fibroma/ fibromatosis	0/1
Palmar/plantar fibromatosis	0/6 (ref. 3—data for desmoid-type fibromatosis—0/19)
Monophasic synovial sarcoma (MSS)	0/5 (ref. 3—0/36)

(*Am J Surg Pathol* 2018;42:1325–1333)

EWSR1-SMAD3 rearranged fibroblastic tumor: Case series and review

Omar Habeeb MD[1] | Katelen E. Korty DO[2] | Elizabeth M. Azzato MD, PhD[2] | Caroline Astbury PhD[2] | Daniel H. Farkas PhD, HCLD[2] | Jennifer S. Ko MD, PhD[2] | Steven D. Billings MD[2]

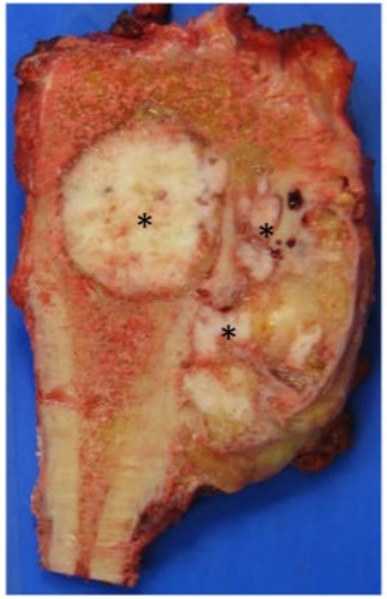
J Cutan Pathol. 2021;48:255–262.

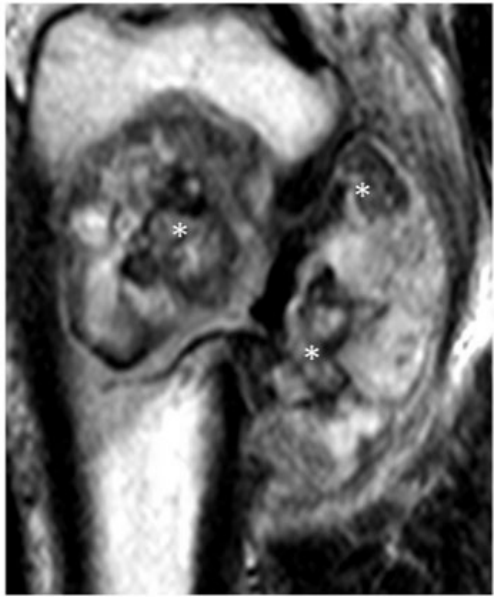


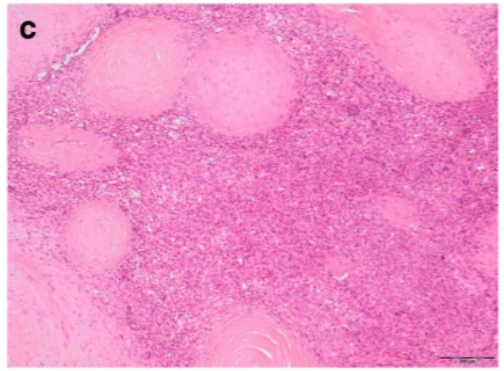
CASE REPORT

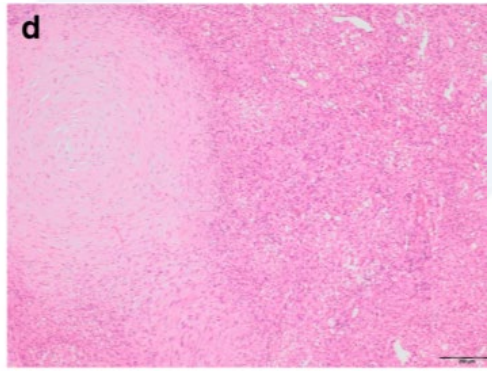
EWSR1-SMAD3 fibroblastic tumour of bone: expanding the clinical spectrum

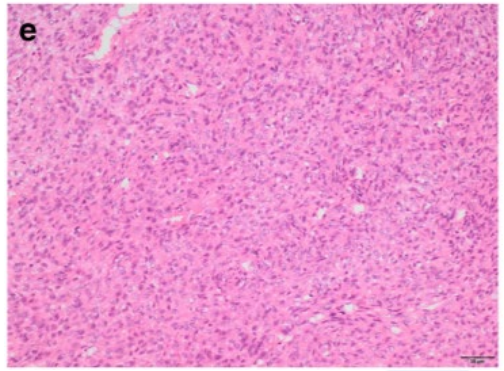
Solange De Noon [1] · Adrienne M Flanagan [1,2] · Roberto Tirabosco [1] · Paul O'Donnell [3,4] · Fernanda Amary [1,2]

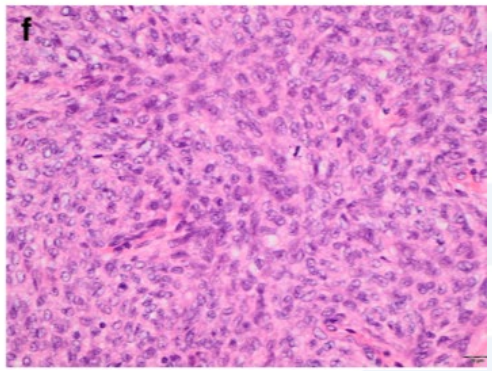












Skeletal Radiology (2021) 50:445–450

A A A
Definition
ICD-O coding
ICD-11 coding
Related terminology
Subtype(s)
Localization
Clinical features
Epidemiology
Etiology
Pathogenesis
Macroscopic appearance
Histopathology
Cytology
Diagnostic molecular pathology
Essential and desirable diagnostic criteria
Staging
Prognosis and prediction

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EWSR1::SMAD3 rearranged fibroblastic tumour

Definition
EWSR1::SMAD3 rearranged fibroblastic tumour is a distinct benign fibroblastic neoplasm with strong predilection for hands and feet.

ICD-O coding
None

ICD-11 coding
2B53.Y Other specified fibroblastic or myofibroblastic tumour, primary site

Related terminology
Acceptable: EWSR1::SMAD3 positive fibroblastic tumour

Subtype(s)
None.

Localization
Tumours are superficially located within the dermis and/or subcutaneous fat. Dermal involvement may abut the epidermis. The large majority occur in hands and feet { 29957732 ; 29309308 }, while lower extremity represents the most common nonacral site { 32901982 }.

Clinical features
Patients usually present with a small painless superficial tumour in acral sites.

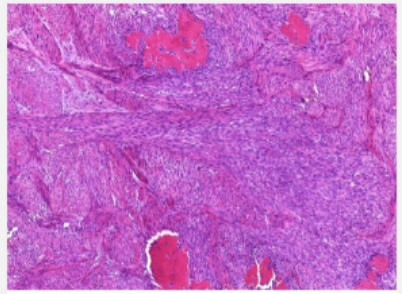
Epidemiology
EWSR1::SMAD3 rearranged fibroblastic tumours are rare, with <20 reported to date. Patients have a wide age range (1-68 years, median 39 years) and most are female (4:1) { 32901982 }.

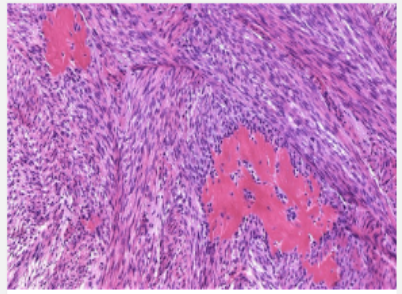
Etiology
Unknown.

Pathogenesis
SMAD3 is an important signal transducer in the TGF-β/Smad signaling pathway, which is involved in extracellular matrix synthesis by fibroblasts.

Macroscopic appearance
Tumours are relatively small, measuring 10 - 20 mm in largest dimension, with a nodular appearance.

Histopathology
These tumours are typically well demarcated, but can infiltrate subcutaneous fat. In particular, in adults, the acellular centre of the tumour appears hyalinized, which can resemble collagen rosettes. The peripheral zones consist of intersecting cellular fascicles of fibroblastic spindle cells within collagenous to more myxoid stroma. However, about half lack this zonation pattern. Lesional cells lack nuclear pleomorphism, hyperchromasia, prominent nucleoli and mitotic activity. Myopericytomatous growth is rare. There may be focal stippled dystrophic calcification { 29309308 ; 29957732 ; 32901982 }.
By immunohistochemistry, the fibroblastic tumour cells consistently show strong diffuse nuclear ERG expression, whereas SMA and CD34 are negative. When *EWSR1* rearrangement is detected by FISH, a myoepithelial tumour may be considered in the differential diagnosis. However, IHC for cytokeratins, EMA, S100 and SOX10 is negative.


#32453
EWSR1::SMAD3 fusion positive fibroblastic tumour


#32454
EWSR1::SMAD3 fusion positive fibroblastic tumour

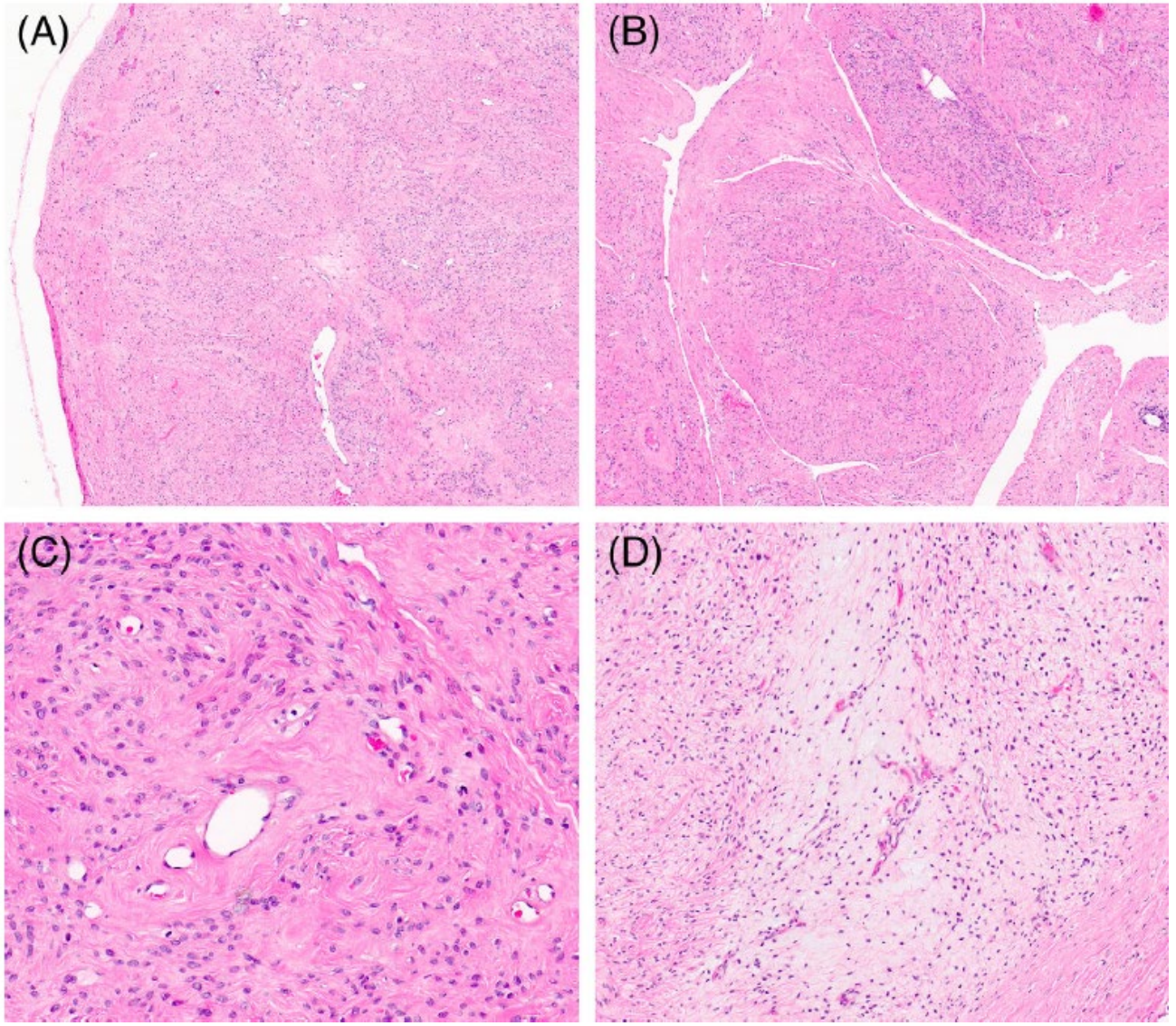
PRRX::NCOA1/2 rearranged-fibroblastic tumor

PRRX-NCOA1/2 rearrangement characterizes a distinctive fibroblastic neoplasm

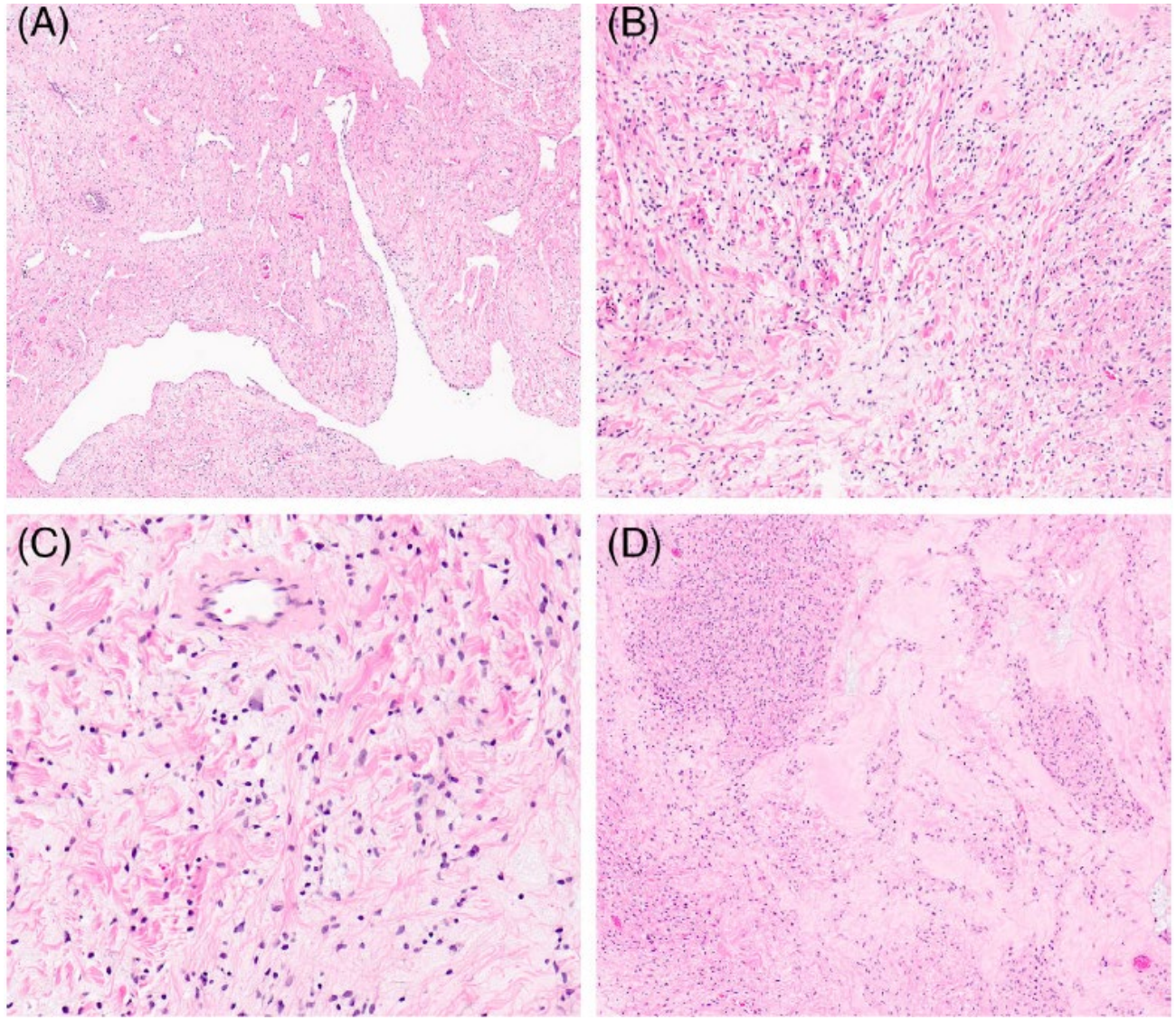
Maribel D. Lacambra[1] | Ilan Weinreb[2,3] | Elizabeth G. Demicco[3,4] | Chit Chow[1] | Yun-Shao Sung[5] | David Swanson[2,3] | Ka-Fai To[1] | Kwok-Chuen Wong[6] | Cristina R. Antonescu[5] | Brendan C. Dickson[3,4]

Genes Chromosomes Cancer. 2019;58:705–712

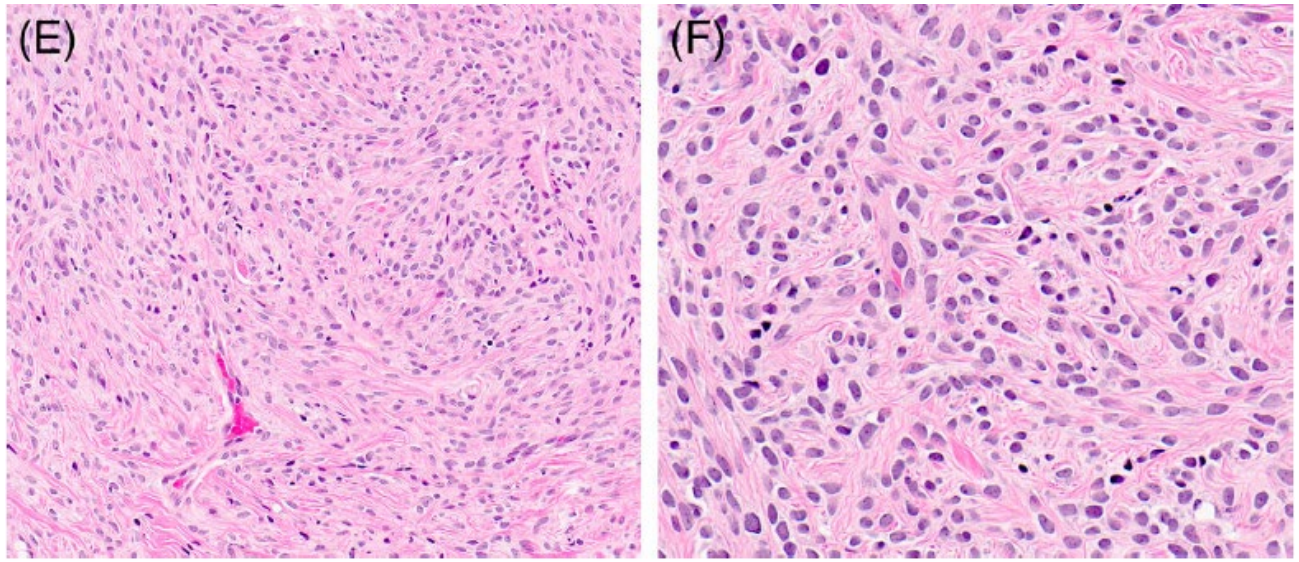
Patient	Age (y)	Sex	Location	Size (cm)	Depth	Fusion gene	
1	55	F	Thigh	4	Subcutis	*PRRX1* exon 1	*NCOA1* exon 13
2	33	M	Neck	14	Subcutis	*PRRX1* exon 1	*NCOA1* exon 13
3	43	F	Neck	3	Subcutis	*PRRX1* exon 1	*NCOA1* exon 13
4	21	F	Groin	2	Subcutis	*PRRX1* exon 1	*NCOA2* exon 15

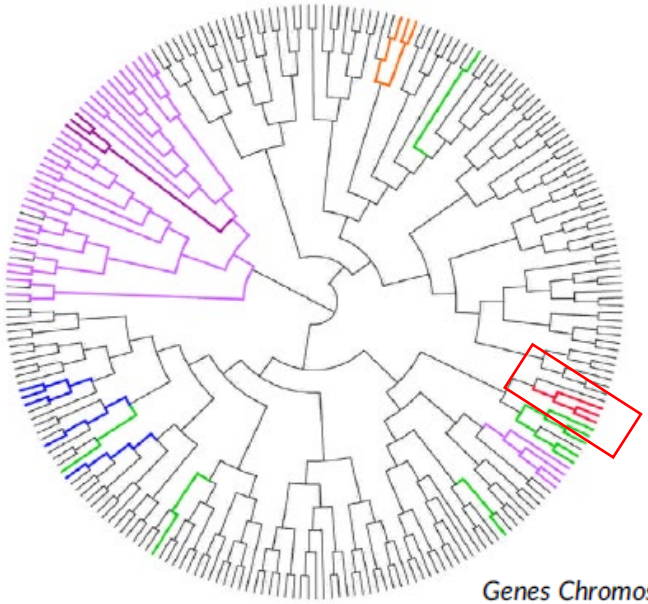


Genes Chromosomes Cancer. 2019;58:705–712



Genes Chromosomes Cancer. 2019;58:705–712





Genes Chromosomes Cancer. 2019;58:705–712

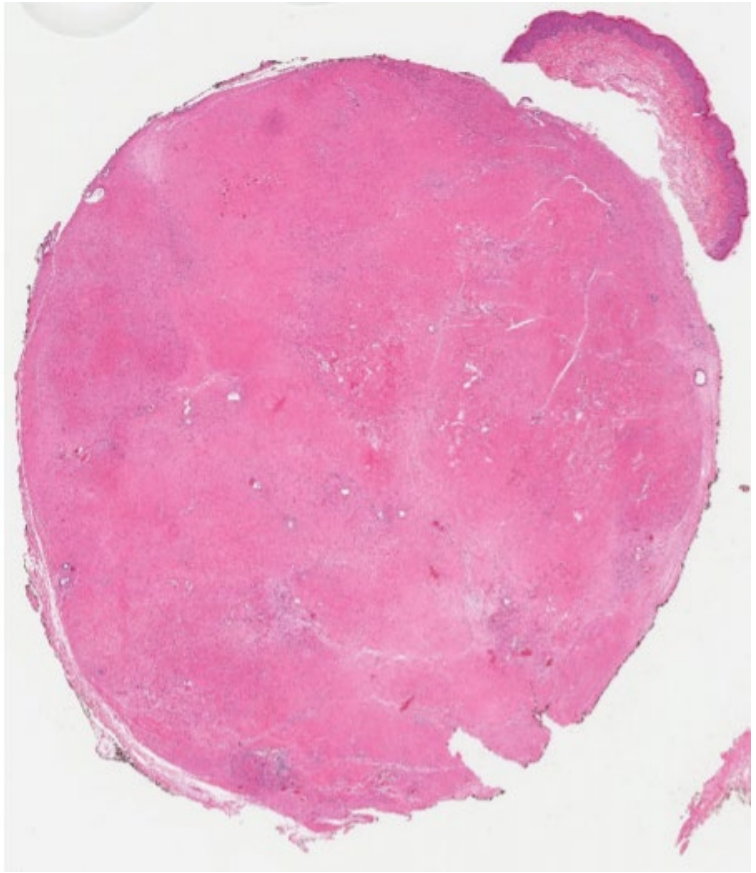
Histopathology

Histopathology 2021 DOI: 10.1111/his.14454

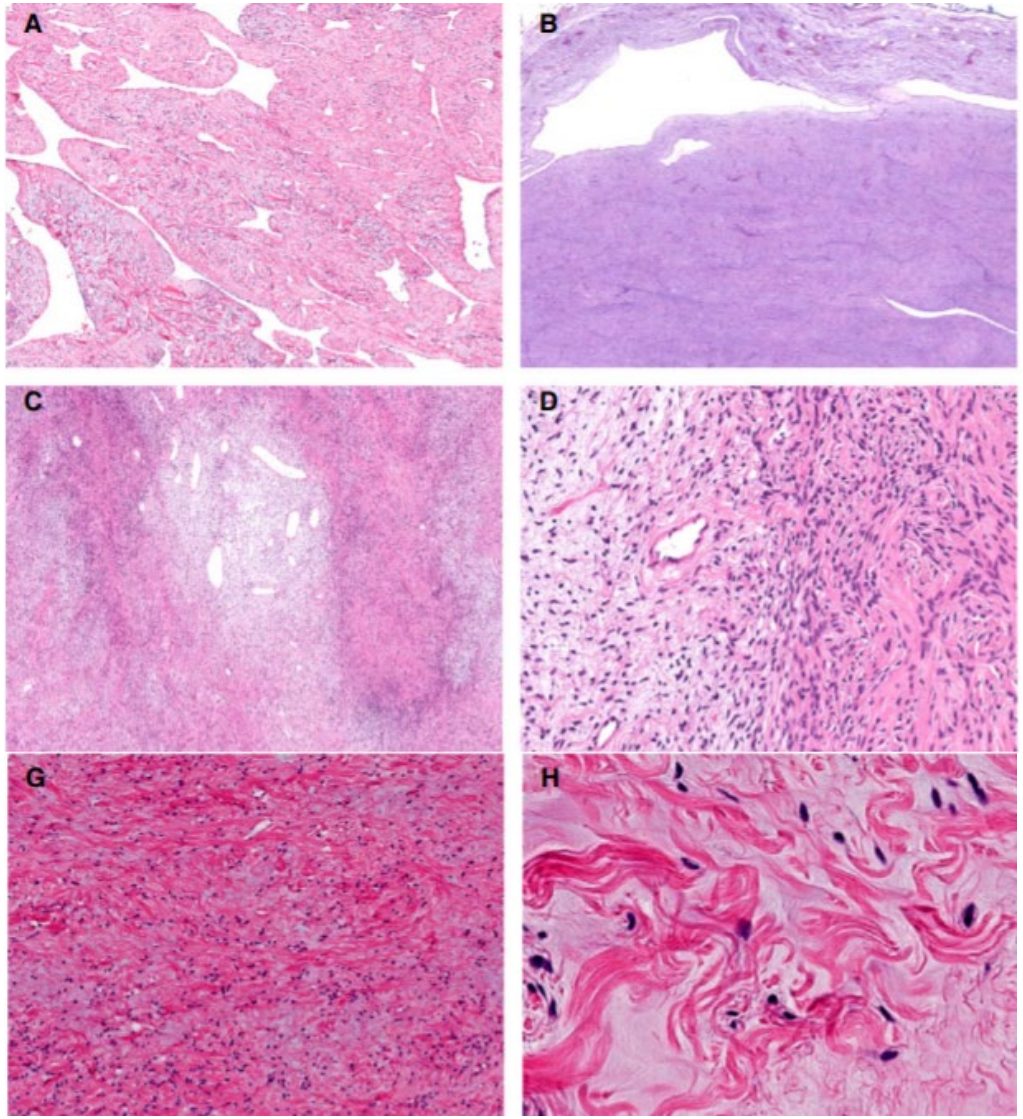
PRRX1–NCOA1-rearranged fibroblastic tumour: a clinicopathological, immunohistochemical and molecular genetic study of six cases of a potentially under-recognised, distinctive mesenchymal tumour

Josephine K Dermawan,[1] Elizabeth M Azzato,[1] Judith Jebastin Thangaiah,[2] Sandra Gjorgova-Gjeorgievski,[1] Brian P Rubin,[1] Andrew L Folpe,[2] Abbas Agaimy[3] & Karen J Fritchie[1]

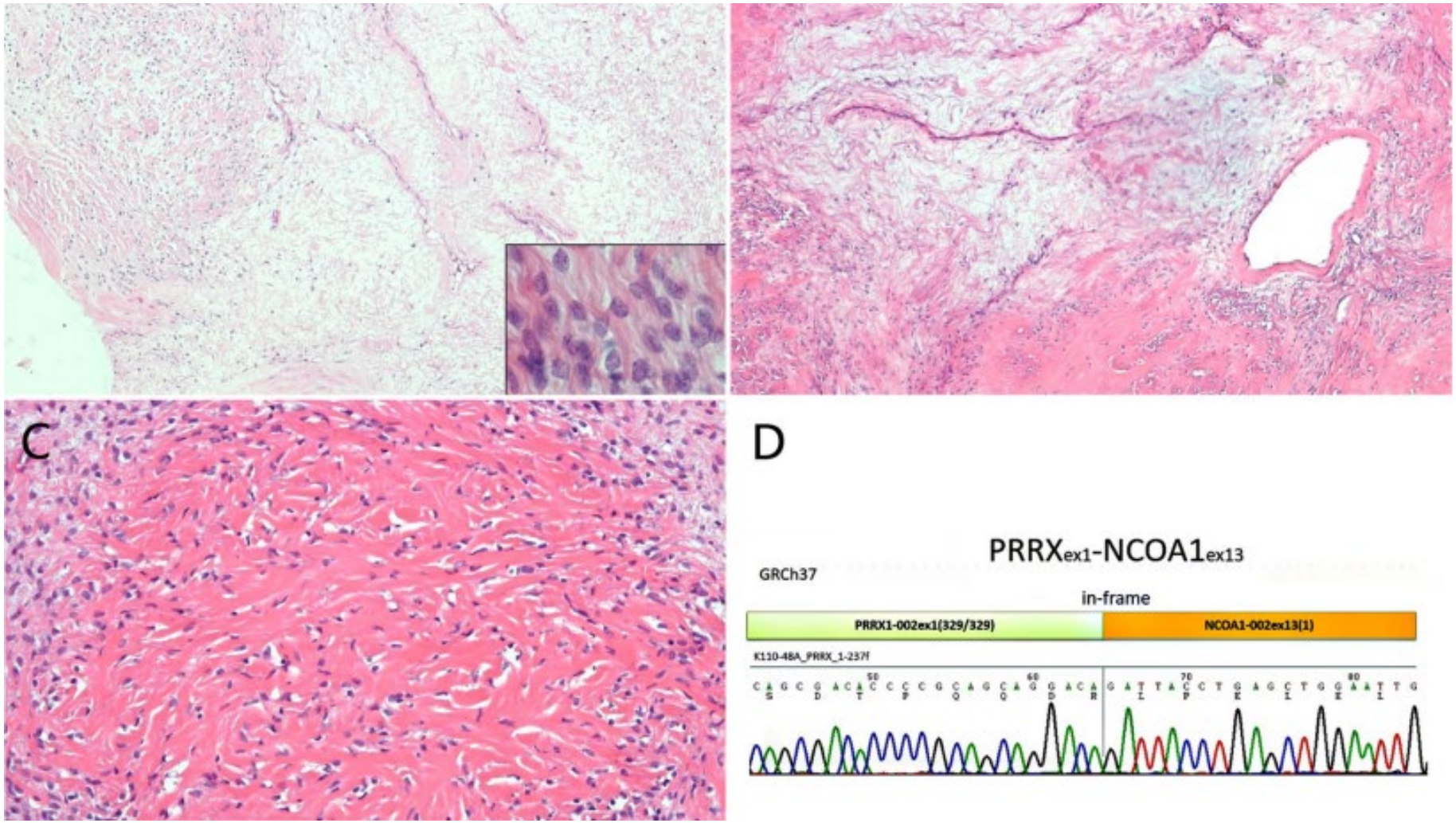
Case	Age (years)	Sex	Location	Depth	Size (mm)	Outcome	Follow-up period (months)	Negative immunohistochemical markers
1	49	M	Abdominal wall	Subcutaneous	40	ANED	2	CD34, SMA, desmin, S100, AE1/AE3, MUC4, STAT6
2	43	M	Right axilla*	Subcutaneous	55	ANED	3	CD34, SMA, desmin, S100, AE1/AE3, MUC4, STAT6, ER
3	34	F	Right shoulder	Subcutaneous	NA	NA	NA	Desmin, S100, MUC4, ALK D5F3, β-catenin; Rb1 retained
4	41	F	Abdominal wall	Subcutaneous	40	NA	NA	CD34, SMA, desmin, H-caldesmon, S100, SOX10, EMA, MUC4, STAT6, ALK1, ER, PR, CD31, MDM2; Rb1 retained
5	76	F	Abdominal wall†	Subcutaneous	26	ANED	1	CD34, muscle cocktail, desmin, S100, SOX10, MUC4, STAT6, ER, PAX8
6	20	M	Right lateral hip	Subcutaneous	50	ANED	1.5	CD34, SMA, myogenin, MyoD1, S100, HMB45, MUC4, STAT6, ALK1



Histopathology 2021 DOI: 10.1111/his.14454



Histopathology 2021 DOI: 10.1111/his.14454



Virchows Archiv (2022) 481:111–116

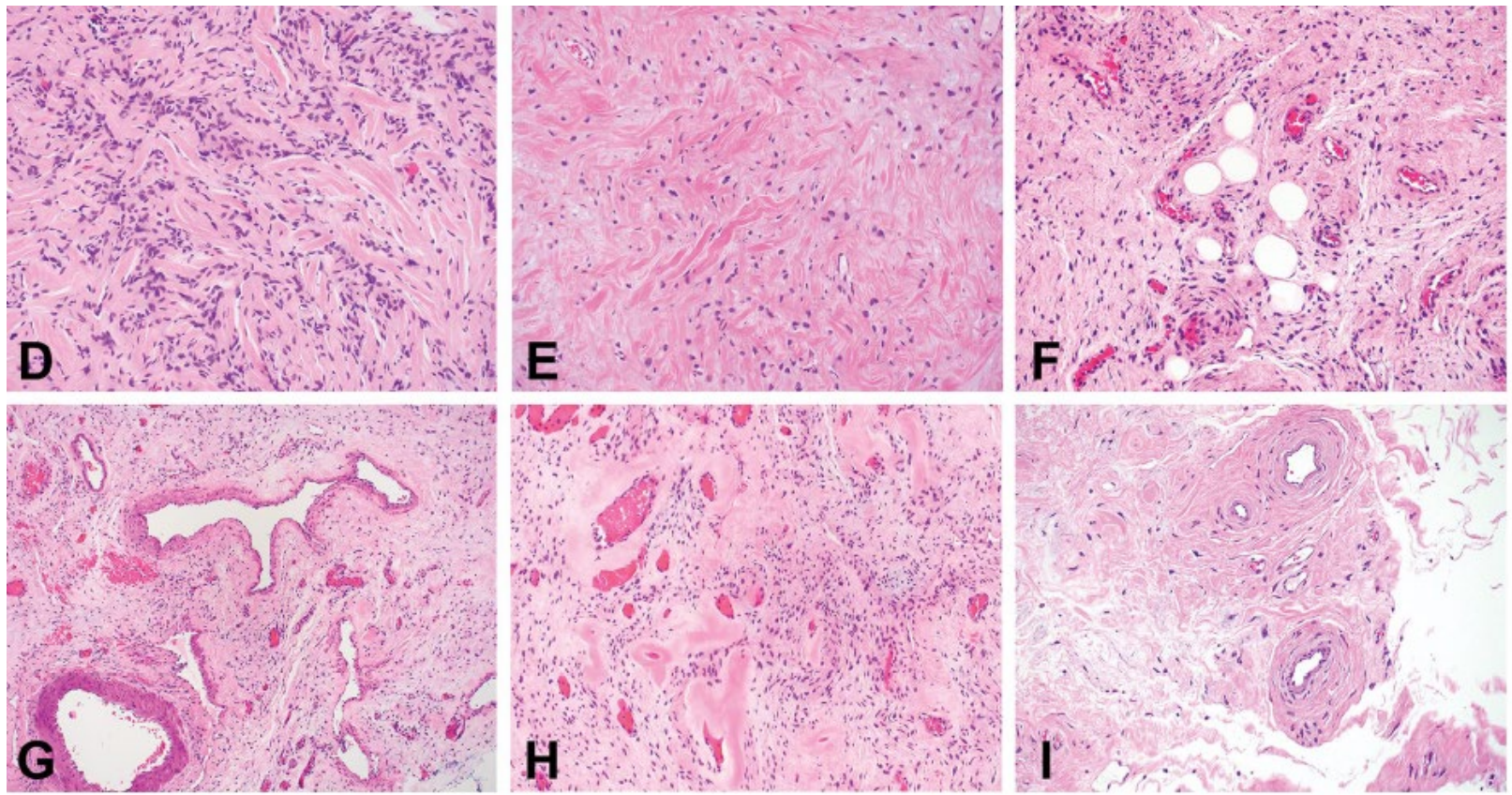
Patient	Age (y)	Sex	Location	Size (cm)	Depth	Fusion gene	Outcome	Follow-up period (months)	Ref
1	55	F	Thigh	4.0	Subcutis	*PRRX1* exon 1-*NCOA1* exon 13	ANED	24	Lacambra et al. [1]
2	33	M	Neck	14.0	Subcutis	*PRRX1* exon 1-*NCOA1* exon 13	ANED	6–18	
3	43	F	Neck	3.0	Subcutis	*PRRX1* exon 1-*NCOA1* exon 13	ANED	6–18	
4	21	F	Groin	2.0	Subcutis	*PRRX1* exon 1-*NCOA2* exon 15	ANED	6–18	
5	49	M	Abdominal wall	4.0	Subcutis	*PRRX1* exon 1-*NCOA1* exon 13	ANED	2	Dermawan et al. [2]
6	43	M	Axilla	5.5	Subcutis	*PRRX1* exon 1-*NCOA1* exon 13	ANED	3	
7	34	F	Shoulder	N/A	Subcutis	*PRRX1* exon 1-*NCOA1* exon 13	N/A	N/A	
8	41	F	Abdominal wall	4.0	Subcutis	*PRRX1* exon 1-*NCOA1* exon 13	N/A	N/A	
9	76	F	Abdominal wall	2.6	Subcutis	*PRRX1* exon 1-*NCOA1* exon 13	ANED	1	
10	20	M	Hip	5.0	Subcutis	*PRRX1* exon 1-*NCOA1* exon 13	ANED	1.5	
11	23	M	Scalp	2.9	Subcutis	*PRRX1* exon 1-*NCOA1* exon 13	ANED	26	Our cases
12	46	M	Groin	5.0	Subcutis	*PRRX1* exon 1-*NCOA1* exon 13	ANED	7	

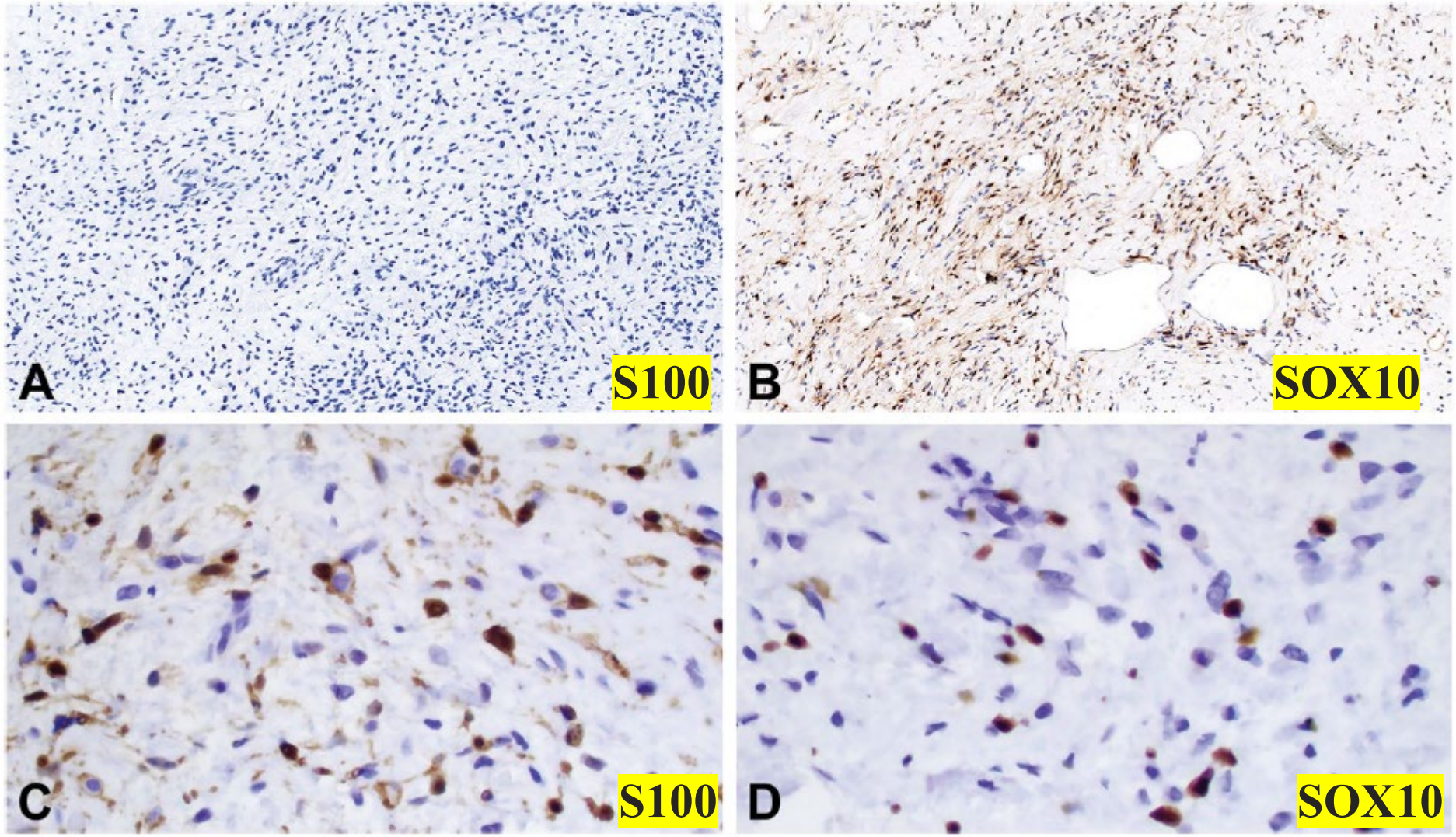
Virchows Archiv (2022) 481:111–116

"*PRRX1*-rearranged mesenchymal tumors": expanding the immunohistochemical profile and molecular spectrum of a recently described entity with the proposed revision of nomenclature

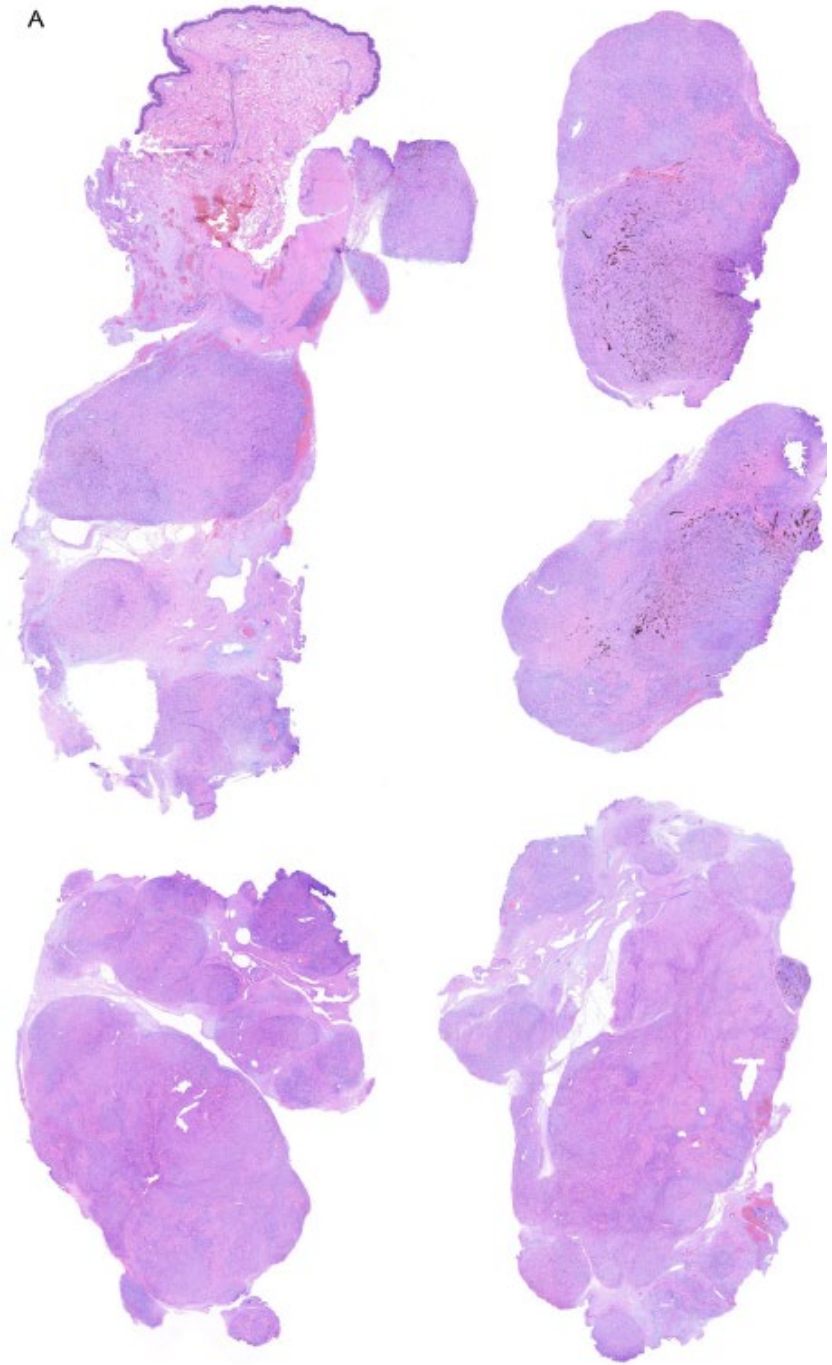
Laura M. Warmke[1] · Michael Michal[2,3] · Petr Martínek[3] · Abbas Agaimy[4] · Nasir Ud Din[5] · Raul Perret[6] · Isabelle Hostein[6] · François Le Loarer[6,7] · Lysandra Voltaggio[8] · John M. Gross[8]

Virchows Archiv (2023) 483:207–214





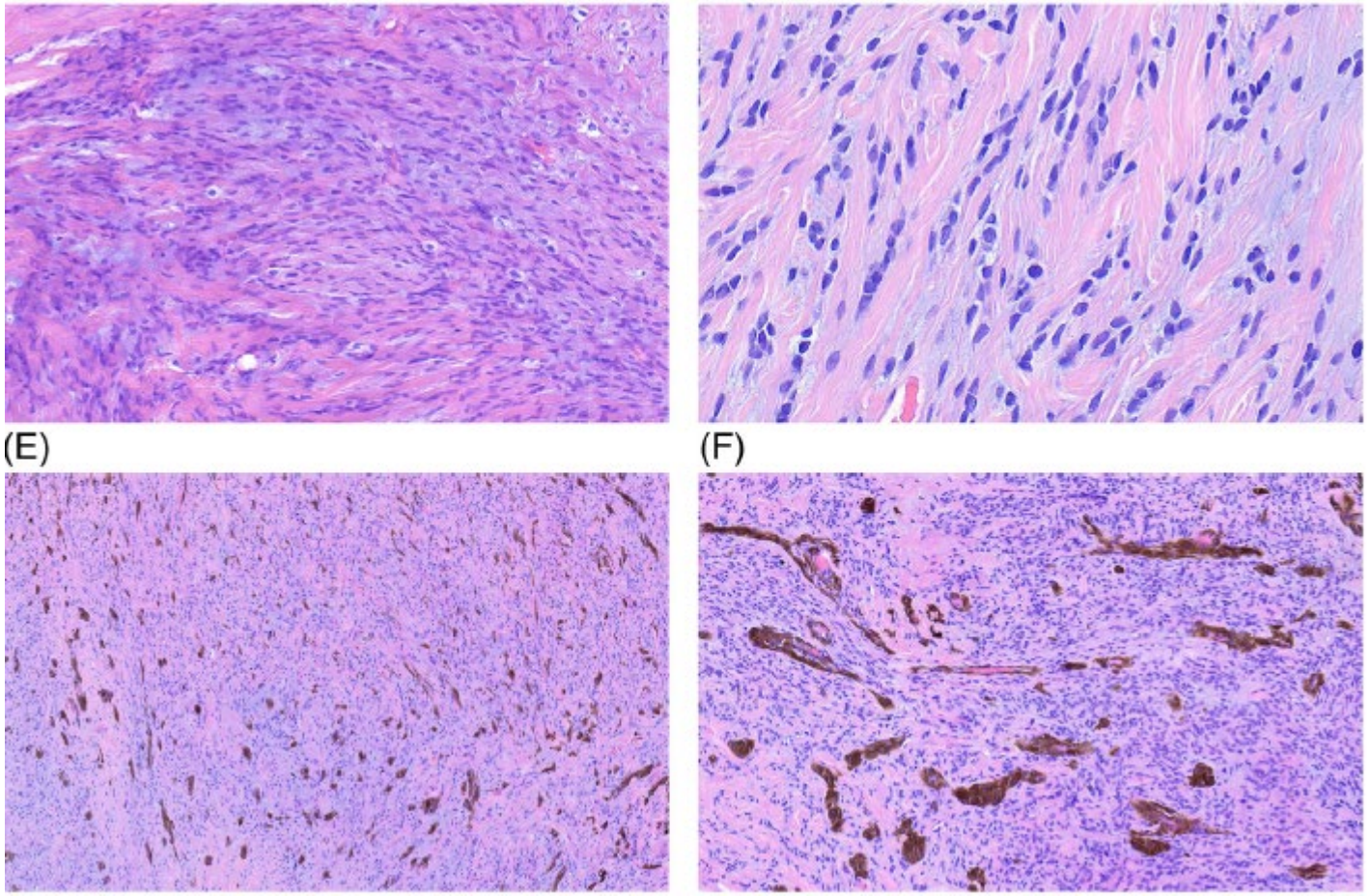
17	65/F	Chest wall (intramuscular)	4.0	Positive (focal)	Positive (focal)	*PRRX1* (exon 1)::*KMT2D* (exons 25–27)	ANED (12)	Current series (Case 3)


A

Pigmented *PRRX1::NCOA1*-rearranged fibroblastic tumor: A rare morphologic variant of an emerging mesenchymal tumor

Jeffrey M. Cloutier[1] | Nolan S. Maloney[1] | Wei-Lien Wang[1] | Alexander J. Lazar[1,2,3]

J Cutan Pathol. 2022;49:802–807.



nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-022-30484-4 OPEN

PRRX1 is a master transcription factor of stromal fibroblasts for myofibroblastic lineage progression

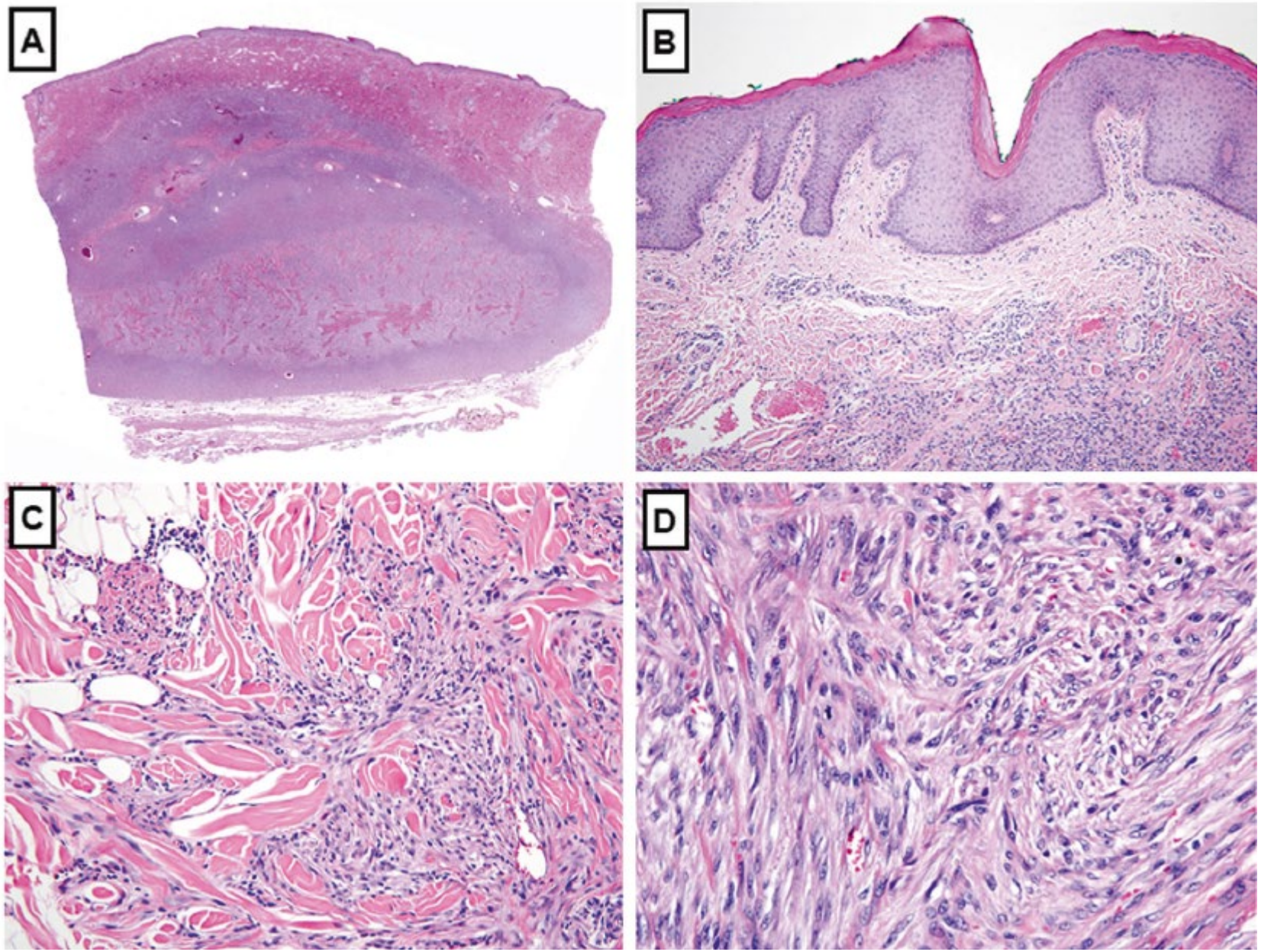
Keun-Woo Lee[1,9], So-Young Yeo[1,9], Jeong-Ryeol Gong[2,9], Ok-Jae Koo[3], Insuk Sohn[4], Woo Yong Lee[5], Hee Cheol Kim[5], Seong Hyeon Yun[5], Yong Beom Cho[5], Mi-Ae Choi[1], Sugyun An[2], Juhee Kim[2], Chang Ohk Sung[6✉], Kwang-Hyun Cho[2✉] & Seok-Hyung Kim[1,7,8✉]

Although stromal fibroblasts play a critical role in cancer progression, their identities remain unclear as they exhibit high heterogeneity and plasticity. Here, a master transcription factor (mTF) constructing core-regulatory circuitry, *PRRX1*, which determines the fibroblast lineage with a myofibroblastic phenotype, is identified for the fibroblast subgroup. *PRRX1* orchestrates the functional drift of fibroblasts into myofibroblastic phenotype via TGF-β signaling by remodeling a super-enhancer landscape. Such reprogrammed fibroblasts have myofibroblastic functions resulting in markedly enhanced tumorigenicity and aggressiveness of cancer. PRRX1 expression in cancer-associated fibroblast (CAF) has an unfavorable prognosis in multiple cancer types. Fibroblast-specific *PRRX1* depletion induces long-term and sustained complete remission of chemotherapy-resistant cancer in genetically engineered mice models. This study reveals CAF subpopulations based on super-enhancer profiles including *PRRX1*. Therefore, mTFs, including *PRRX1*, provide another opportunity for establishing a hierarchical classification system of fibroblasts and cancer treatment by targeting fibroblasts.

Dermatofibroma (benign fibrous histiocytoma)

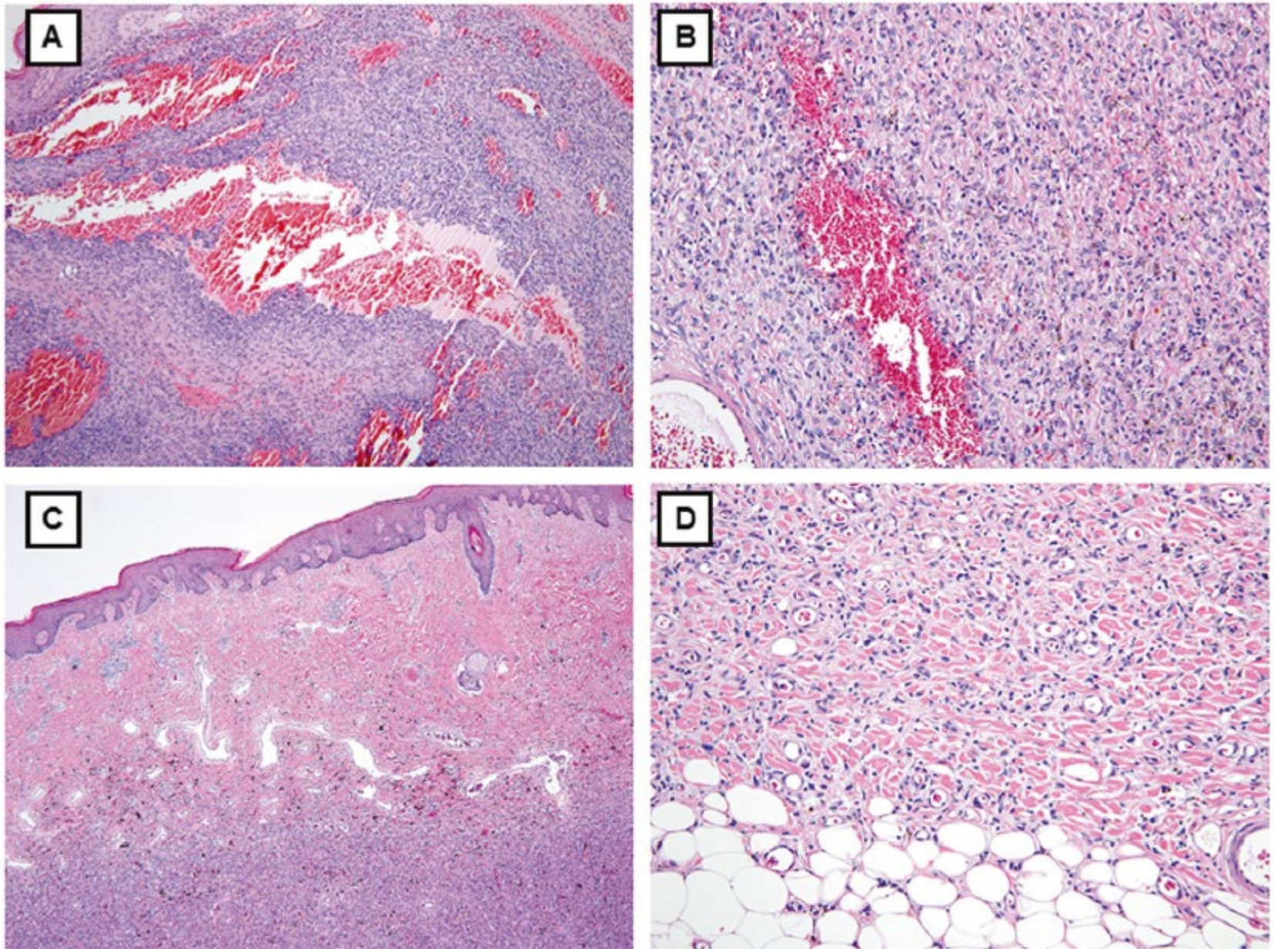
Recurrence rates for dermatofibroma (fibrous histiocytoma) and variants

Variant	Recurrence
Common dermatofibroma	<5%
Cellular dermatofibroma	20%
Aneurysmal dermatofibroma	20%
Atypical dermatofibroma	20%

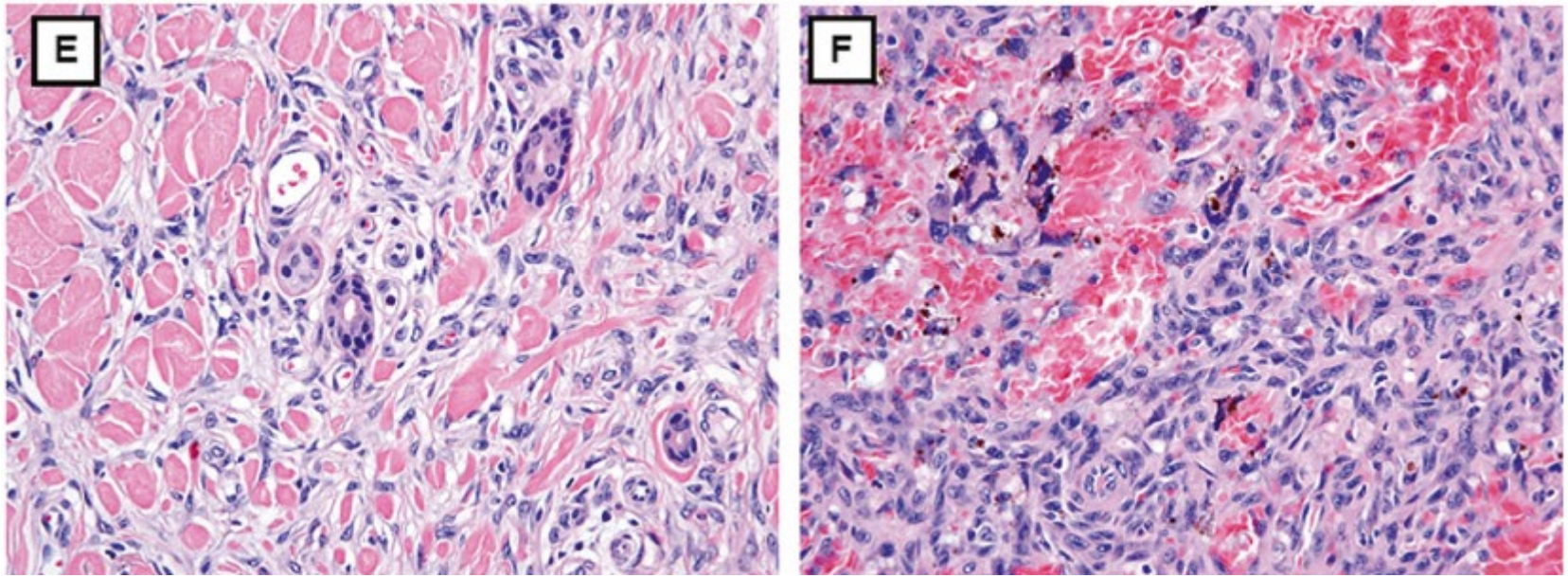

A
B
C
D

Cellular Dermatofibroma

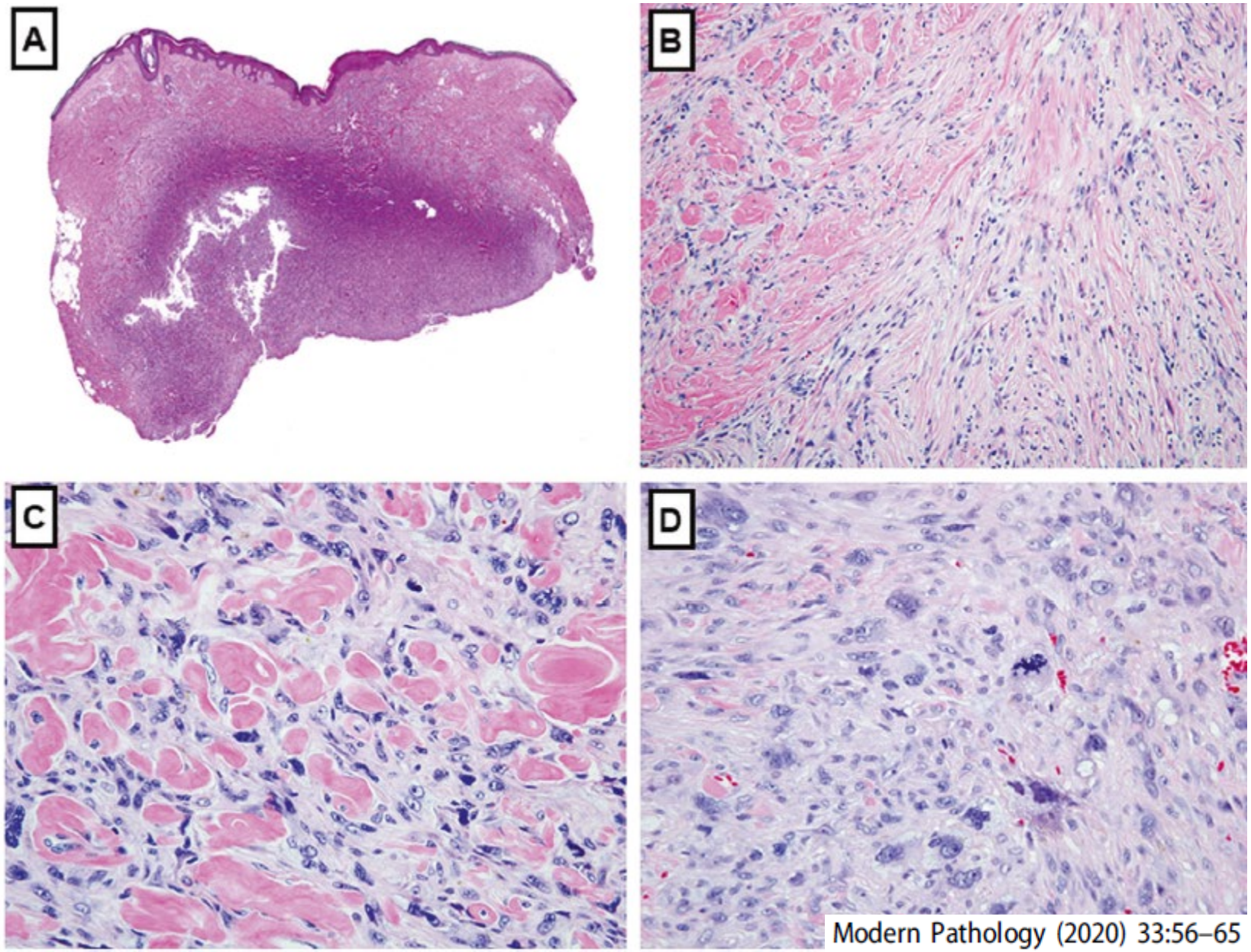
- Often superficial entrapment of adipose tissue
- Around 10% central necrosis
- Focal CD34 + in ~5% of cases
- IHC limited role
  - Factor XIIIa NOT useful
    - Stains dermal fibroblasts (“dendrocytes”)



Modern Pathology (2020) 33:56–65



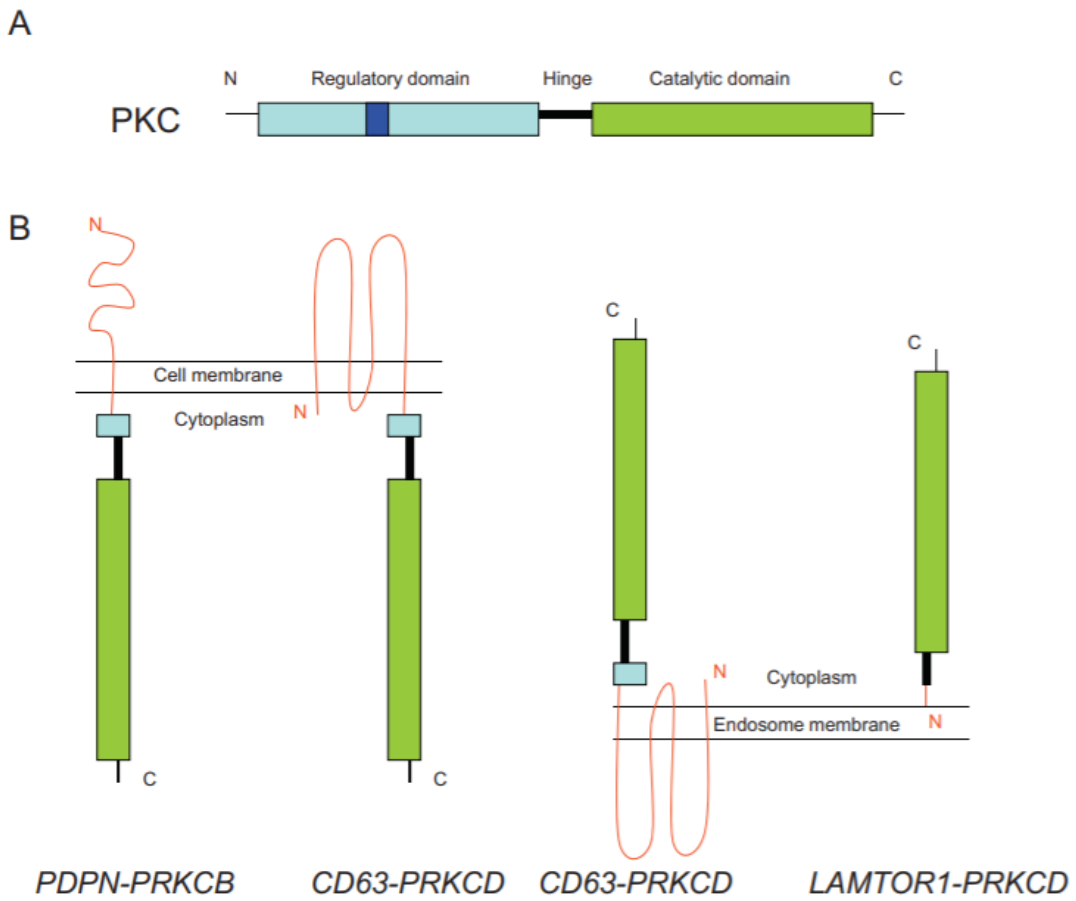
Modern Pathology (2020) 33:56–65



Modern Pathology (2020) 33:56–65

Fusions involving protein kinase C and membrane-associated proteins in benign fibrous histiocytoma☆

Anna Płaszczyca[a], Jenny Nilsson[a], Linda Magnusson[a], Otte Brosjö[b], Olle Larsson[c], Fredrik Vult von Steyern[d], Henryk A. Domanski[e], Henrik Lilljebjörn[a], Thoas Fioretos[a], Johnbosco Tayebwa[a], Nils Mandahl[a], Karolin H. Nord[a], Fredrik Mertens[a,*]



NOT to be confused with
Angiomatoid Fibrous Histiocytoma!!!

The American Journal of Surgical Pathology *14(12): 1126–1132, 1990*

Angiomatoid Malignant Fibrous Histiocytoma

A Follow-up Study of 108 Cases with Evaluation of Possible Histologic Predictors of Outcome

Michael J. Costa, M.D., and Sharon W. Weiss, M.D.

Angiomatoid "Malignant" Fibrous Histiocytoma: A Clinicopathologic Study of 158 Cases and Further Exploration of the Myoid Phenotype

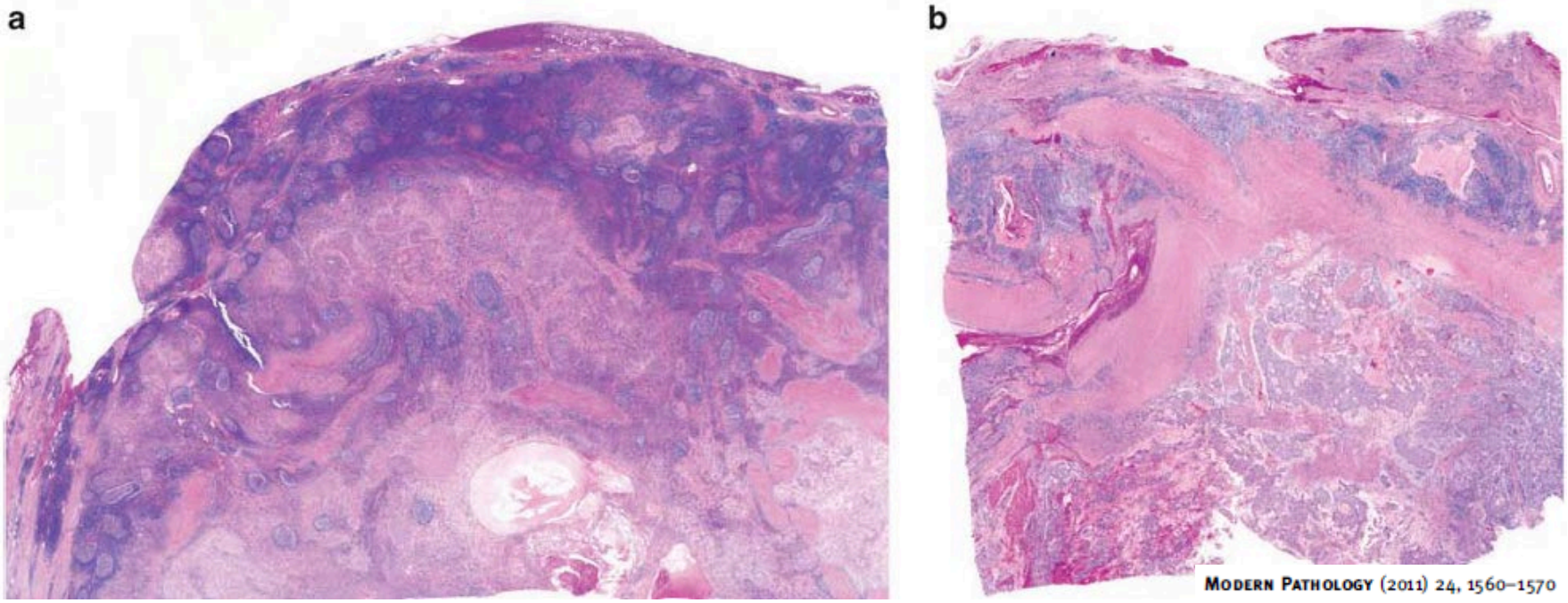
J.C. FANBURG-SMITH, MD, AND M. MIETTINEN, MD

MODERN PATHOLOGY (2011) 24, 1560–1570

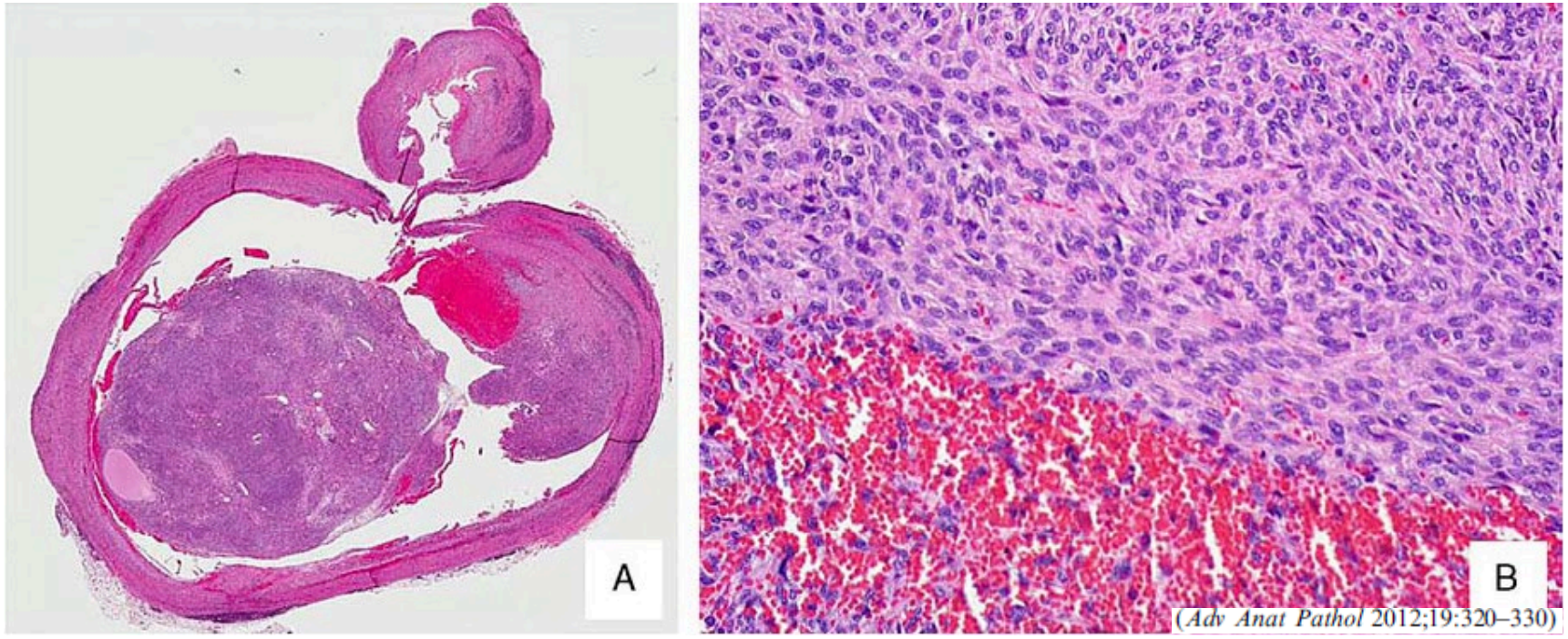
Angiomatoid fibrous histiocytoma: unusual sites and unusual morphology

Gang Chen[1], Andrew L Folpe[2], Thomas V Colby[3], Kesavan Sittampalam[4], Martine Patey[5], Ming-Guang Chen[6] and John KC Chan[7]

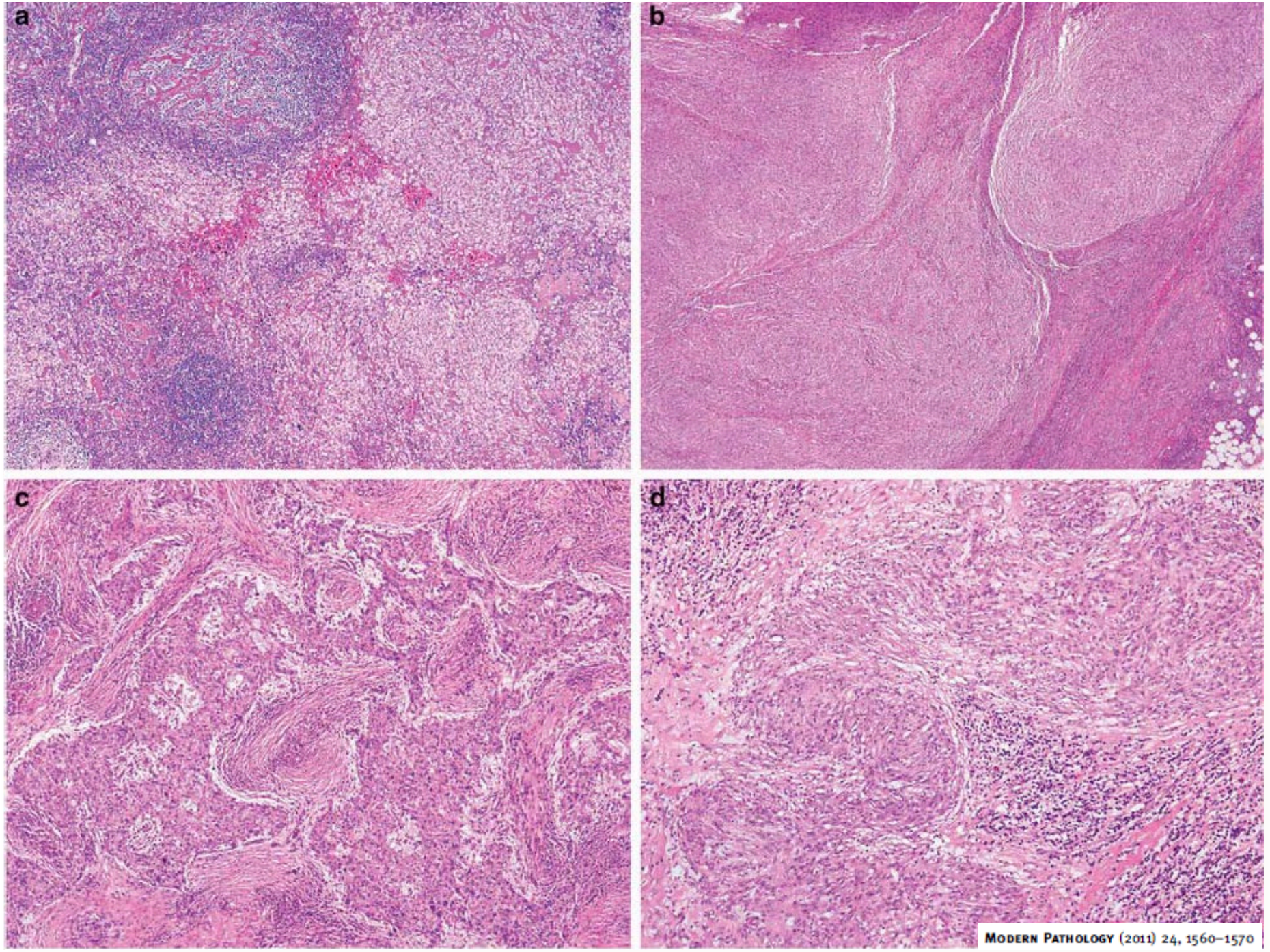
[1]Department of Pathology, Fujian Provincial Tumor Hospital, Fuzhou, Fujian, China; [2]Department of Pathology, Mayo Clinic, Rochester, MN, USA; [3]Department of Pathology, Mayo Clinic, Scottsdale, AZ, USA; [4]Department of Pathology, Singapore General Hospital, Singapore; [5]Department of Pathology, Hopital Robert Debre—CHU, Cedex, France; [6]Department of Pathology, The First Affiliated Hospital in Nanping of Fujian Medical University, Nanping, Fujian, China and [7]Department of Pathology, Queen Elizabeth Hospital, Kowloon, Hong Kong



Modern Pathology (2011) 24, 1560–1570



(*Adv Anat Pathol* 2012;19:320–330)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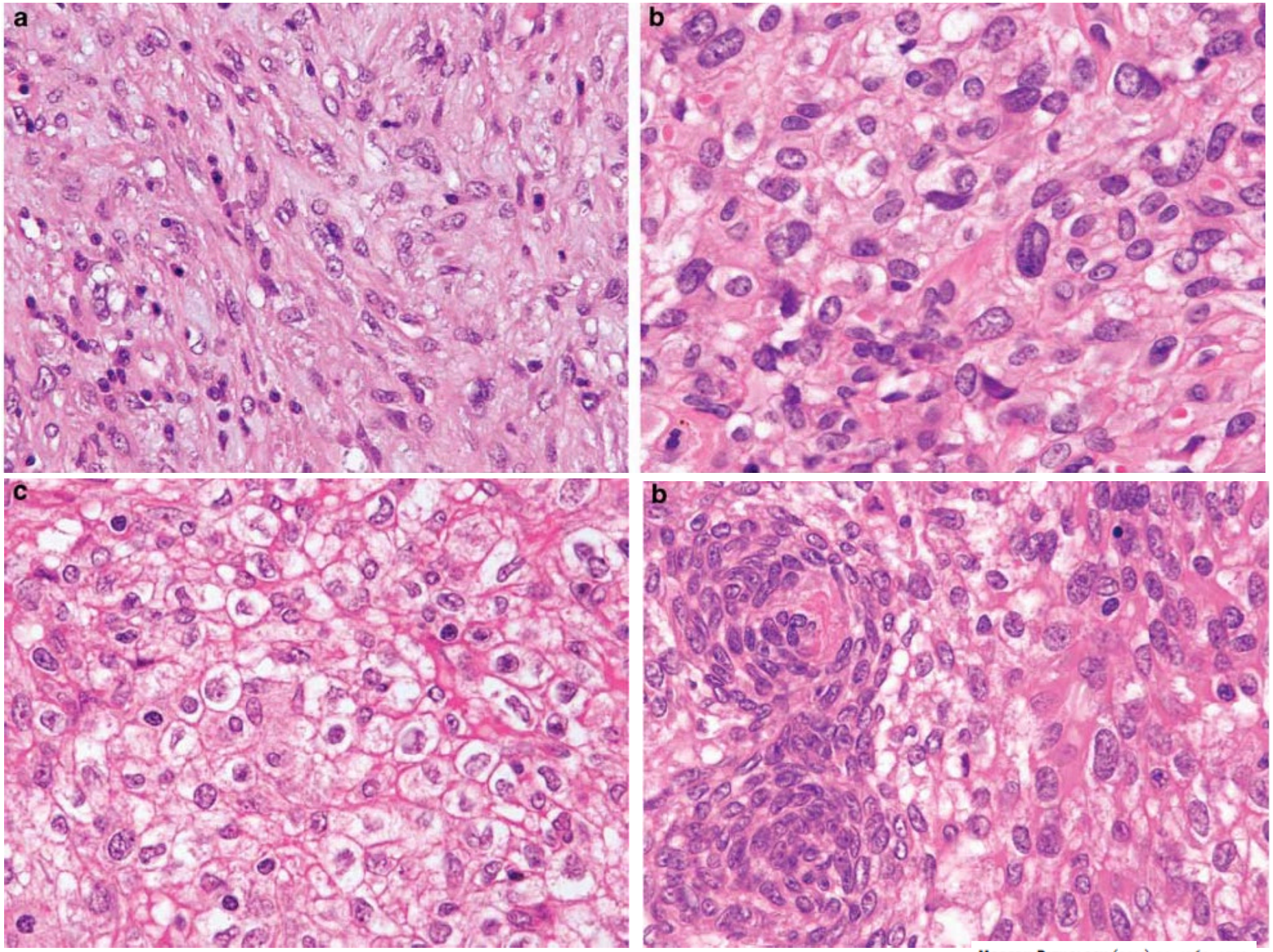
a
b
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b

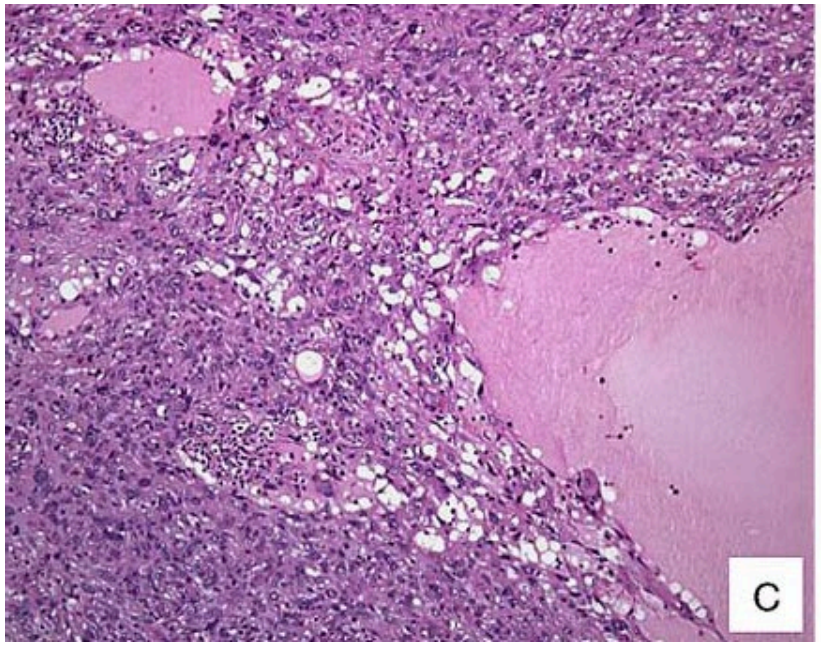
J Cutan Pathol 2008: 35: 855–860
doi: 10.1111/j.1600-0560.2007.00908.x
Blackwell Munksgaard. Printed in Singapore

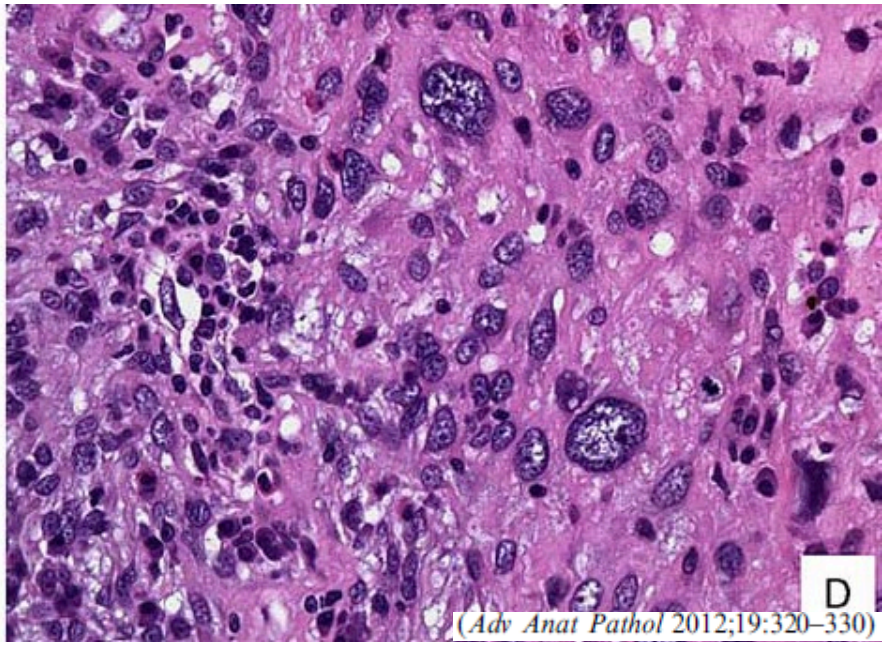
Journal of
Cutaneous Pathology

Pleomorphic angiomatoid fibrous histiocytoma: a case confirmed by fluorescence *in situ* hybridization analysis for EWSR1 rearrangement

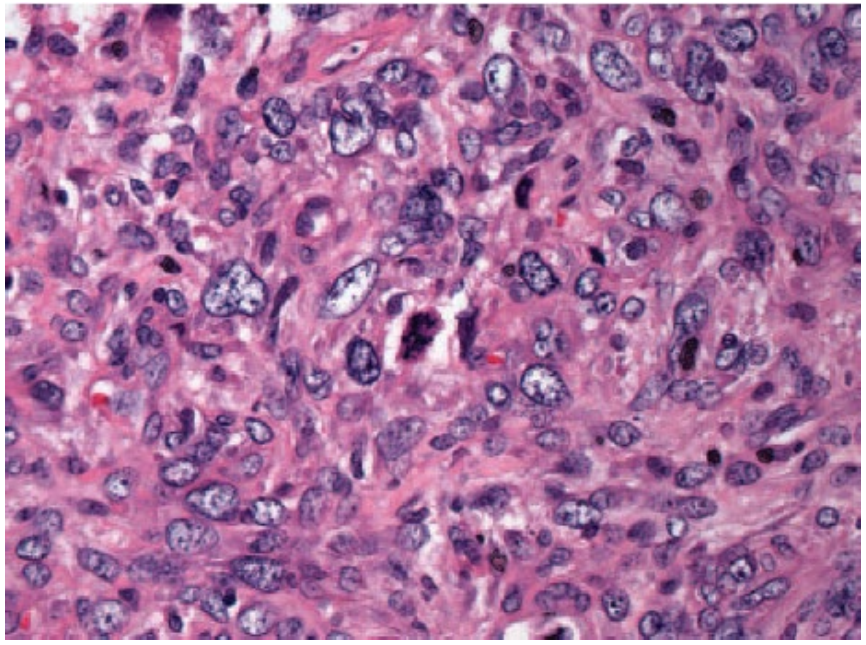
Ilan Weinreb[1,2], Brian P. Rubin[3] and John R. Goldblum[3]

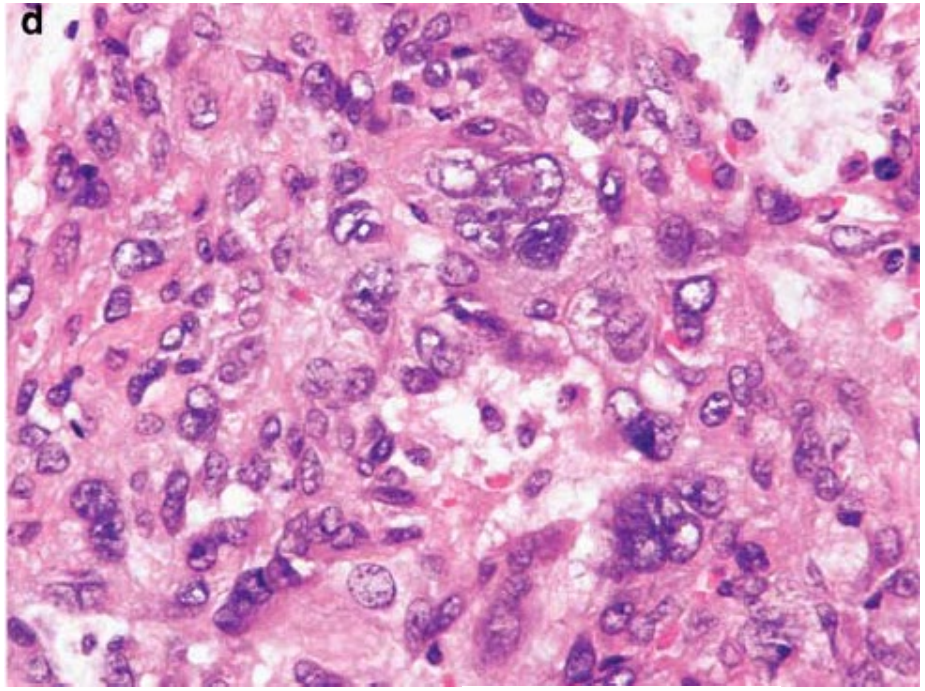
[1]Department of Pathology, University Health Network, Toronto, Ontario, Canada,
[2]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada and
[3]Department of Pathology, Cleveland Clinic Foundation, Cleveland, OH, USA





(*Adv Anat Pathol* 2012;19:320–330)





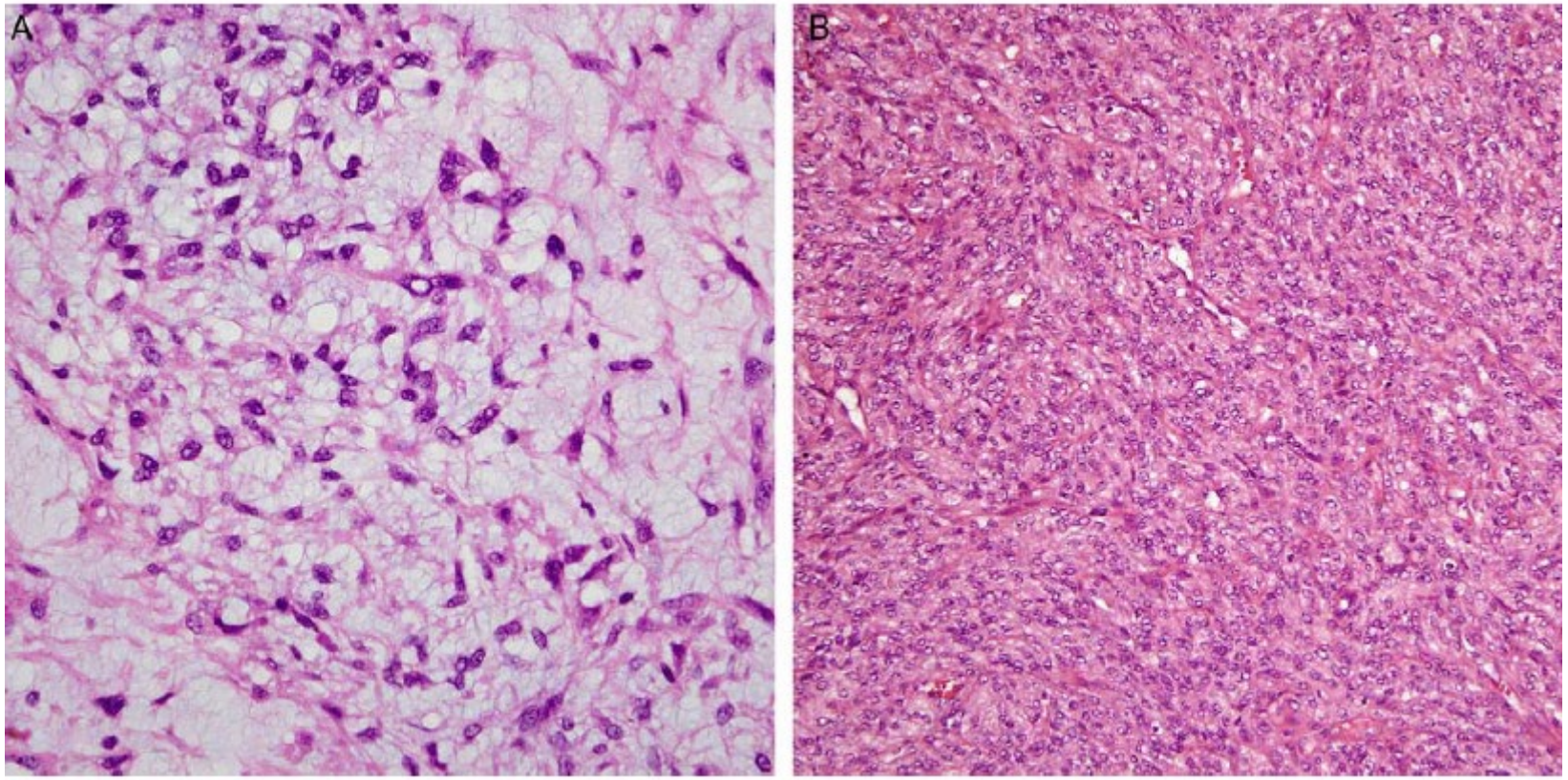
J Cutan Pathol 2008: 35: 855–860

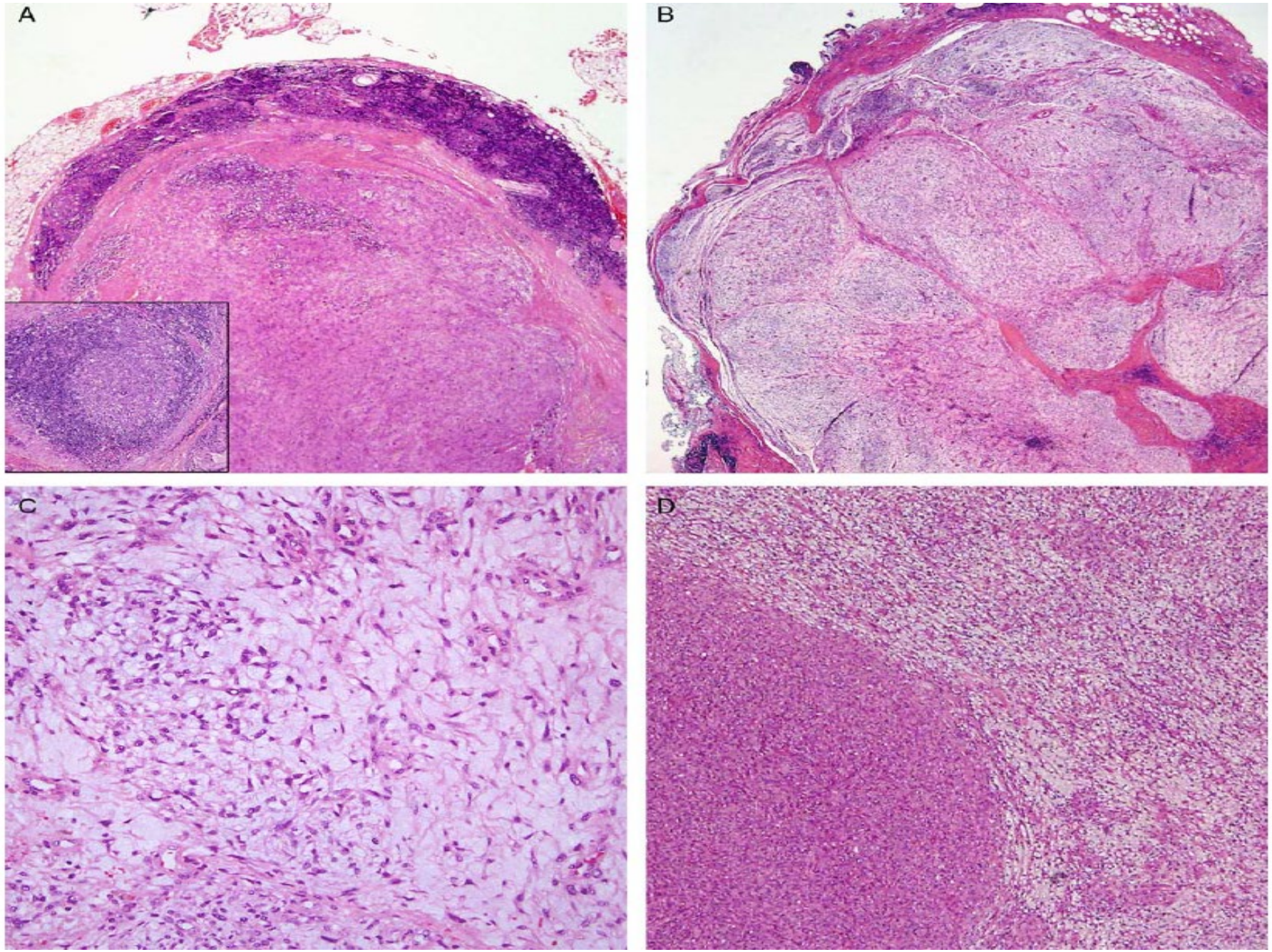
Myxoid Variant of So-called Angiomatoid "Malignant Fibrous Histiocytoma"

Clinicopathologic Characterization in a Series of 21 Cases

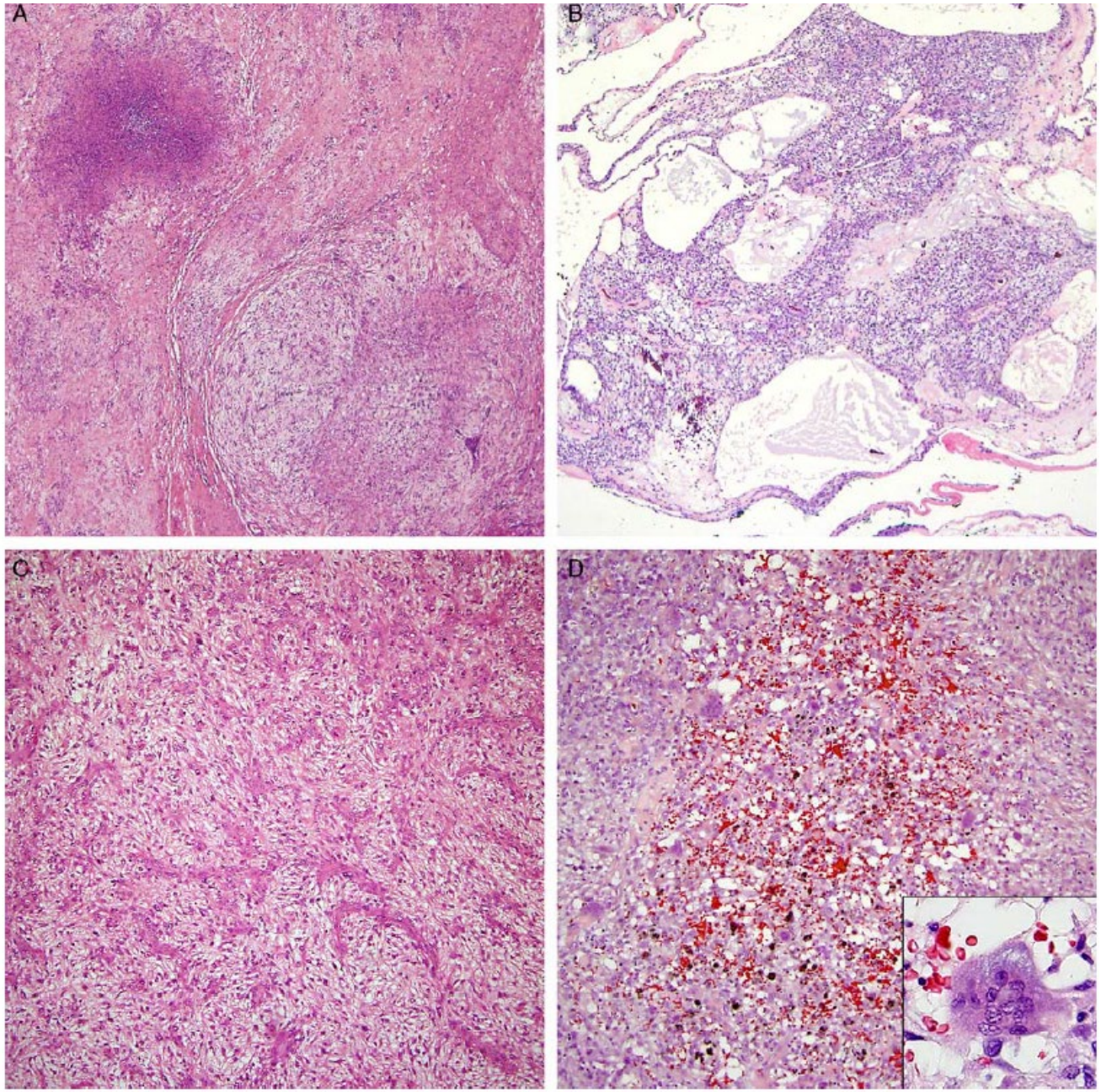
Inga-Marie Schaefer, MD and Christopher D.M. Fletcher, MD, FRCPath

(*Am J Surg Pathol* 2014;38:816–823)

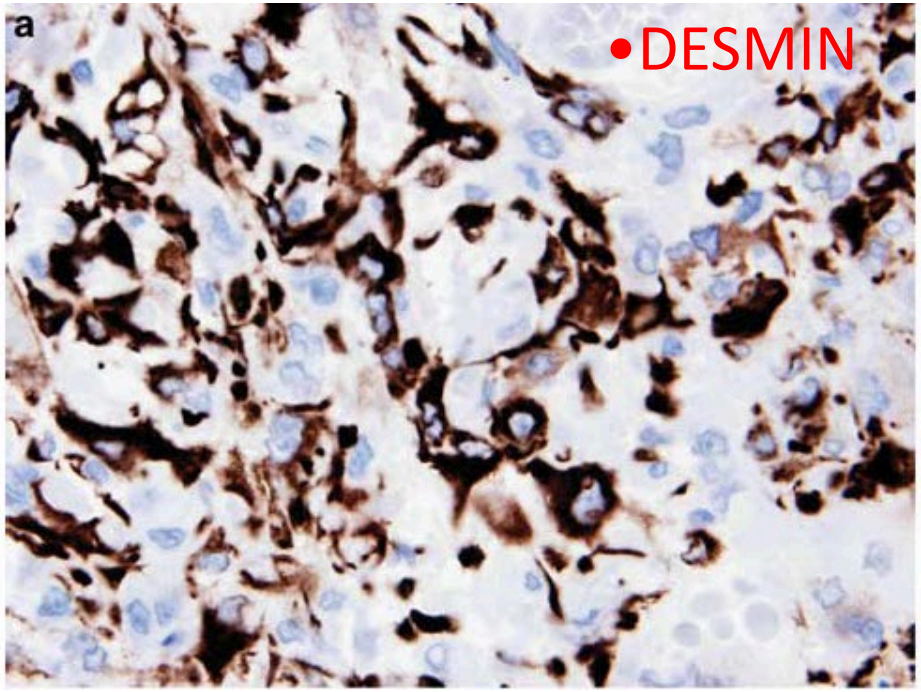


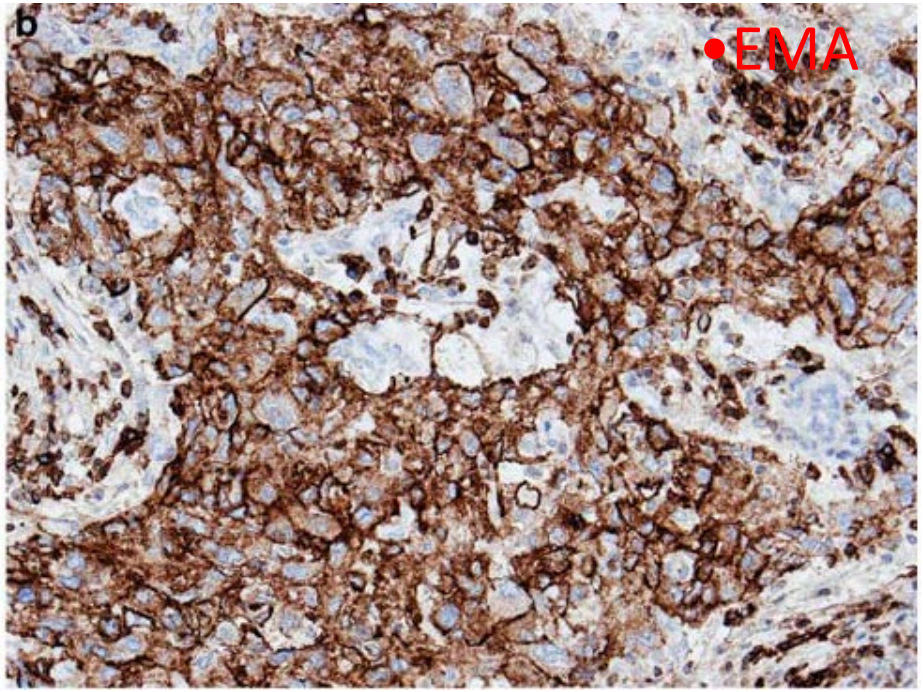


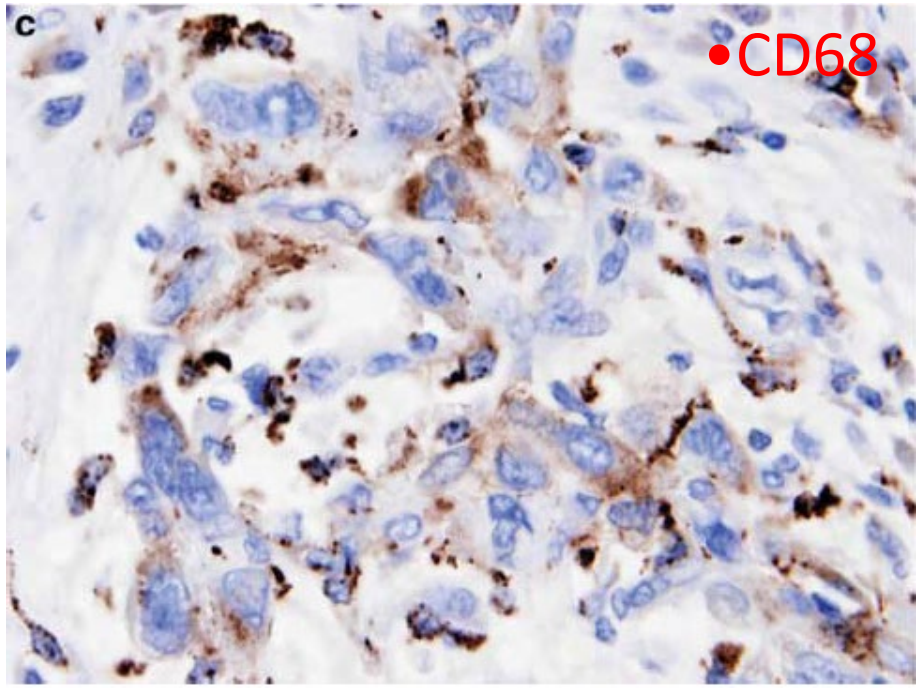
(*Am J Surg Pathol* 2014;38:816–823)



(*Am J Surg Pathol* 2014;38:816–823)







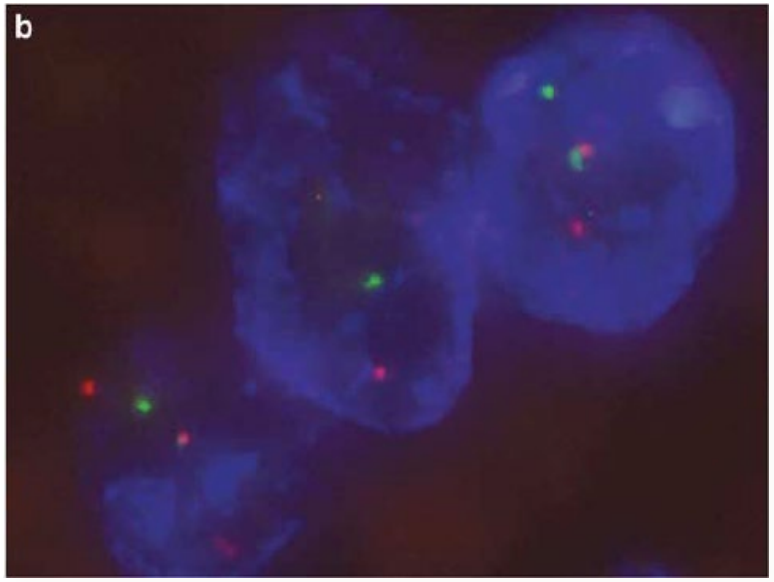
MODERN PATHOLOGY (2011) 24, 1560–1570

MODERN PATHOLOGY (2010) 23, 93–97

Utility of FISH in the diagnosis of angiomatoid fibrous histiocytoma: a series of 18 cases

Munir R Tanas[1], Brian P Rubin[1], Elizabeth A Montgomery[3], Sondra L Turner[2], James R Cook[2], Raymond R Tubbs[2], Steven D Billings[1] and John R Goldblum*,[1]

[1]*Department of Anatomic Pathology, Pathology and Laboratory Medicine Institute, The Cleveland Clinic and The Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA;* [2]*Department of Molecular Pathology, Pathology and Laboratory Medicine Institute, The Cleveland Clinic and The Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA and* [3]*Department of Pathology, Johns Hopkins Hospital, Johns Hopkins University, Baltimore, MD, USA*



- t(2;22)(q33;q12) EWSR1/CREB1
- t(12;22)(q13;q12)=EWSR1/ATF1
- t(12;16)(q13;p11)= FUS/ATF1

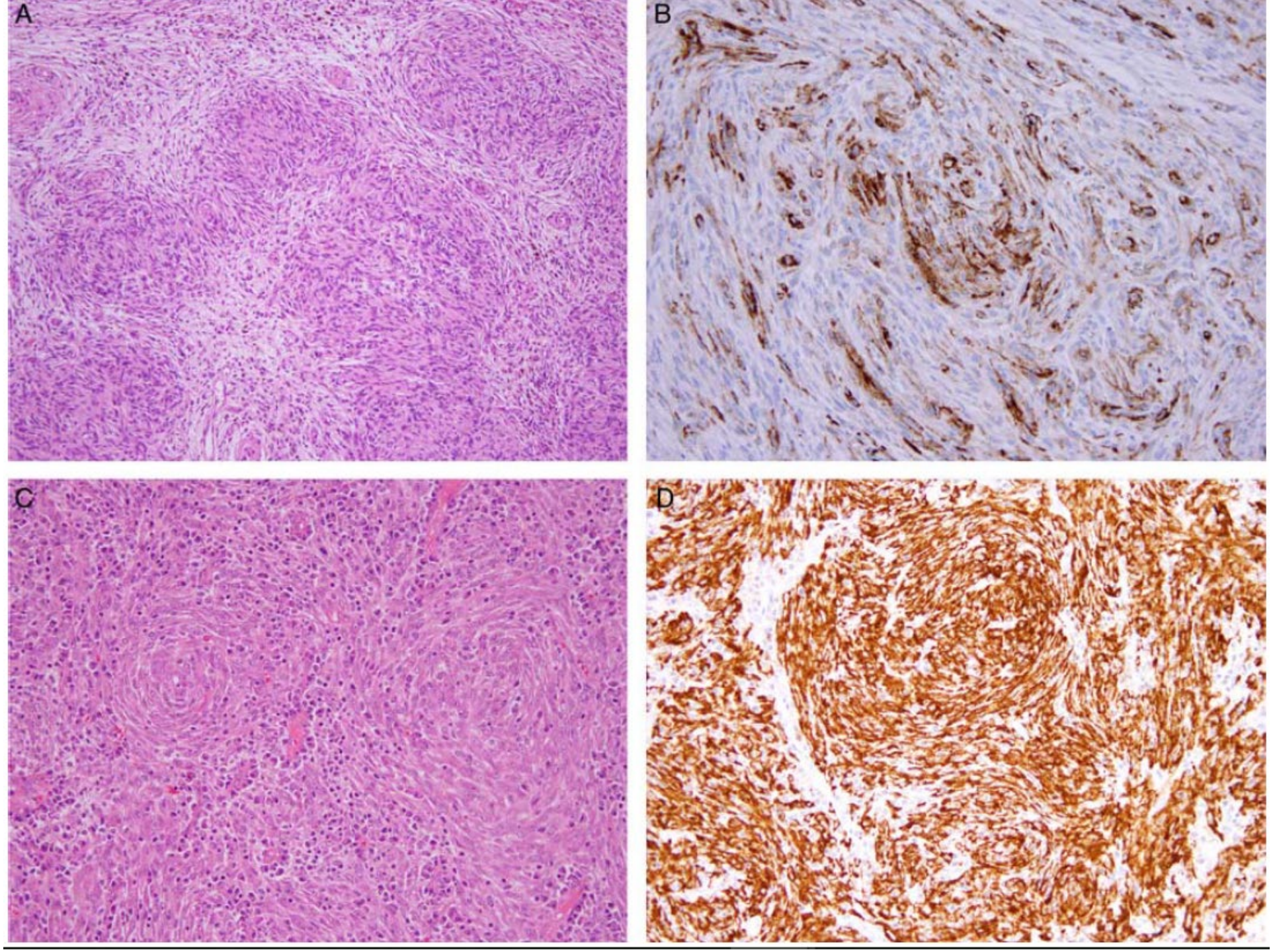
ALK Expression in Angiomatoid Fibrous Histiocytoma

A Potential Diagnostic Pitfall

Alison L. Cheah, MBBS, Youran Zou, MD,† Christopher Lanigan, MS,‡ Steven D. Billings, MD,† Brian P. Rubin, MD, PhD,† Jason L. Hornick, MD, PhD,§ and John R. Goldblum, MD†*

Am J Surg Pathol 2018

Case	D5F3	5A4	ALK1	*EWSR1*	*ALK*	*ALK* Copy No.
AFH1	3+ strong	NA	NA	POS	NEG	NA
AFH2	3+ strong	2+ mod	0	POS	NEG	1.6
AFH3	3+ strong	2+ mod	0	POS	NEG	1.8
AFH4	1+ strong	1+ mod	0	POS	UNS	UNS
AFH5	3+ strong	2+ weak	0	UNS	UNS	UNS
AFH6	1+ mod	0	0	POS	NEG	1.8
AFH7	3+ strong	3+ mod	0	POS	NEG	NA
AFH8	3+ strong	2+ mod	1+ weak	POS	NEG	2.1
AFH9	0	0	0	POS	NA	NA
AFH10	0	0	0	POS	NA	NA
AFH11	3+ strong	NA	NA	POS	NA	NA


A
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D

ALK Expression in Angiomatoid Fibrous Histiocytoma

Confirmation of the Findings of Cheah et al

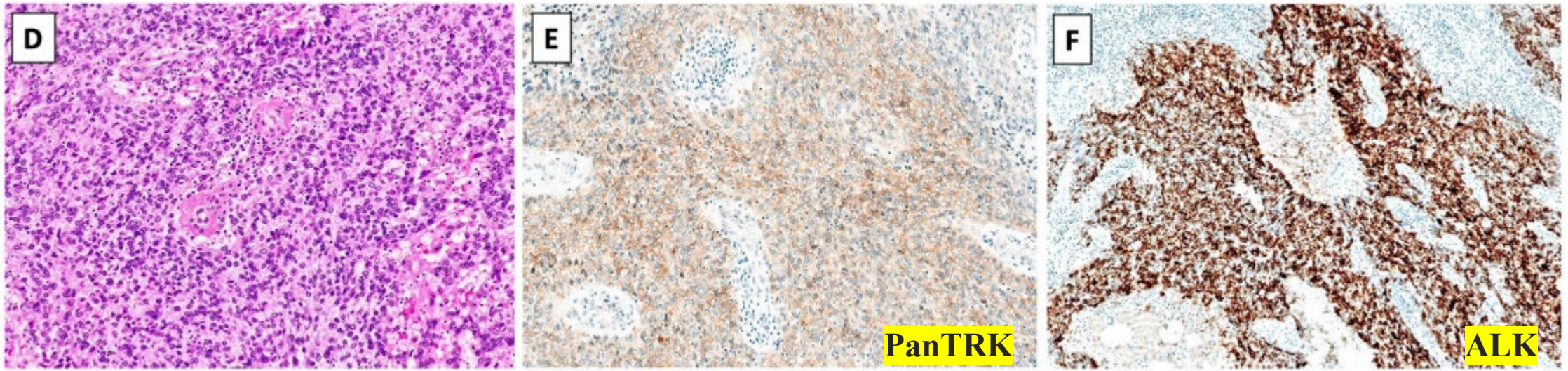
Am J Surg Pathol • Volume 43, Number 8, August 2019

Peter Van Zwam, MD*
Thomas Mentzel, MD, PhD†
Uta Flucke, MD, PhD‡
*Department of Pathology PAMM Institute, Eindhoven
‡Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands
†Dermatopathology Bodensee Friedrichshafen, Germany

Kinase expression in angiomatoid fibrous histiocytoma: panTRK is commonly expressed in the absence of *NTRK* rearrangement

Ana Cristina Vargas ,[1,2] Christopher Joy,[3] Fiona M Maclean,[2] Fiona Bonar,[2] Daniel D Wong,[4] Anthony J Gill,[1,5] Alison L Cheah[2]

Vargas AC, *et al*. *J Clin Pathol* 2023;**0**:1–4.



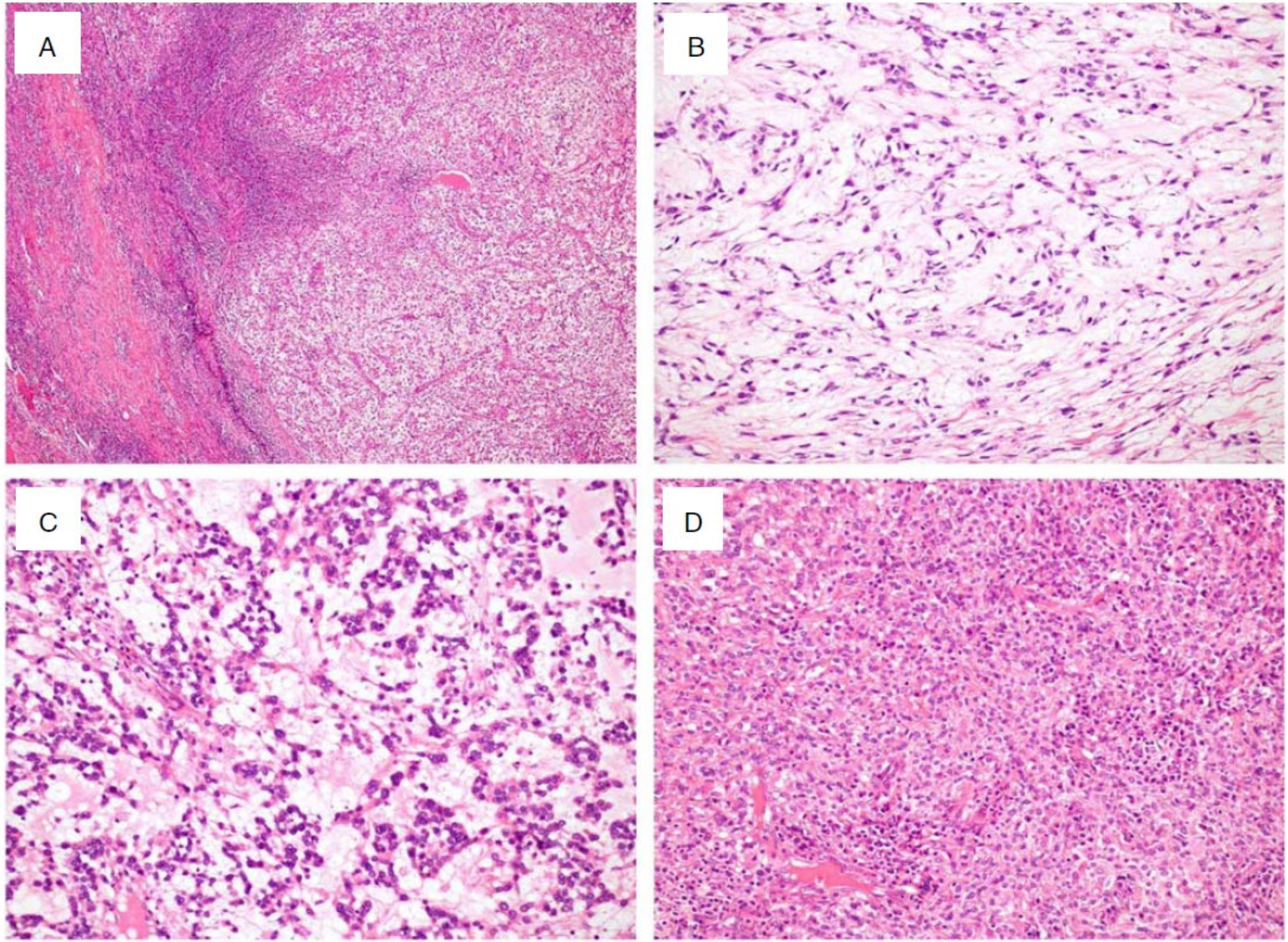
Expanding the Phenotypic Spectrum of Mesenchymal Tumors Harboring the *EWSR1-CREM* Fusion

Akihiko Yoshida, MD, PhD,† Susumu Wakai, CT,* Eijitsu Ryo, PhD,‡ Kazuyuki Miyata, MD, PhD,§ Masahisa Miyazawa, MD, PhD,‖ Ken-ichi Yoshida, MD,* Toru Motoi, MD, PhD,¶ Chitose Ogawa, MD,# Shintaro Iwata, MD, PhD,†** Eisuke Kobayashi, MD, PhD,†** Shun-ichi Watanabe, MD,†† Akira Kawai, MD, PhD,†** and Taisuke Mori, DMD, PhD*‡*

(*Am J Surg Pathol* 2019;00:000–000)

TABLE 2. Clinicopathologic Summary of Mesenchymal Tumors Harboring the *EWSR1-CREM* Fusion

Case	Age (y)/Sex	Primary Site	Histology	Treatment	Outcome (mo)
1	49/F	Hand	Clear cell sarcoma	Resection	AWD (39)
2	47/M	Lung	Myxoid AFH	Lobectomy	NED (58)
3	50/M	Finger	Myxoid AFH	Ray amputation	NED (45)
4	54/M	Hand	Myxoid AFH	Ray amputation	NED (51)
5	15/M	Abdominal cavity	Unclassifiable spindle cell tumor (CK^+, $CD34^+$, ALK^+)	Chemotherapy	DOD (18)
6	63/F	Chest wall	Unclassifiable round cell tumor ($MUC4^+$, $synapto^+$)	Wide resection	NED (17)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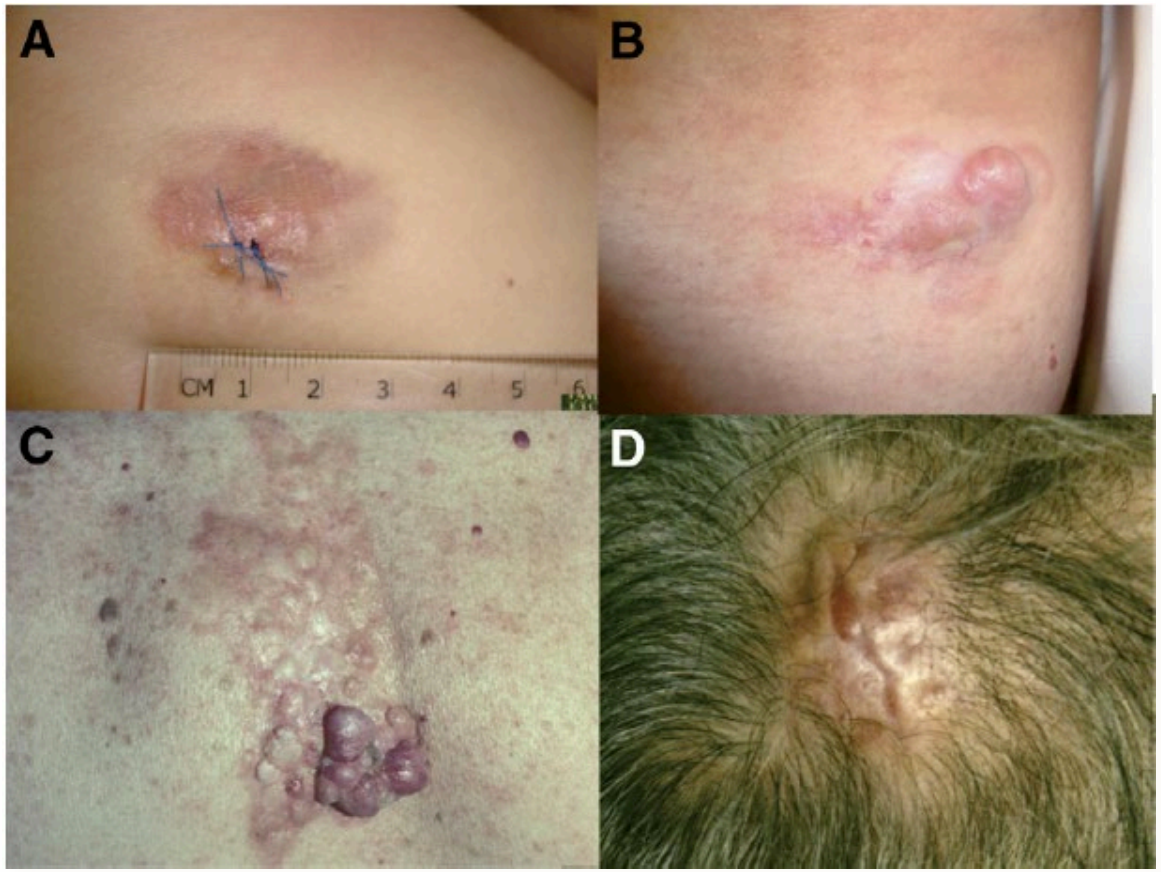
Dermatofibrosarcoma Protuberans (DFSP)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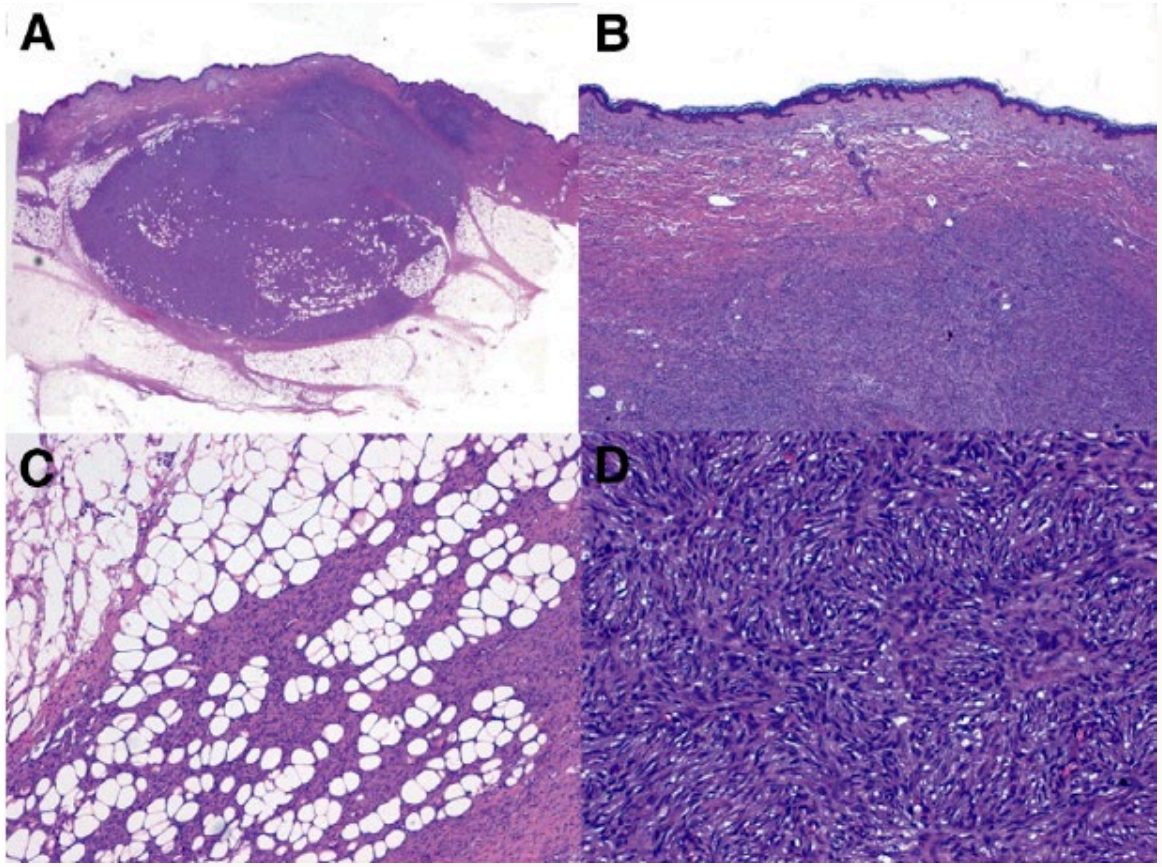
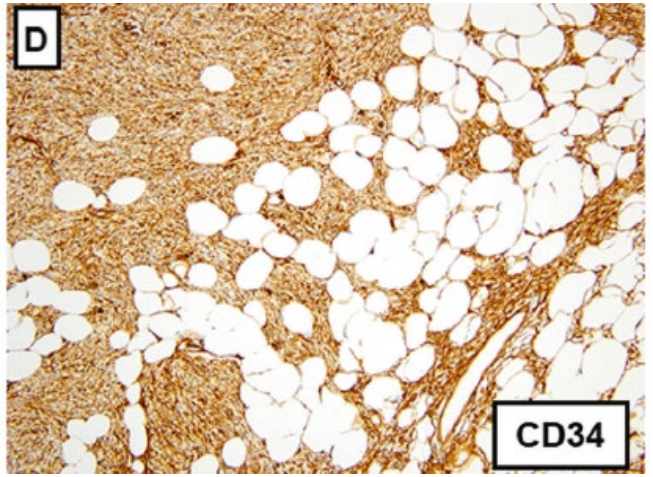




Seminars in Diagnostic Pathology (2013) 30, 13-28

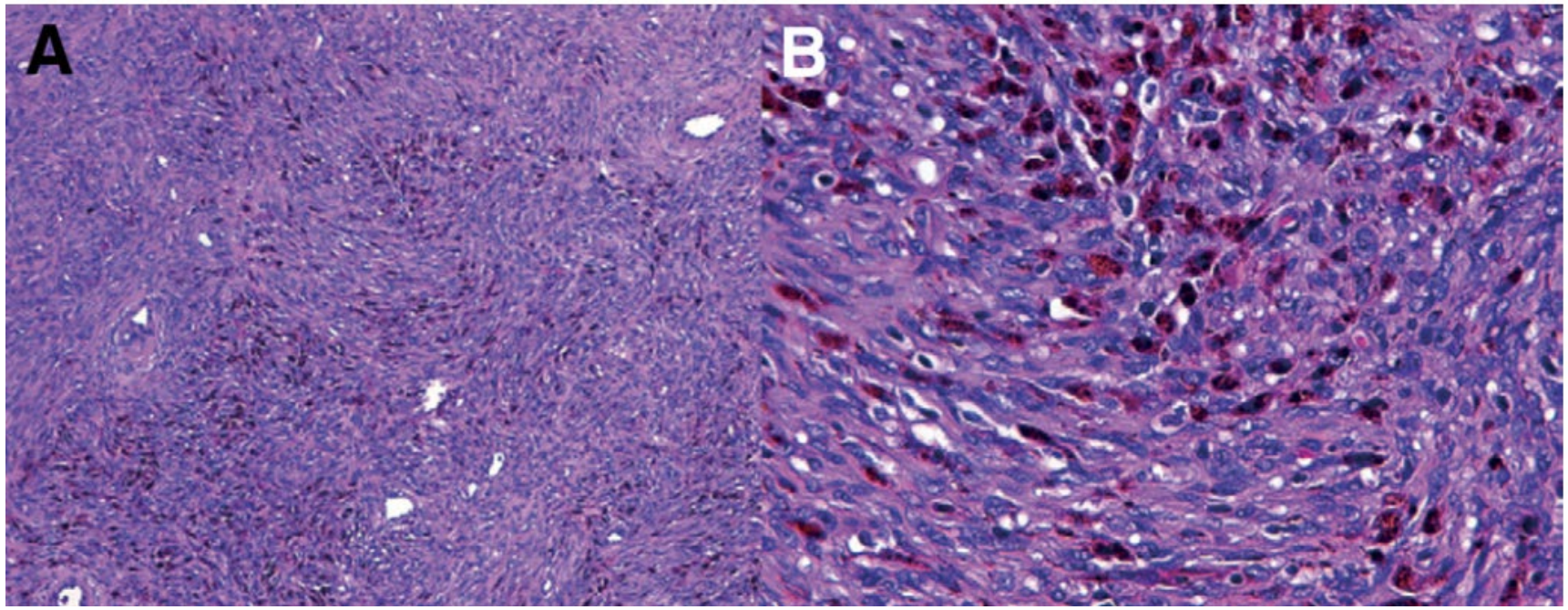
Cellular dermatofibroma	Dermatofibrosarcoma protuberans
Epidermal hyperplasia	No epidermal hyperplasia
Lateral hyaline collagen entrapment	Diffuse infiltration of dermis
Mixed fascicular and storiform pattern	Tight storiform pattern
Pale eosinophilic cytoplasm	Minimal cytoplasm
Superficial fat entrapment	Diffuse infiltration of fat
CD34 usually negative	CD34 positive
SMA multifocally positive	SMA negative

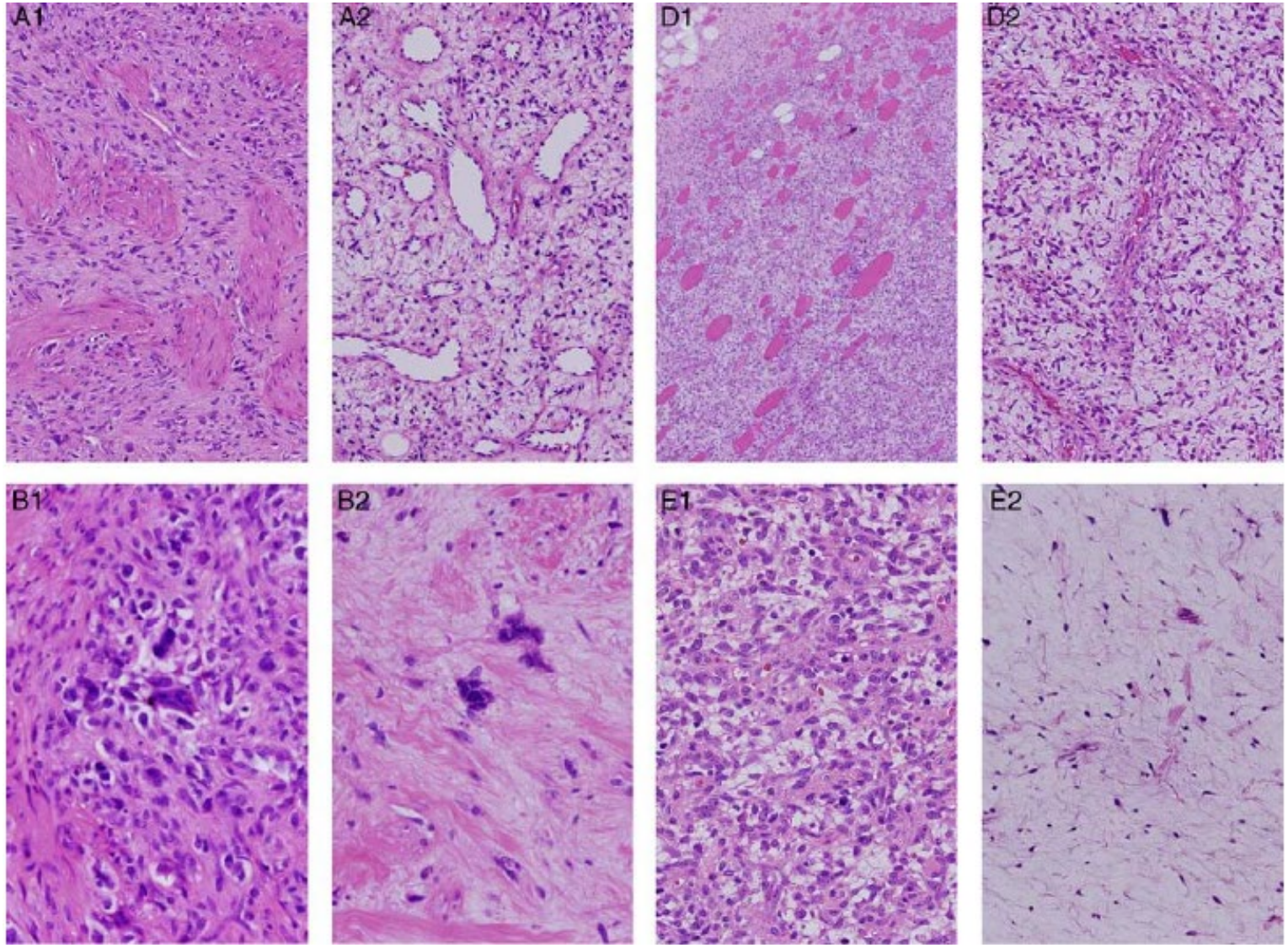
Modern Pathology (2020) 33:56–65

Variants of DFSP

- Giant cell fibroblastoma
- Pigmented DFSP (Bednar’s tumor)
- DFSP with myoid nodules
- Myxoid DFSP
- Fibrosarcomatous DFSP
- Plaque-like DFSP (atrophic DFSP)
- Sclerosing DFSP (sclerotic DFSP)
- Granular cell DFSP

Pigmented DFSP (Bednar Tumor)




A1
A2
D1
D2
B1
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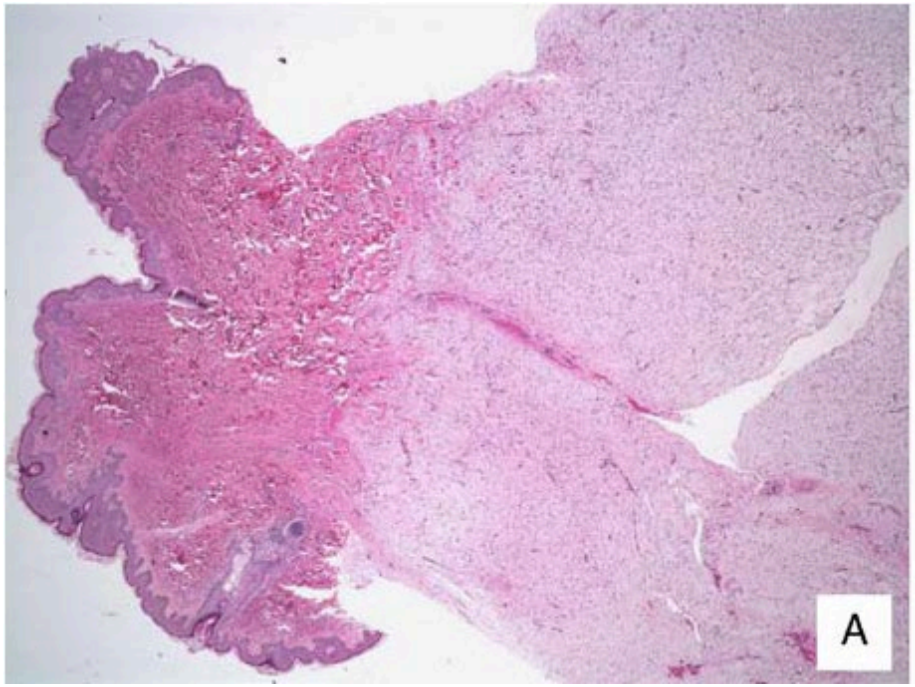
E1
E2

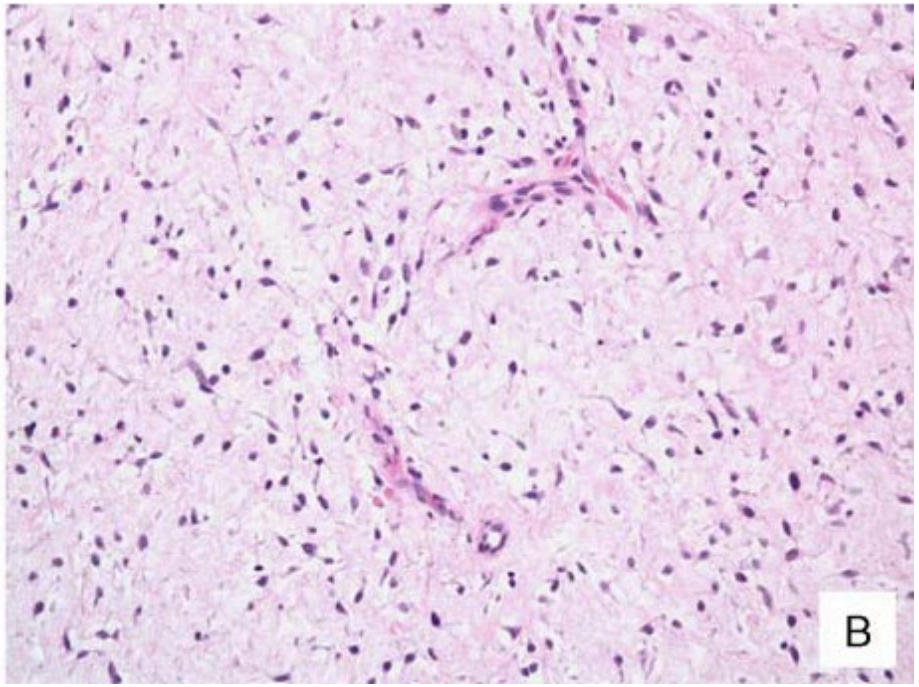
ORIGINAL ARTICLE

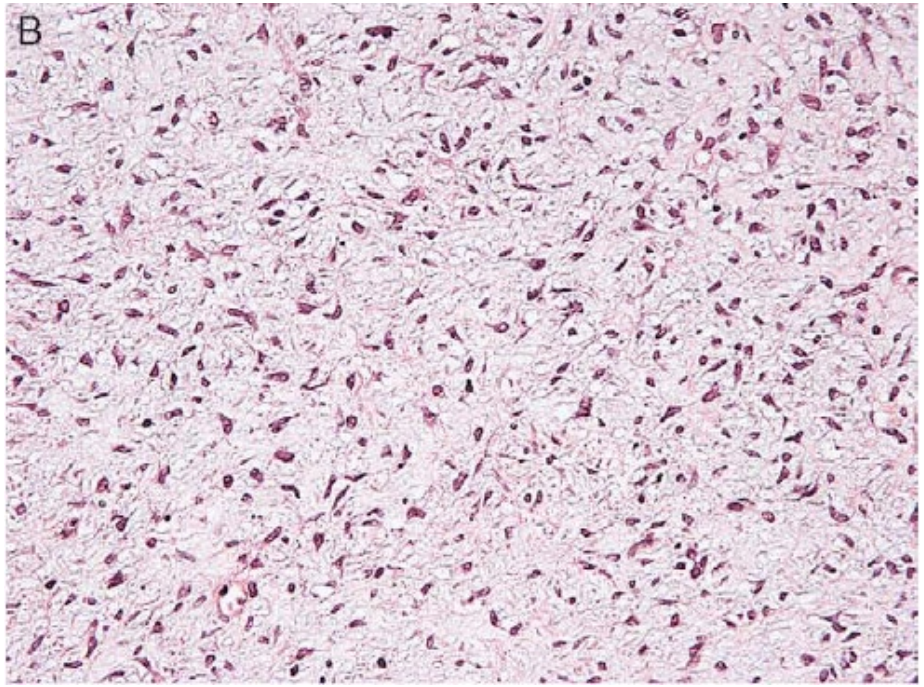
Myxoid Dermatofibrosarcoma Protuberans: A Rare Variant Analyzed in a Series of 23 Cases

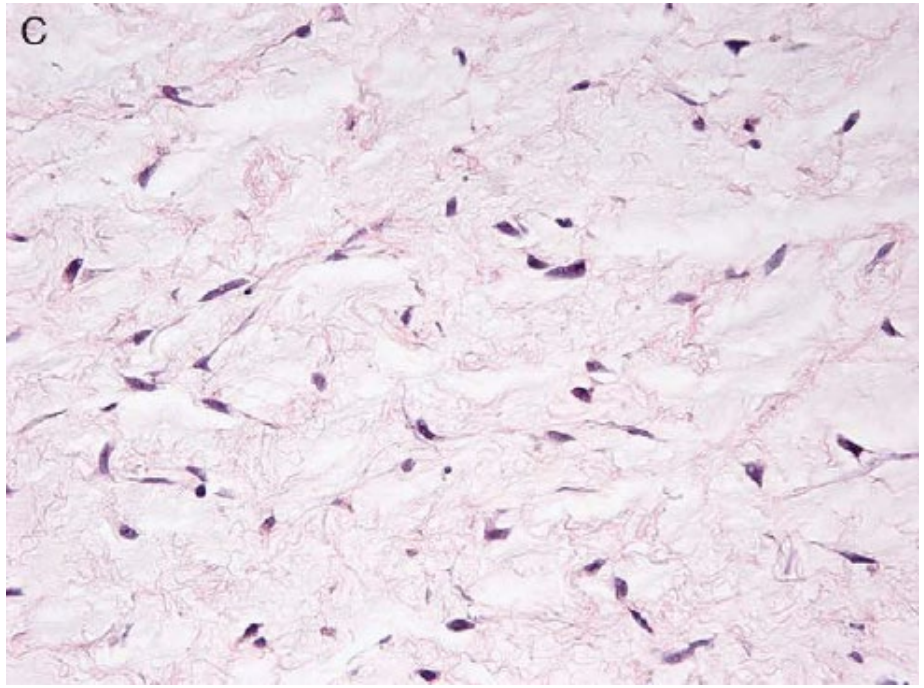
Julie D.R. Reimann, MD, PhD and Christopher D.M. Fletcher, MD, FRCPath

Am J Surg Pathol • Volume 31, Number 9, September 2007

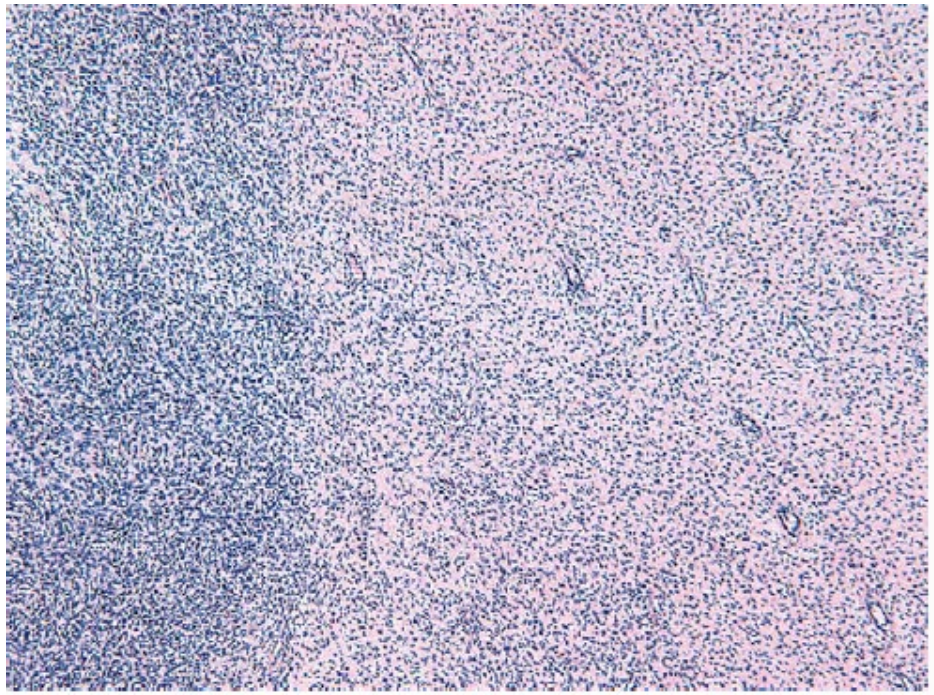


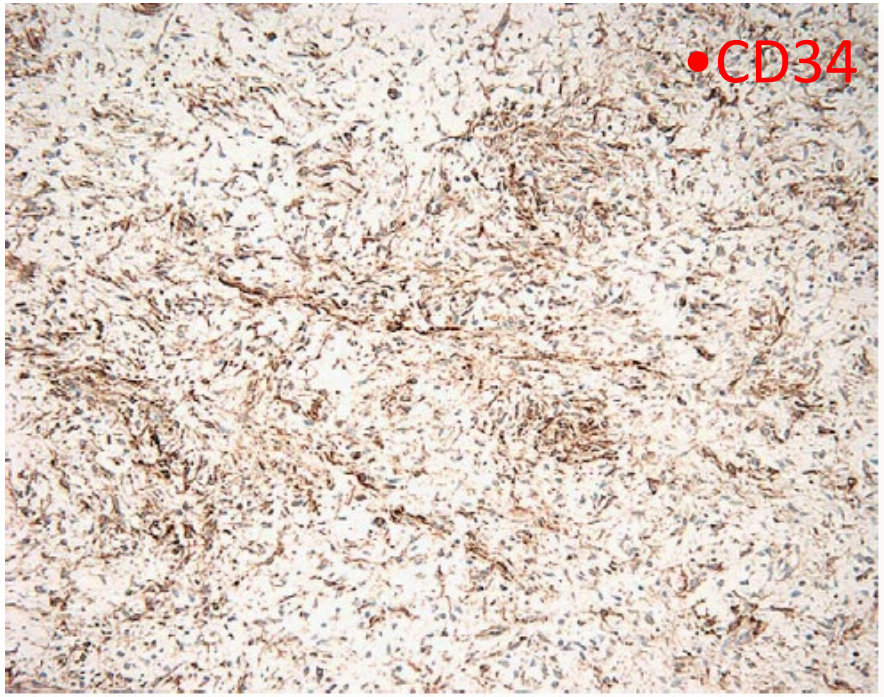




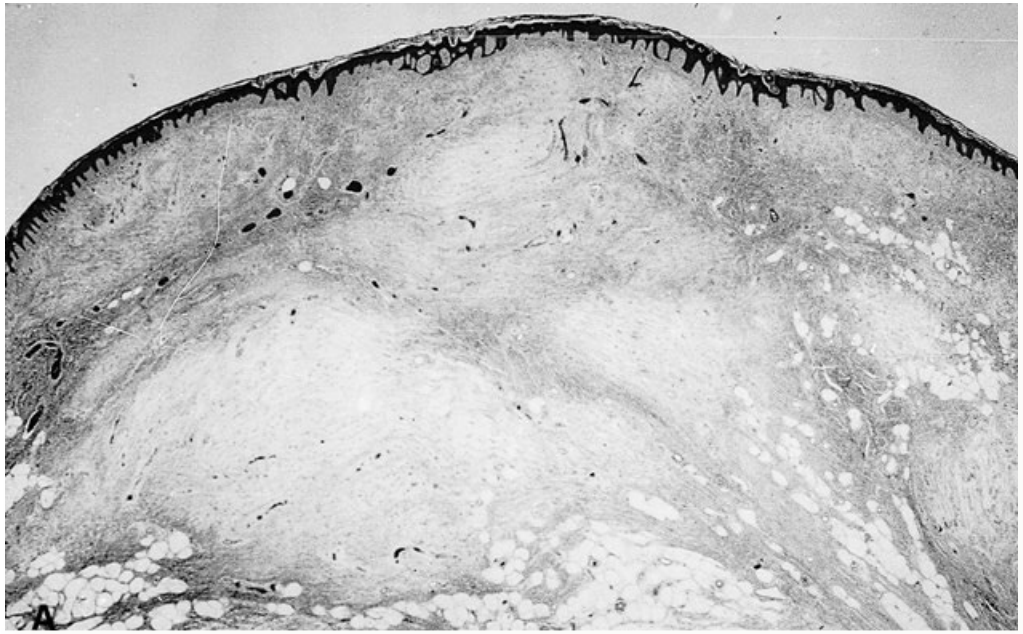


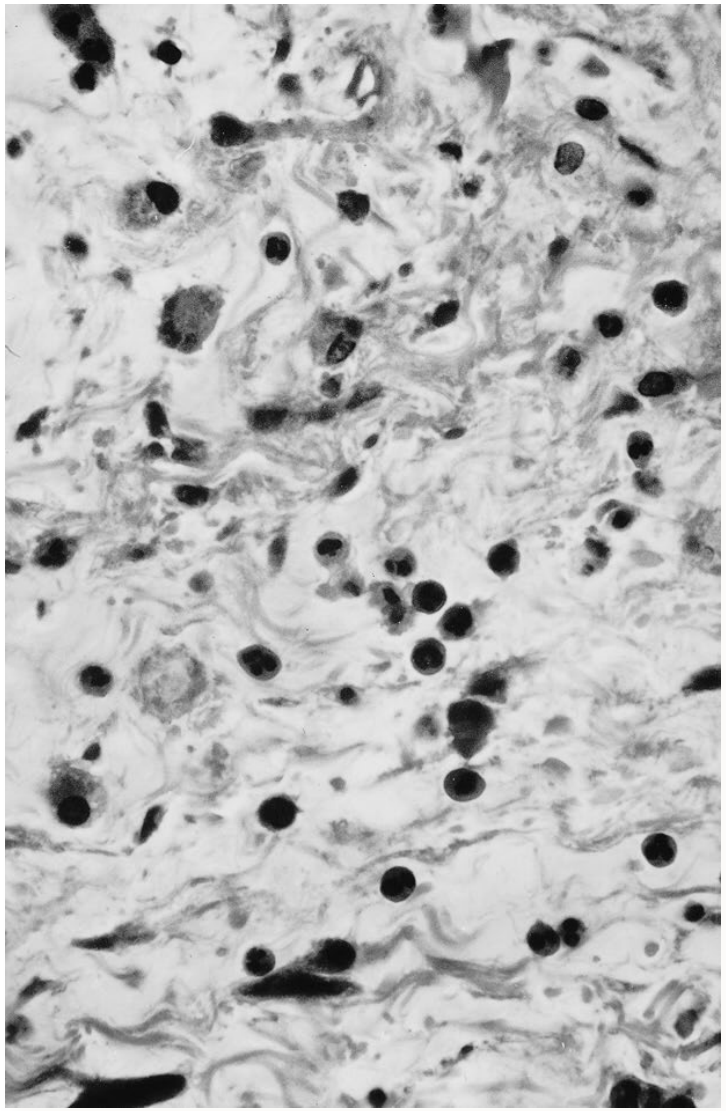
(*Am J Surg Pathol* 2007;31:1371–1377)



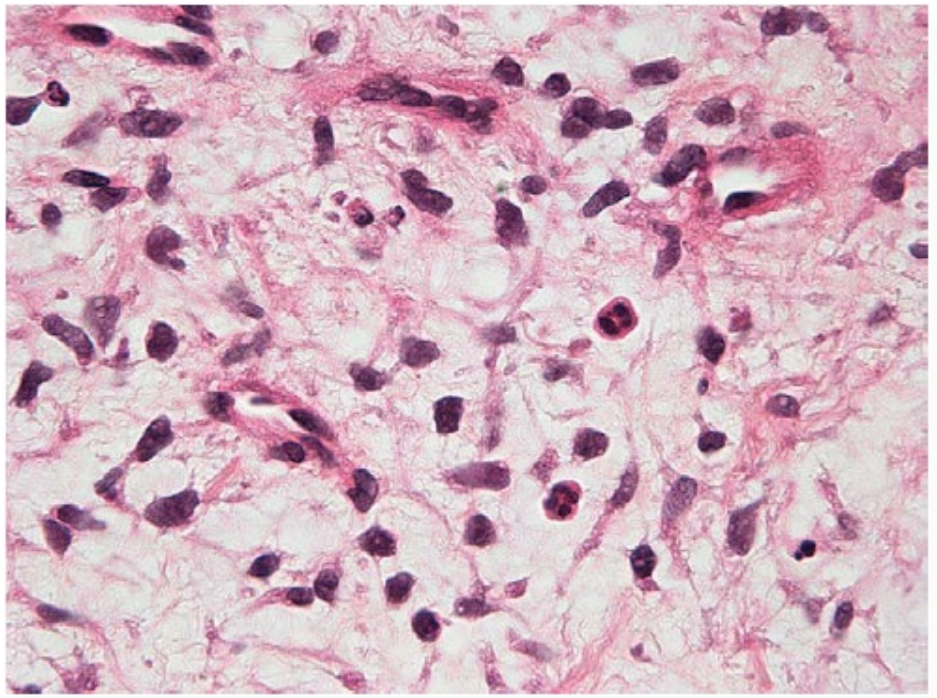


(*Am J Surg Pathol* 2007;31:1371–1377)



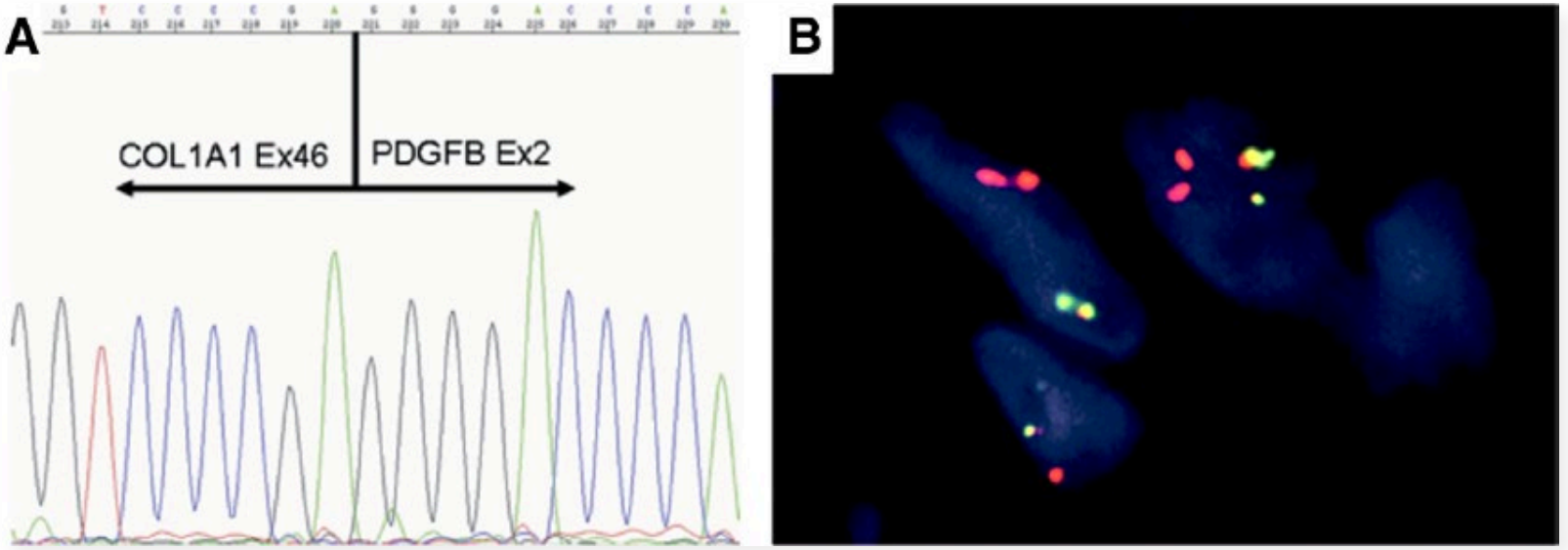


•Superficial Angiomyxoma



•Myxoid DFSP

(*Am J Surg Pathol* 2007;31:1371–1377)



- t(17;22)(q22;q13)=*COL1A1-PDGFB*

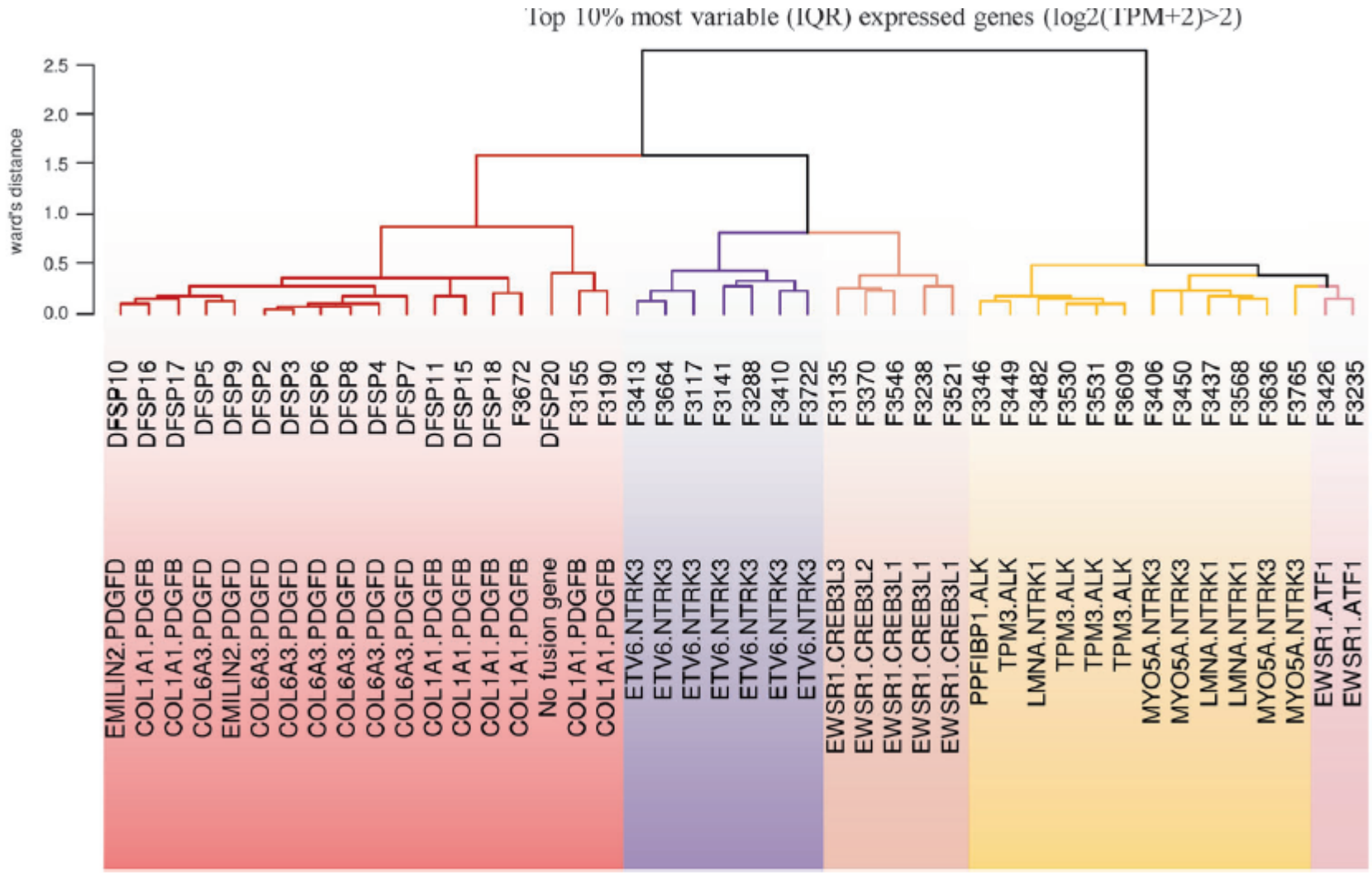
Seminars in Diagnostic Pathology (2013) 30, 13-28

Modern Pathology
https://doi.org/10.1038/s41379-018-0089-4

ARTICLE

Alternative *PDGFD* rearrangements in dermatofibrosarcomas protuberans without *PDGFB* fusions

Bérengère Dadone-Montaudié[1] · Laurent Alberti[2,3] · Adeline Duc[3] · Lucile Delespaul[4,5,11] · Tom Lesluyes[4,5,11] · Gaëlle Pérot[6] · Agnès Lançon[3] · Sandrine Paindavoine[3] · Ilaria Di Mauro[1] · Jean-Yves Blay[2,7] · Arnaud de la Fouchardière[3] · Frédéric Chibon[4,6,11] · Marie Karanian[3] · Gaëtan MacGrogan[6] · Valérie Kubiniek[1] · Frédérique Keslair[1] · Nathalie Cardot-Leccia[8] · Audrey Michot[9] · Virginie Perrin[10] · Yanis Zekri[10] · Jean-Michel Coindre[5,6] · Franck Tirode[2,10] · Florence Pedeutour[1] · Dominique Ranchère-Vince[3] · François Le Loarer[5,6] · Daniel Pissaloux[2,3]


Top 10% most variable (IQR) expressed genes (log2(TPM+2)>2)
ward's distance
2.5
2.0
1.5
1.0
0.5
0.0
DFSP10
DFSP16
DFSP17
DFSP5
DFSP9
DFSP2
DFSP3
DFSP6
DFSP8
DFSP4
DFSP7
DFSP11
DFSP15
DFSP18
F3672
DFSP20
F3155
F3190
F3413
F3664
F3117
F3141
F3288
F3410
F3722
F3135
F3370
F3546
F3238
F3521
F3346
F3449
F3482
F3530
F3531
F3609
F3406
F3450
F3437
F3568
F3636
F3765
F3426
F3235
EMILIN2.PDGFD
COL1A1.PDGFB
COL1A1.PDGFB
COL6A3.PDGFD
EMILIN2.PDGFD
COL6A3.PDGFD
COL6A3.PDGFD
COL6A3.PDGFD
COL6A3.PDGFD
COL6A3.PDGFD
COL6A3.PDGFD
COL1A1.PDGFB
COL1A1.PDGFB
COL1A1.PDGFB
COL1A1.PDGFB
No fusion gene
COL1A1.PDGFB
COL1A1.PDGFB
ETV6.NTRK3
ETV6.NTRK3
ETV6.NTRK3
ETV6.NTRK3
ETV6.NTRK3
ETV6.NTRK3
ETV6.NTRK3
EWSR1.CREB3L3
EWSR1.CREB3L2
EWSR1.CREB3L1
EWSR1.CREB3L1
EWSR1.CREB3L1
PPFIBP1.ALK
TPM3.ALK
LMNA.NTRK1
TPM3.ALK
TPM3.ALK
TPM3.ALK
MYO5A.NTRK3
MYO5A.NTRK3
LMNA.NTRK1
LMNA.NTRK1
MYO5A.NTRK3
MYO5A.NTRK3
EWSR1.ATF1
EWSR1.ATF1

WILEY

RESEARCH ARTICLE

Dermatofibrosarcoma protuberans with a novel *COL6A3-PDGFD* fusion gene and apparent predilection for breast

Brendan C. Dickson[1] | Jason L. Hornick[2] | Christopher D. M. Fletcher[2] | Elizabeth G. Demicco[1] | David J. Howarth[1] | David Swanson[1] | Lei Zhang[3] | Yun-Shao Sung[3] | Cristina R. Antonescu[3]

Received: 16 May 2018 | Revised: 14 June 2018 | Accepted: 15 June 2018

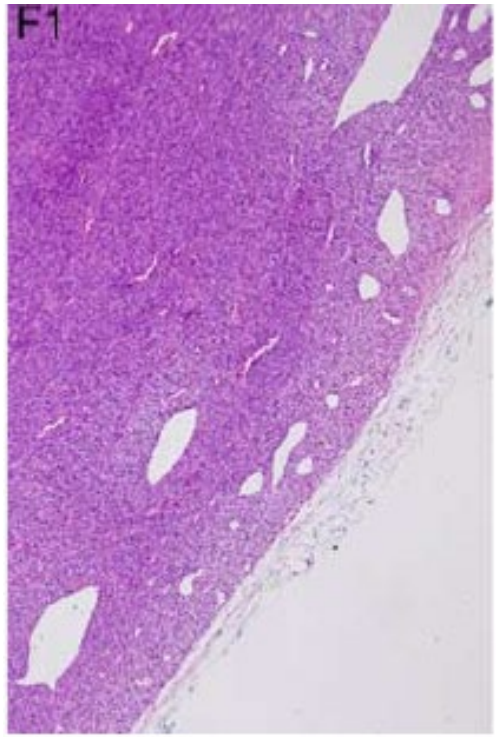
Molecular Characterization of Dermatofibrosarcoma Protuberans

The Clinicopathologic Significance of Uncommon Fusion Gene Rearrangements and Their Diagnostic Importance in the Exclusively Subcutaneous and Circumscribed Lesions

Pei-Hang Lee, MD, Shih-Chiang Huang, MD,†‡ Pao-Shu Wu, MD, PhD,§‖ Hui-Chun Tai, MD,¶ Chih-Hung Lee, MD, PhD,# Jen-Chieh Lee, MD, PhD,** Yu-Chien Kao, MD,††‡‡ Jen-Wei Tsai, MD,§§ Tsung-Han Hsieh, PhD,‖‖ Chien-Feng Li, MD, PhD,¶¶ Wan-Shan Li, MD,## Ting-Ting Liu, MD,**** Yu-Li Su, MD,††† Shih-Chen Yu, MS,* and Hsuan-Ying Huang, MD**

TABLE 2. Clinicopathologic and Molecular Findings of Cryptic *PDGFB*-rearranged and *PDGFD*-rearranged DFSPs

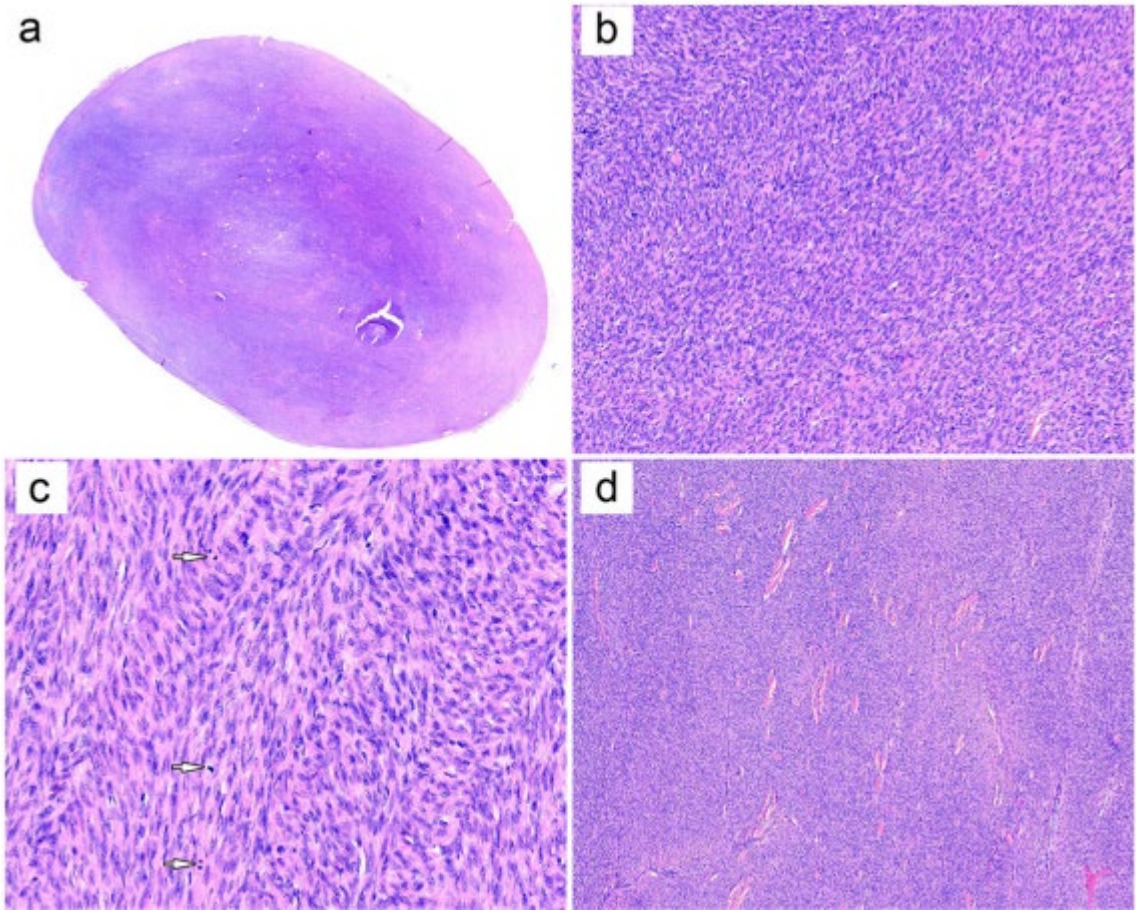
Case No.	Age (y)	Sex	Size (cm)	Location	Subtype	Tumor Contour	Depth
1	31	F	3.5	Groin	FS	Circumscribed	Subcutis
2	64	F	6.5	Abdominal wall	Typical	Circumscribed	Dermis
3	24	F	2.2	Back	Typical	Circumscribed	Dermis
4	30	M	NA	Back	Typical	Infiltrative	Dermis
5	18	F	2	Eyebrow	Typical	Infiltrative	Dermis
6	60	F	3	Sacral area	Typical	Infiltrative	Dermis
7	43	M	NA	Inguinal	Typical	Infiltrative	Dermis
8	34	M	3.5	Eyebrow	FS	Infiltrative	Dermis
9	24	M	3.8	Thigh	FS	Circumscribed	Subcutis
10	31	F	0.6	Flank	FS	Infiltrative	Dermis
11	14	F	3	Neck	Typical	Infiltrative	Dermis
12	20	F	2	Back	Typical	Infiltrative	Subcutis
13	32	M	3.7	Back	Typical	Circumscribed	Subcutis
14	43	M	4.5	Shoulder	FS	Circumscribed	Subcutis
15	15	F	5.0	Thigh	FS	Circumscribed	Subcutis
16	45	M	2	Leg	FS	Infiltrative	Dermis

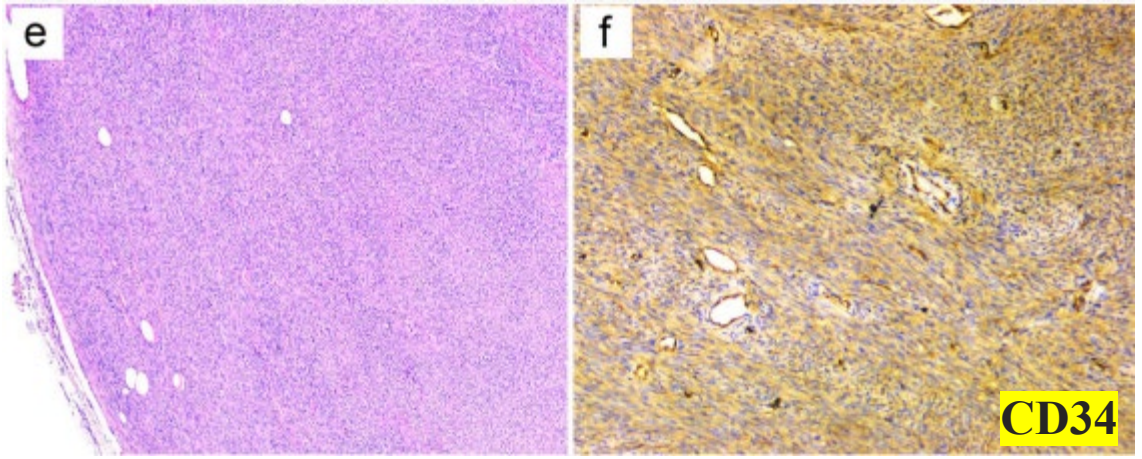


Novel *TNC-PDGFD* fusion in fibrosarcomatous dermatofibrosarcoma protuberans: a case report

Yuan Chen[1†], Ying-zhou Shi[1†], Xiao-he Feng[2], Xiao-tong Wang[3], Xiang-lei He[1] and Ming Zhao[1*]

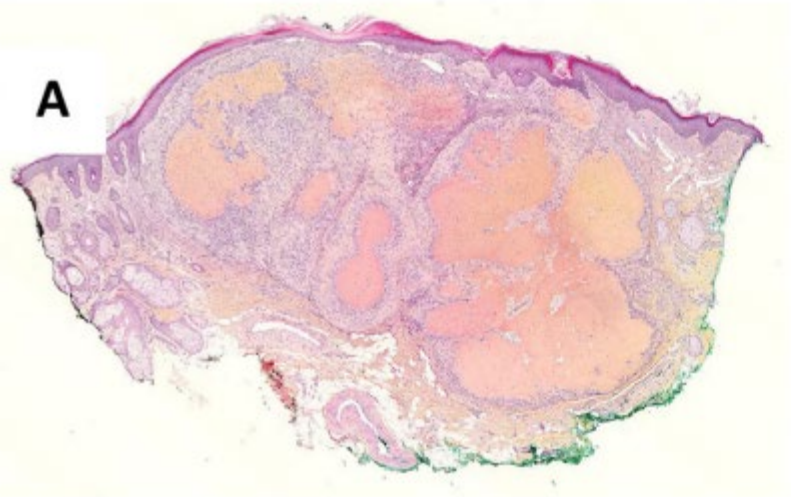
Chen *et al. Diagnostic Pathology* (2021) 16:63

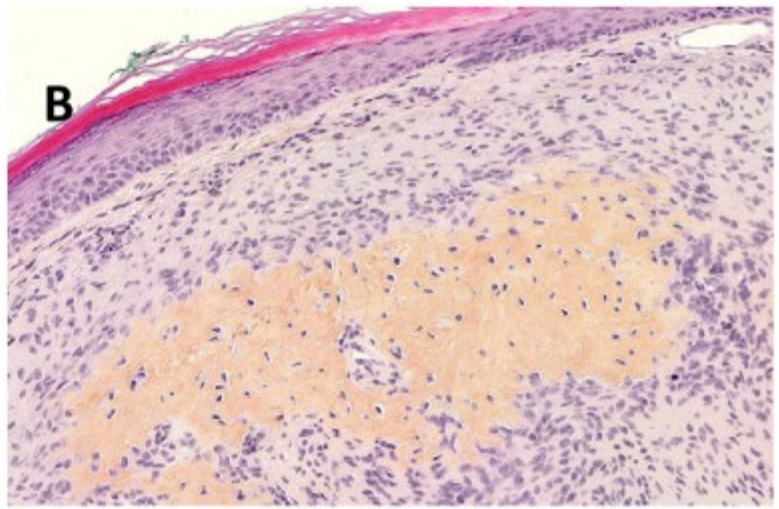


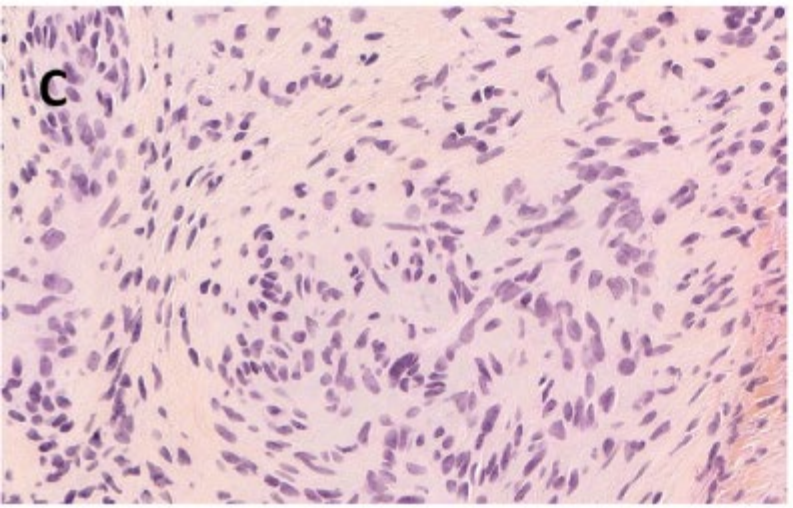


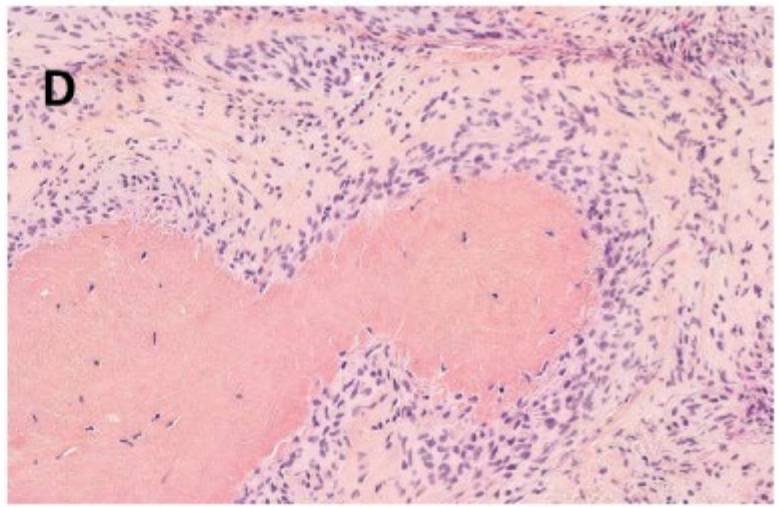
Superficial spindle cell tumour with *TNC::PDGFD* fusion is a distinct entity from dermatofibrosarcoma protuberans

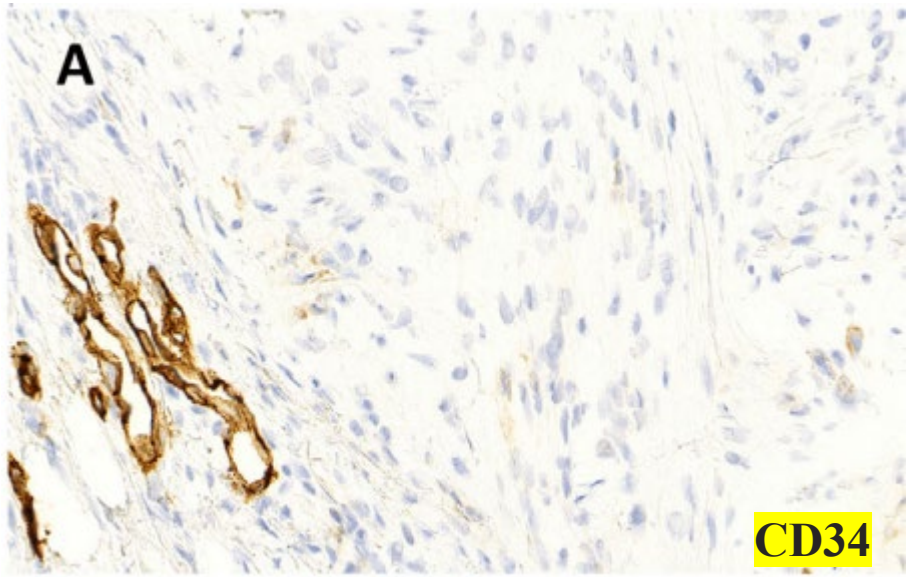
Pathology (2023), **55(4)**, June









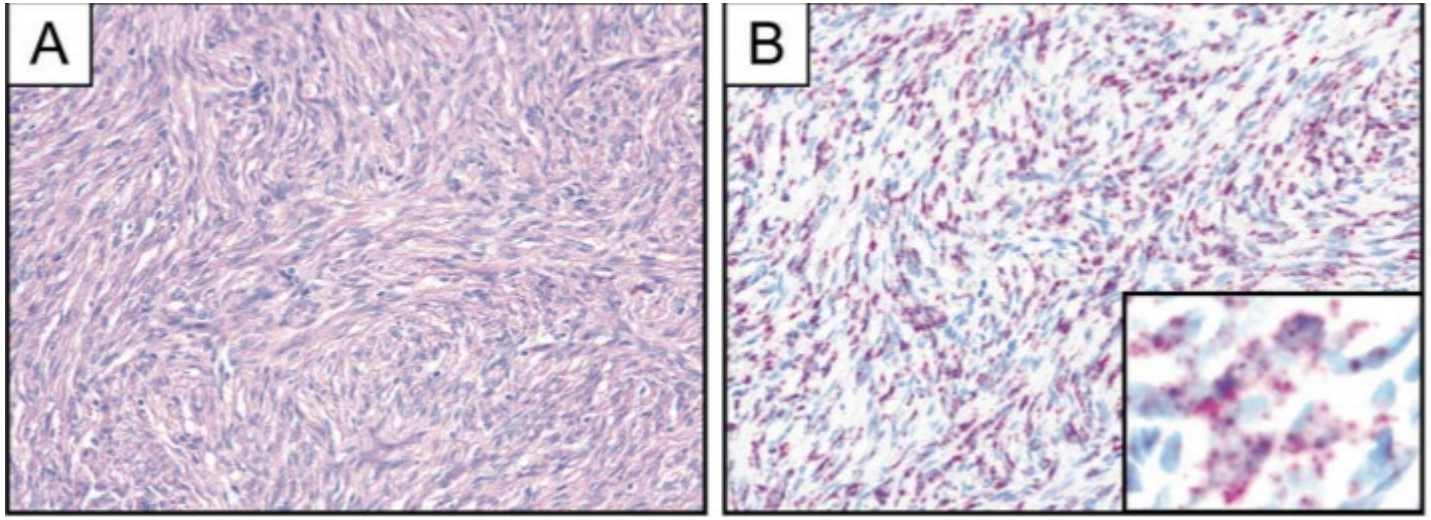


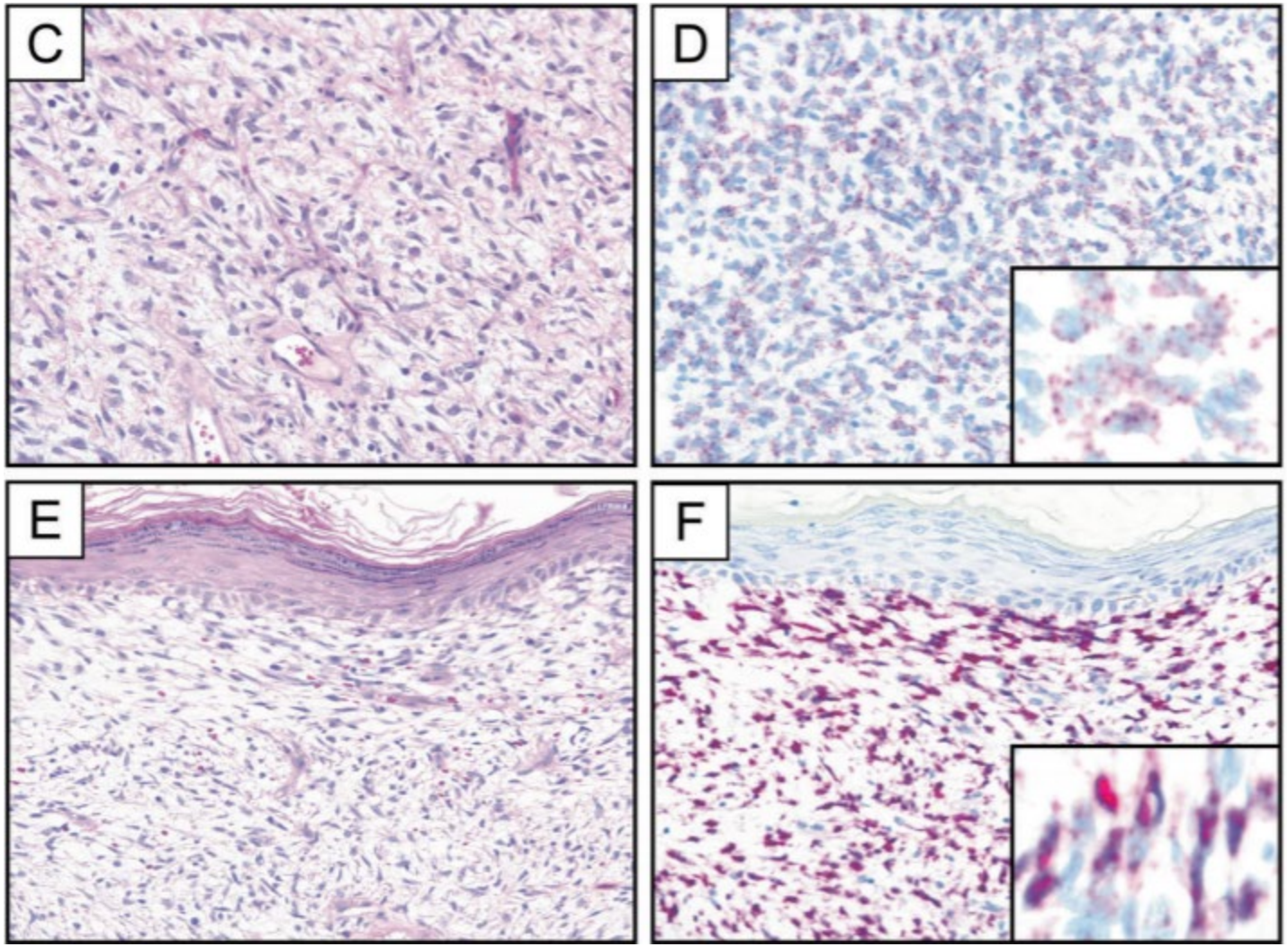
Modern Pathology
https://doi.org/10.1038/s41379-021-00800-2

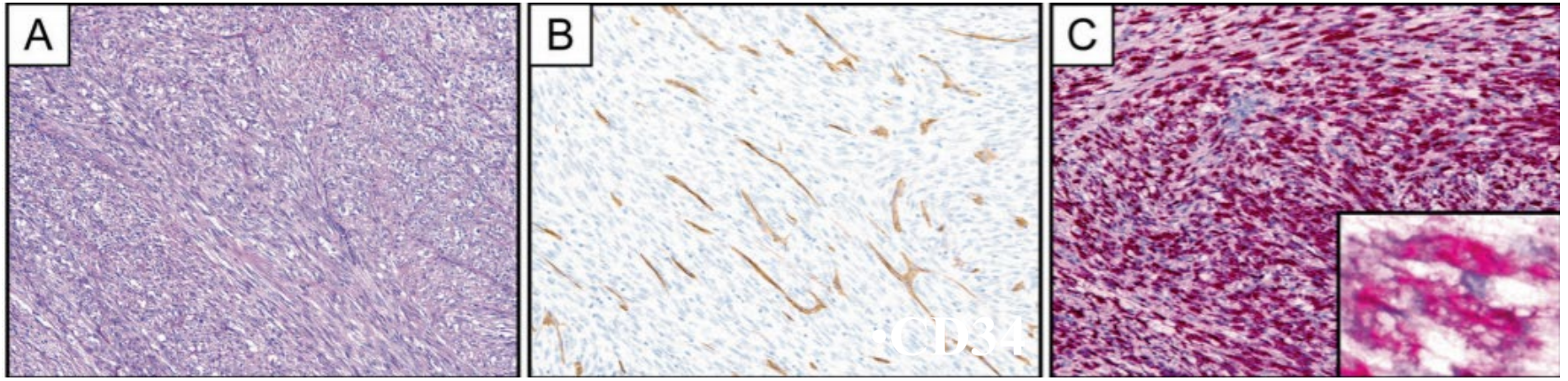
ARTICLE

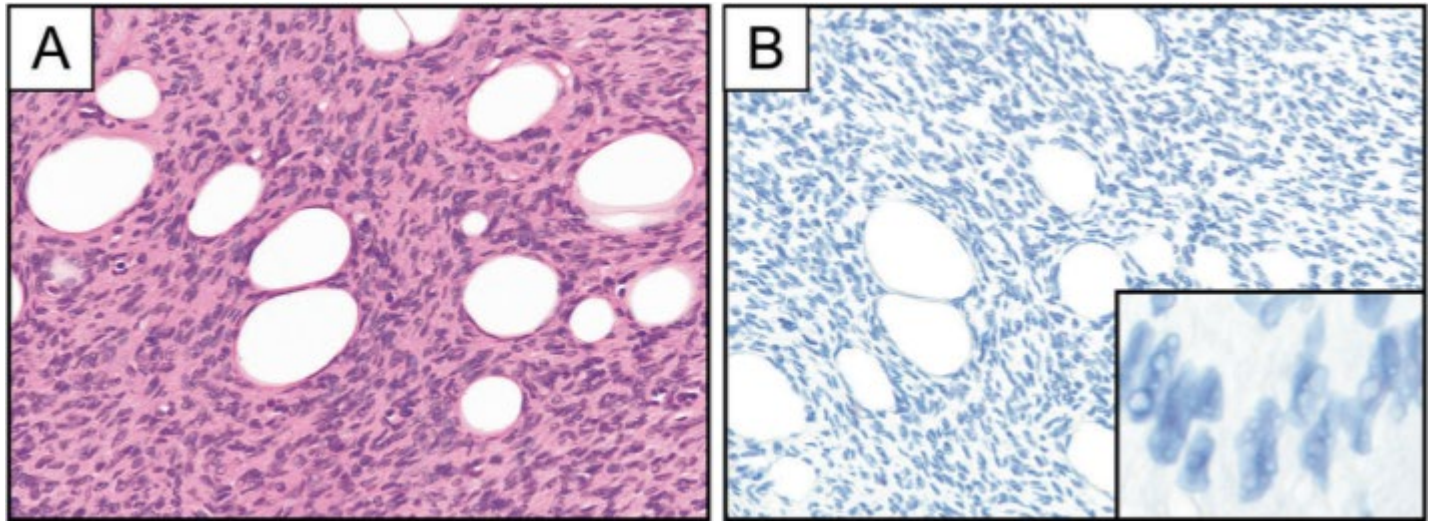
PDGFB RNA in situ hybridization for the diagnosis of dermatofibrosarcoma protuberans

Jeffrey M. Cloutier[1] · Grace Allard[1] · Gregory R. Bean[1] · Jason L. Hornick[2] · Gregory W. Charville[1]

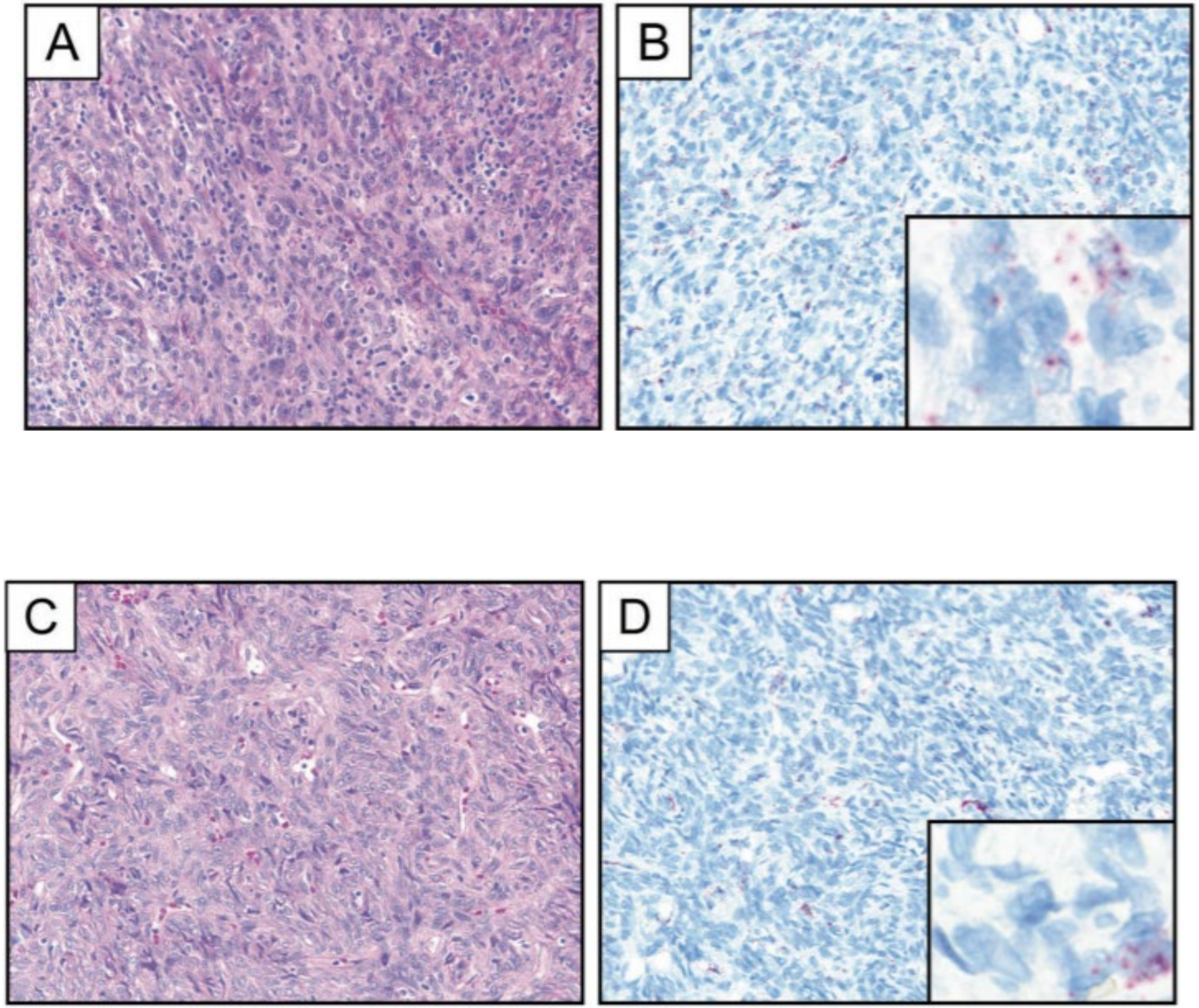



C
D
E
F

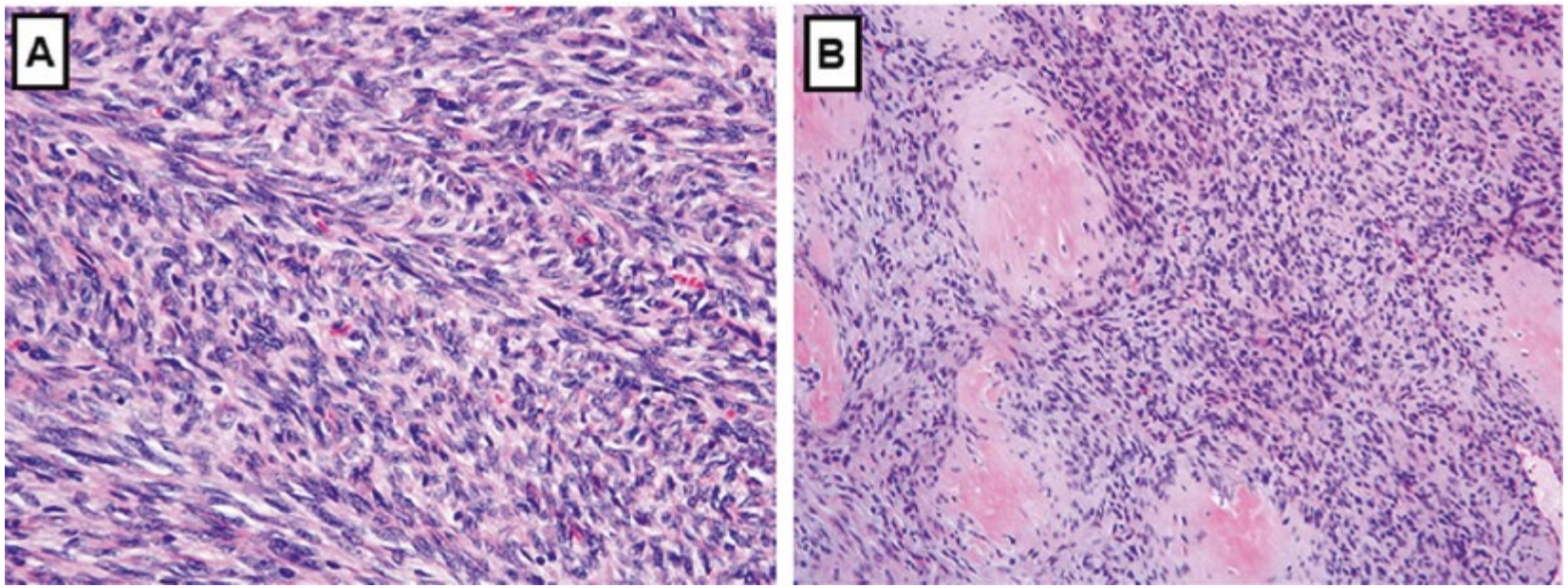

A
B
CD34
C


A
B

Tumor type	Total cases	*PDGFB* overexpression (%)	*PDGFB* limited (%)	*PDGFB* negative (%)
Conventional DFSP	26	24 (92)	0 (0)	2 (8)
PDGFD-rearranged DFSP	1	0	0 (0)	1 (100%)
Fibrosarcomatous DFSP	11	11 (100)	0 (0)	0 (0)
Dermatofibroma	14	0 (0)	0 (0)	14 (100)
Cellular dermatofibroma	11	0 (0)	0 (0)	11 (100)
Atypical fibrous histiocytoma	4	0 (0)	0 (0)	4 (100)
Angiomatoid fibrous histiocytoma	2	0 (0)	0 (0)	2 (100)
Superficial acral fibromyxoma	3	0 (0)	0 (0)	3 (100)
Atypical fibroxanthoma	8	0 (0)	0 (0)	8 (100)
Pleomorphic dermal sarcoma	8	0 (0)	2 (25)	6 (75)
Solitary fibrous tumor	15	0 (0)	0 (0)	15 (100)
Synovial sarcoma (monophasic)	13	0 (0)	0 (0)	13 (100)
Angiosarcoma	12	0 (0)	1 (8)	11 (92)
Kaposi sarcoma	3	0 (0)	0 (0)	3 (100)
Melanoma (desmoplastic)	9	0 (0)	2 (22)	7 (78)
Nodular fasciitis	8	0 (0)	0 (0)	8 (100)
Desmoid fibromatosis	28	0 (0)	0 (0)	28 (100)
Leiomyosarcoma (extrauterine)	57	0 (0)	0 (0)	57 (100)
Neurofibroma	41	0 (0)	0 (0)	41 (100)
MPNST	65	0 (0)	2 (3)	63 (97)


A
B
C
D

Fibrosarcomatous DFSP



Modern Pathology (2020) 33:56–65

Fibrosarcomatous DFSP

Often loss (or decreased) of CD34

Acquisition of metastatic potential (10-15%)
- Most often lungs

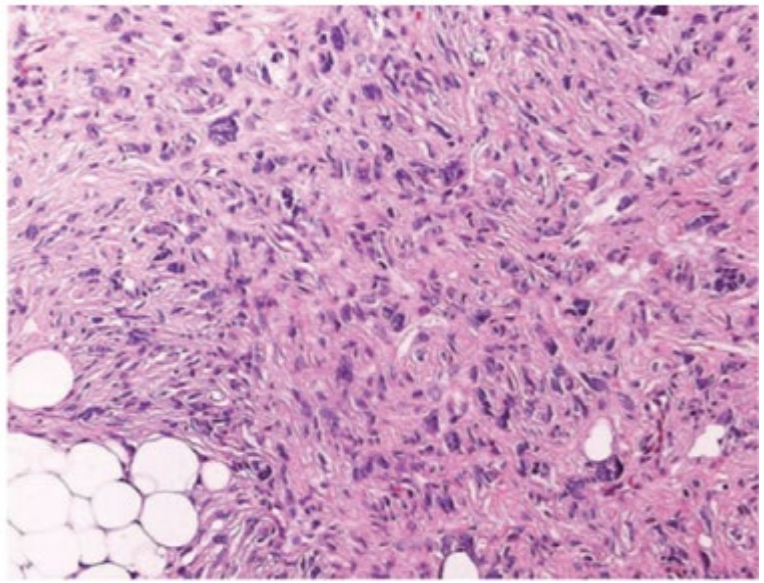
External-beam radiation therapy can be considered

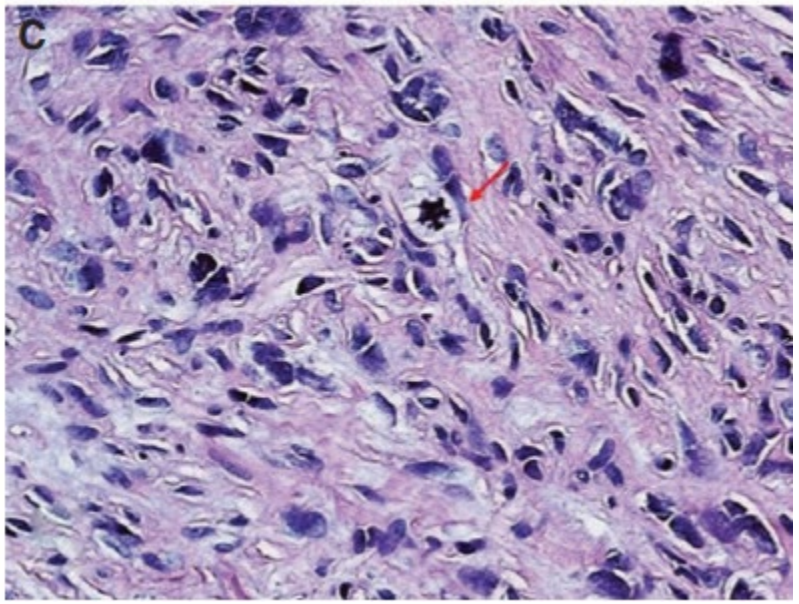
Giant cell fibroblastoma does **not** transform

An unusual presentation of dermatofibrosarcoma protuberans with pleomorphic sarcomatous transformation: potential pitfall and diagnostic strategy

J Cutan Pathol 2016: 43: 589–593

Anna Maria Cesinaro[1], Ema Mataca[1], Claudio Gambini[2] and Heinz Kutzner[3]





Cancer Therapy: Clinical

Clinical Cancer Research

Neoadjuvant Imatinib in Advanced Primary or Locally Recurrent Dermatofibrosarcoma Protuberans: A Multicenter Phase II DeCOG Trial with Long-term Follow-up

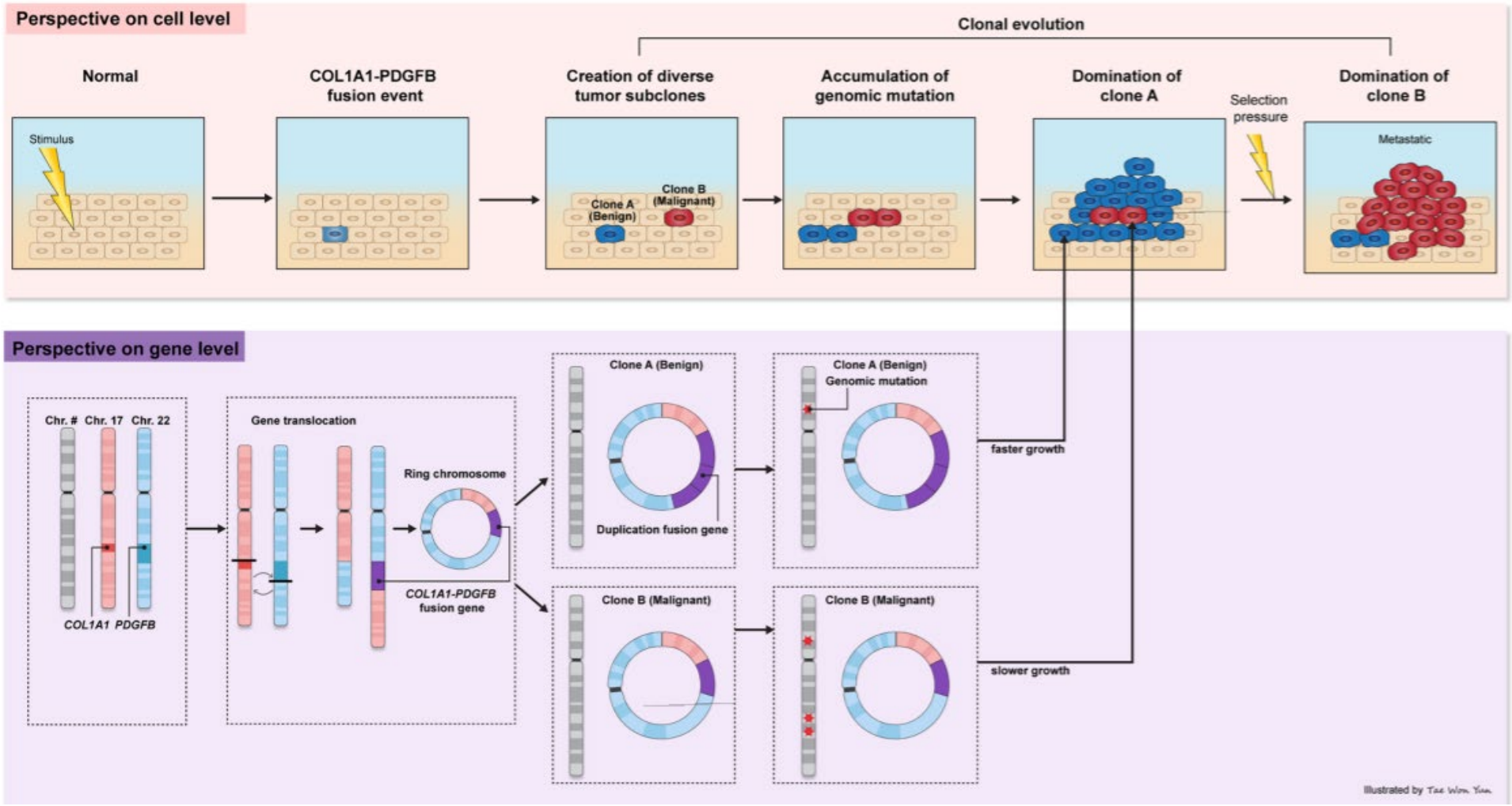
Selma Ugurel[1], Thomas Mentzel[2], Jochen Utikal[3,5], Peter Helmbold[4,6], Peter Mohr[7], Claudia Pföhler[8], Meinhard Schiller[9], Axel Hauschild[10], Rüdiger Hein[11], Eckhardt Kämpgen[12], Ivonne Kellner[13], Martin Leverkus[5], Jürgen C. Becker[16], Philip Ströbel[14], and Dirk Schadendorf[15]

RESEARCH ARTICLE

Unforeseen clonal evolution of tumor cell population in recurrent and metastatic dermatofibrosarcoma protuberans

Ensel Oh[1,2☯], Hae Min Jeong[3☯], Mi Jeong Kwon[4,5], Sang Yun Ha[6], Hyung Kyu Park[6], Ji-Young Song[1], Yu Jin Kim[1], Jong-Sun Choi[7], Eun Hee Lee[8], Jeeyun Lee[9], Yoon-La Choi[1,2,6‡*], Young Kee Shin[3,7‡*]

October 4, 2017


Perspective on cell level
Clonal evolution
Normal
COL1A1-PDGFB fusion event
Creation of diverse tumor subclones
Accumulation of genomic mutation
Domination of clone A
Selection pressure
Domination of clone B
Stimulus
Clone A (Benign)
Clone B (Malignant)
Metastatic
Perspective on gene level
Chr. # Chr. 17 Chr. 22
COL1A1 PDGFB
Gene translocation
Ring chromosome
COL1A1-PDGFB fusion gene
Clone A (Benign)
Duplication fusion gene
Genomic mutation
faster growth
Clone B (Malignant)
slower growth
Illustrated by Tae Won Yun

COL1A1-PDGFB Fusion Associated Fibrosarcoma of the Uterine Corpus: A Case Report and Literature Review

Vandana Panwar, M.D., Yu Liu, M.D., Ph.D., Katja Gwin, M.D., and Hao Chen, M.D., Ph.D.

Int J Gynecol Pathol Vol. 42, No. 2, March 2023

COL1A1::PDGFB fusion uterine sarcoma with a *TERT* promoter mutation

Yang Lu[1] | Xinyi Chen[2] | Wenjing Zeng[3] | Ping Hua[4] | Yangmei Shen[5] | Yan Qiu[1] | Xin He[1] | Hongying Zhang[1]

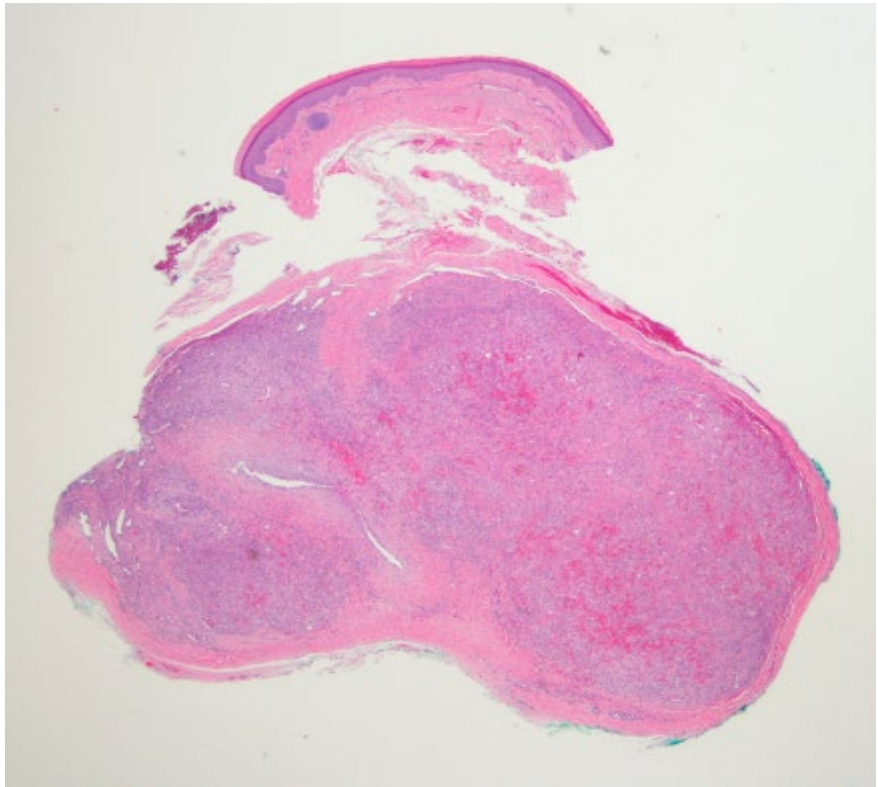
Genes Chromosomes Cancer. 2024;63:e23210.

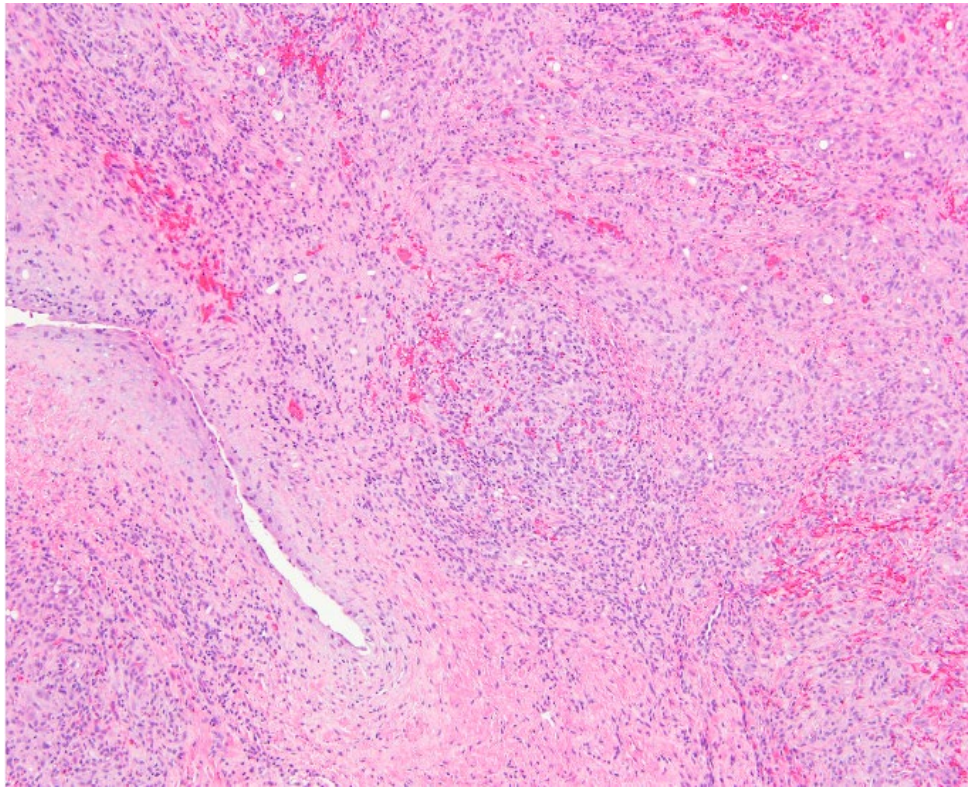
Vascular tumors

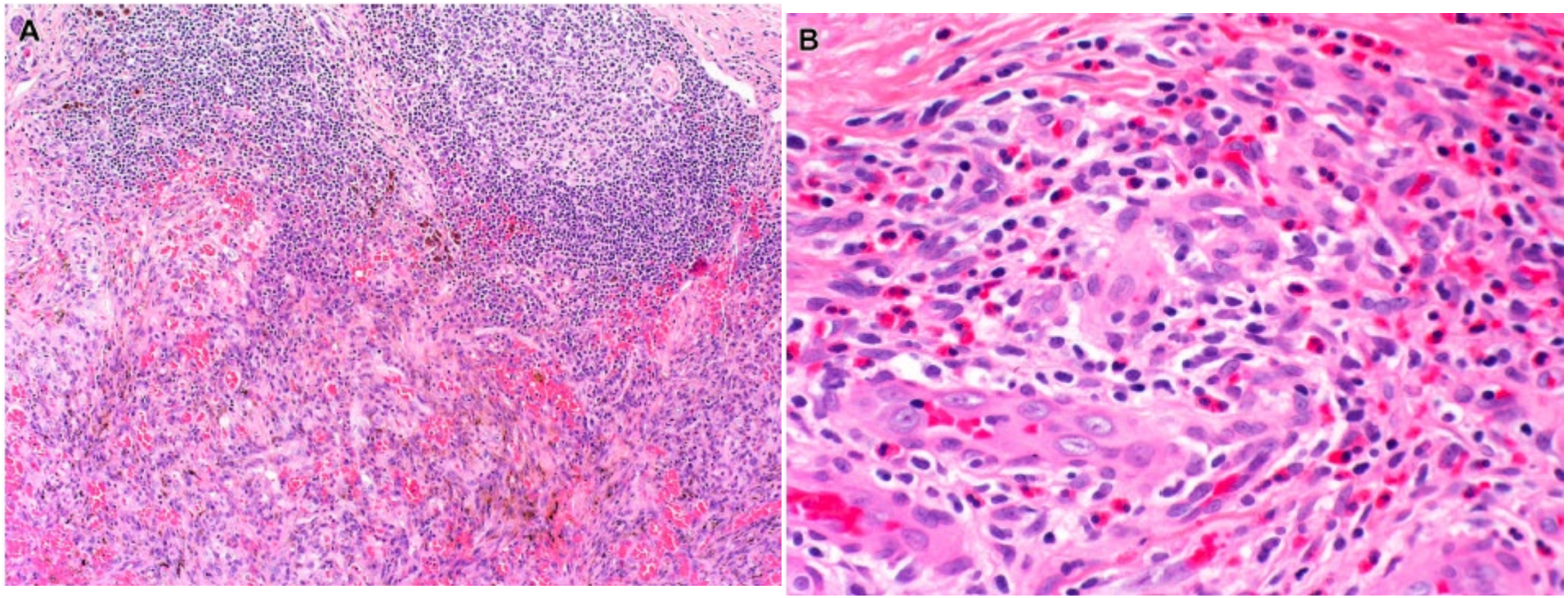
Epithelioid hemangioma

- “Conventional”subtype
- “Angiolymphoid hyperplasia with eosinophilia subtype”
- “Cellular subtype”

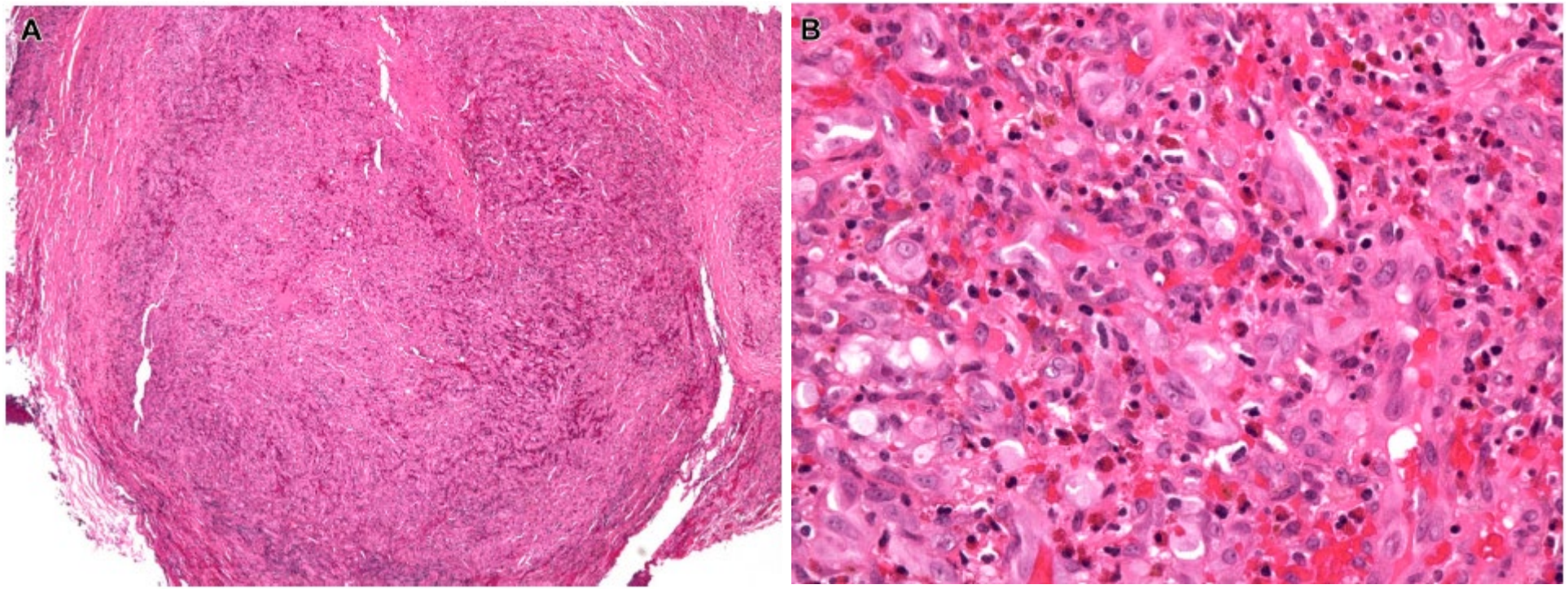
Seminars in Diagnostic Pathology
33 (2016) 284–293







Surgical Pathology 8 (2015) 331–351



Surgical Pathology 8 (2015) 331–351

IHC

Positive for vascular markers

- CD31, CD34, ERG
- Also positive for D2-40

Pitfall!!

- **Immunoreactivity for EMA and keratins may be seen**

Genetic alteration (prevalence)

WWTR1-FOSB	20% cellular subtype
ZFP36-FOSB	
FOS-VIM	50% cellular subtype
FOS-MBLNI	
FOS-lincRNA	
FOS-(unknown)	

Virchows Archiv
https://doi.org/10.1007/s00428-019-02651-4

ZFP36-FOSB Fusion Defines a Subset of Epithelioid Hemangioma with Atypical Features

Cristina R Antonescu,[1]* Hsiao-Wei Chen,[1] Lei Zhang,[1] Yun-Shao Sung,[1] David Panicek,[2] Narasimhan P Agaram,[1] Brendan C Dickson,[3] Thomas Krausz,[4] and Christopher D Fletcher[5]*

[1]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY
[2]Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY
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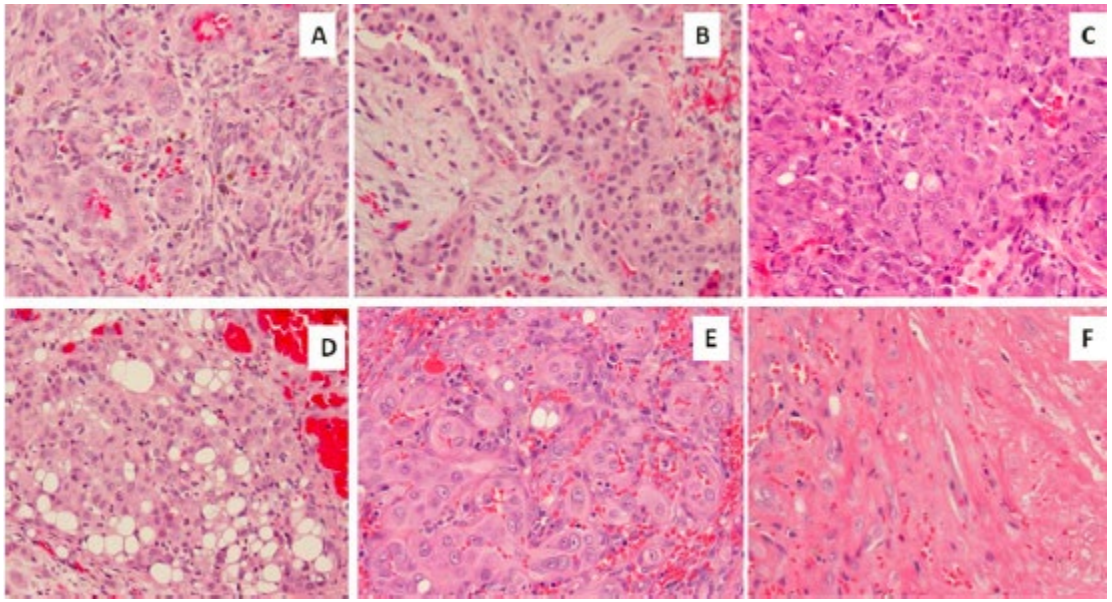


GENES, CHROMOSOMES & CANCER 53:951–959 (2014)

Frequent *FOS* Gene Rearrangements in Epithelioid Hemangioma

A Molecular Study of 58 Cases With Morphologic Reappraisal

Shih-Chiang Huang, MD,† Lei Zhang, MD,† Yun-Shao Sung, MSc,† Chun-Liang Chen, MSc,† Thomas Krausz, MD,‡ Brendan C. Dickson, MD,§ Yu-Chien Kao, MD,‖ Narasimhan P. Agaram, MBBS,† Christopher D.M. Fletcher, MD, FRCPath,¶ and Cristina R. Antonescu, MD†*

Case	Age/Sex	Depth	Location	Multifocal	Histologic Variant	Genetic Alterations
1	45/M	Bone	Rib	No	Typical	*FOS-LMNA*
2	56/F	Bone	Foot	Yes	Cellular	*FOS-VIM*
3	38/F	Bone	Foot (cuboid)	NA	Cellular	*FOS-VIM*
4	48/M	Cutaneous	Penis	Yes	Typical	*FOS* rearrangement
5	63/M	Soft tissue	Arm	No	Cellular	*FOS* rearrangement
6	31/M	Bone	Foot	No	Cellular	*FOS* rearrangement
7	38/M	Soft tissue	Arm	No	Typical	*FOS* rearrangement
8	23/M	Bone	Chest wall	No	Typical	*FOS* rearrangement
9	41/M	Bone	L5 vertebra	No	Cellular	*FOS* rearrangement
10	67/M	Soft tissue	Scalp	NA	Cellular	*FOS* rearrangement
11	46/F	Bone	Metatarsal	NA	Cellular	*FOS* rearrangement
12	45/F	Soft tissue	Foot	NA	Cellular	*FOS* rearrangement
13	54/M	Soft tissue	Arm	NA	Cellular	*FOS* rearrangement
14	67/F	Soft tissue	Hand	NA	Cellular	*FOS* rearrangement
15	15/M	Bone	Toe	No	Typical	*FOS* rearrangement
16	15/M	Bone	Femur	No	Cellular	*FOS* rearrangement
17	18/M	Bone	Radius	No	Cellular	*FOS* rearrangement

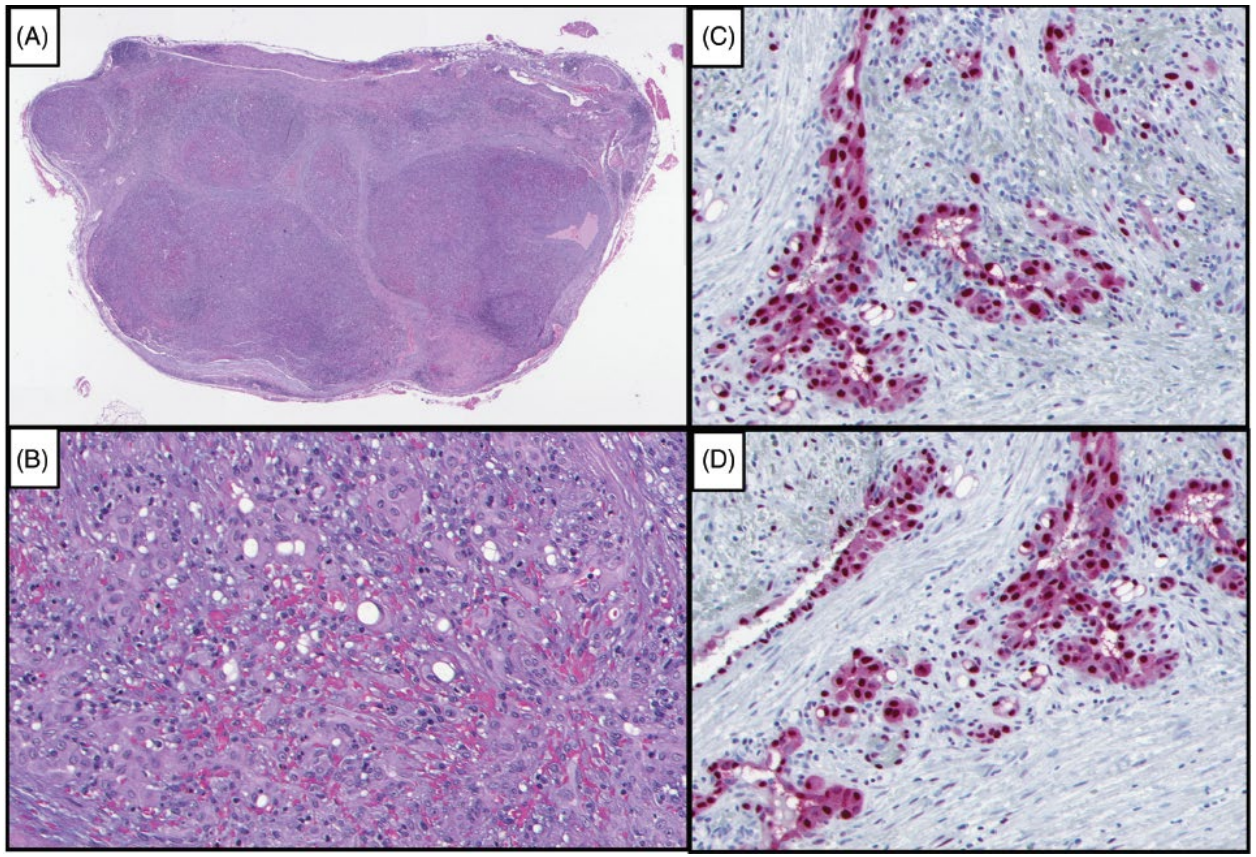
(*Am J Surg Pathol* 2015;39:1313–1321)

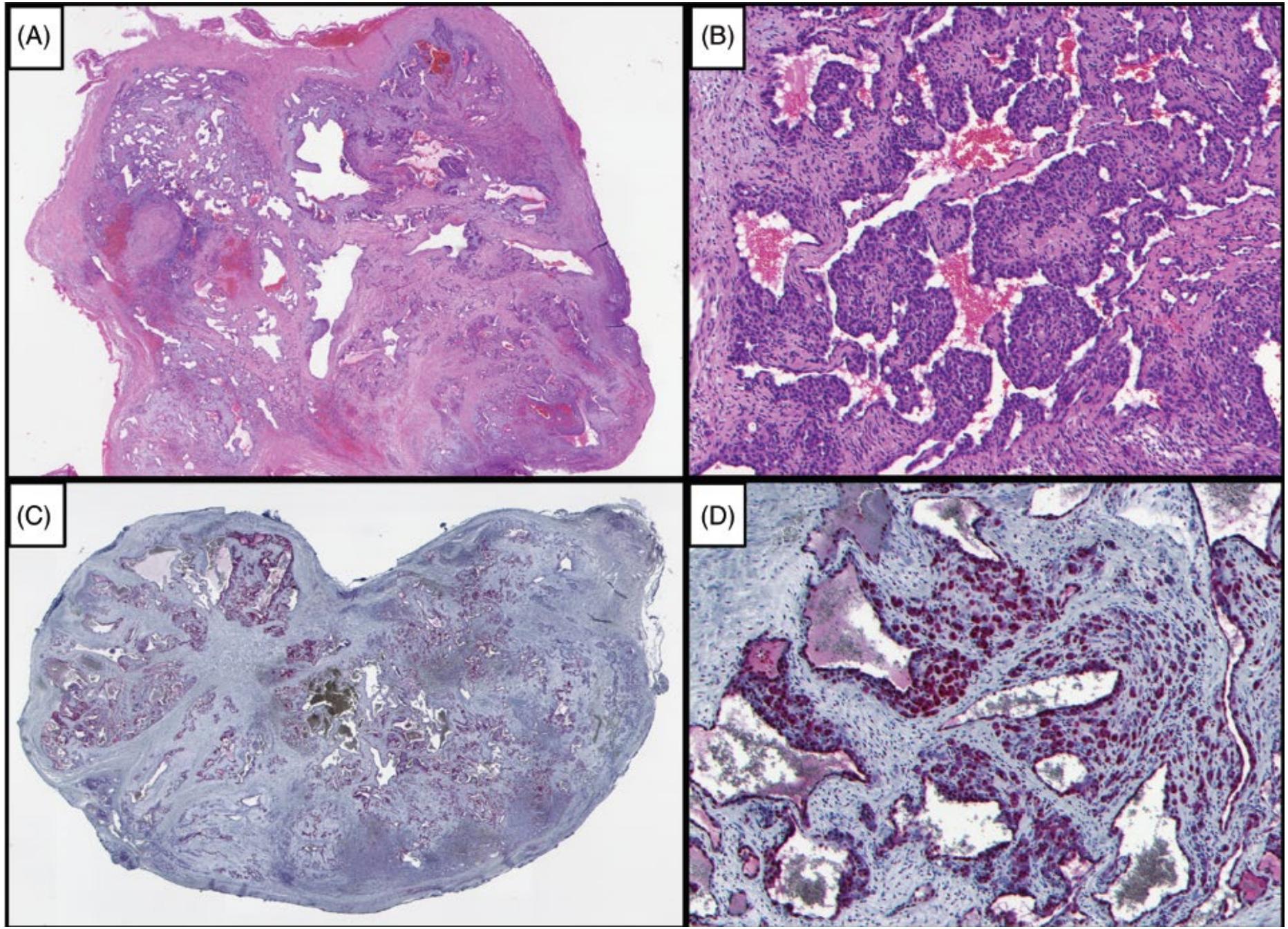
ORIGINAL ARTICLE

FOSB immunoreactivity in endothelia of epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia)

Ana Ortins-Pina[1] | Mar Llamas-Velasco[2] | Sara Turpin[3] | Luís Soares-de-Almeida[1,4,5] | Paulo Filipe[1,4,5] | Heinz Kutzner[6]

J Cutan Pathol. 2018;**45**:395–402.

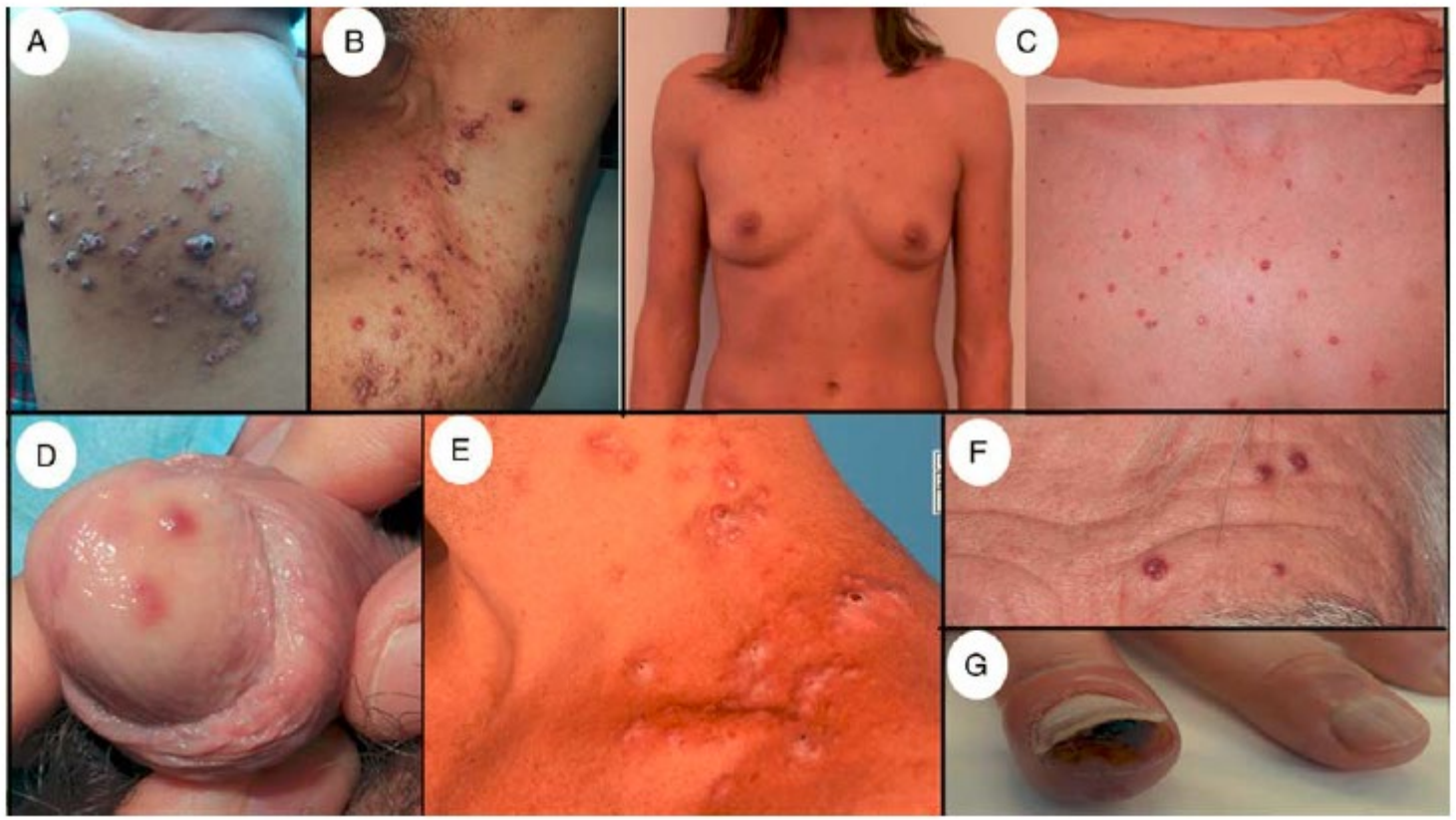



(A)
(B)
(C)
(D)

Multiple Eruptive Epithelioid Hemangiomas

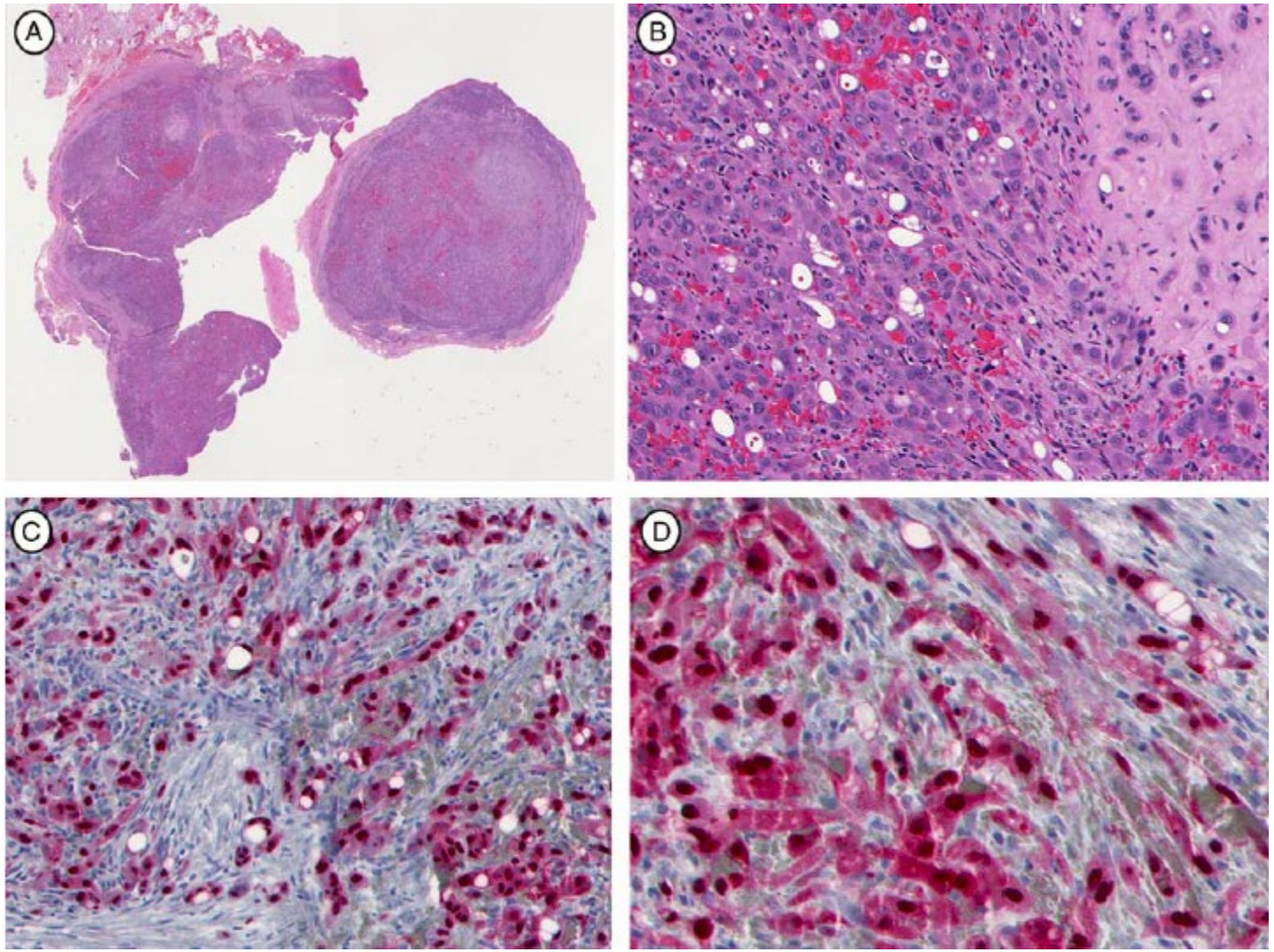
A Subset of Cutaneous Cellular Epithelioid Hemangioma With Expression of FOS-B

Mar Llamas-Velasco, MD, Werner Kempf, MD,† Carlo Cota, MD,‡ Maria Teresa Fernández-Figueras, MD,§ Joyce Lee, MD,‖ Gerardo Ferrara, MD,¶ Christian Sander, MD,# Philip E. Shapiro, MD,** Luis Requena, MD,†† and Heinz Kutzner, MD‡‡*



(*Am J Surg Pathol* 2017;00:000–000)

No.	Age (y)/ Sex	Location	Clinical	Patt	Coll	NP	Ki67 (%)	IHQ/FISH Myc	IHQ/FISH CAMTA-1	IHQ FOS-B	Treatment
1	85/M	Left-side forehead	Erythematous-violaceous papules. Asymptomatic	U	Y	P	<5	Neg	Neg	Pos	EC, Qx
2	50/M	Left scapular area	Painless nodules scattered with profuse bleeding upon trauma	M	Y	P	<5	Neg	Neg	Pos	EC, Qx, cryotherapy
3	UK/M	Left hand and forearm	Purplish nodules. Le lesion on the fourth digit of the left hand progressively became enlarged and ulcerated	M	N	P	5	Neg	Neg	Pos	EC, imiquimod once a day for 3 wk
4	38/F	Arms, legs, and trunk	Slightly erythematous and skin-colored dome-shaped papules and plaques ranging from 0.4 to 1.2 cm, with symmetrical distribution	M	N	A	<5	Neg	Neg	Pos	Acitretin 0.6 mg/kg for 2 mo
5	73/M	Face	Angiomatous papules in an agminated fashion on the centrofacial region	M	Y	P	5	Neg	Neg	Pos	Qx
5	73/M	Idem	Idem	U	N	P	>15	Neg	Neg	Pos	Qx
6	49/M	Neck	Purple papule slightly pruritic	M	Y	P	20	Neg	Neg	Pos	Qx
6	49/M	Left lateral forehead	Purple papule asymptomatic	U	Y	P		Neg	Neg	Pos	Qx
7	45/M	Penis	Slightly painful purplish papules. No erectile dysfunction	U	N	P	<5	Neg	Neg	Pos	Qx
7	45/M	Idem	Idem	M	N	P	<5	Neg	Neg	Pos	Qx
8	34/M	Left shoulder	Persistent erythematous papules	M	N	P	5-10	Neg	Neg	Pos	Laser, EC
9	38/M	Left Shoulder, neck, and arm	Persistent. The patient developed anemia recently	M	N	A	5	Neg	Neg	Pos	Qx
10	45/F	Face, both shoulders, axilla, and genital area	Persistent	U	Y	P	5	Neg	Neg	Pos	Qx
11	27/M	Penis	Persistent lesions	U	N	P	<5	Neg	Neg	Pos	Qx
12	54/M	Right arm	Asymptomatic nodules	U	N	P	<1	Neg	Neg	Pos	Qx
13	67/M	Trunk and extremities	Asymptomatic nodules	U	N	P	<5	Neg	Neg	Pos	Qx

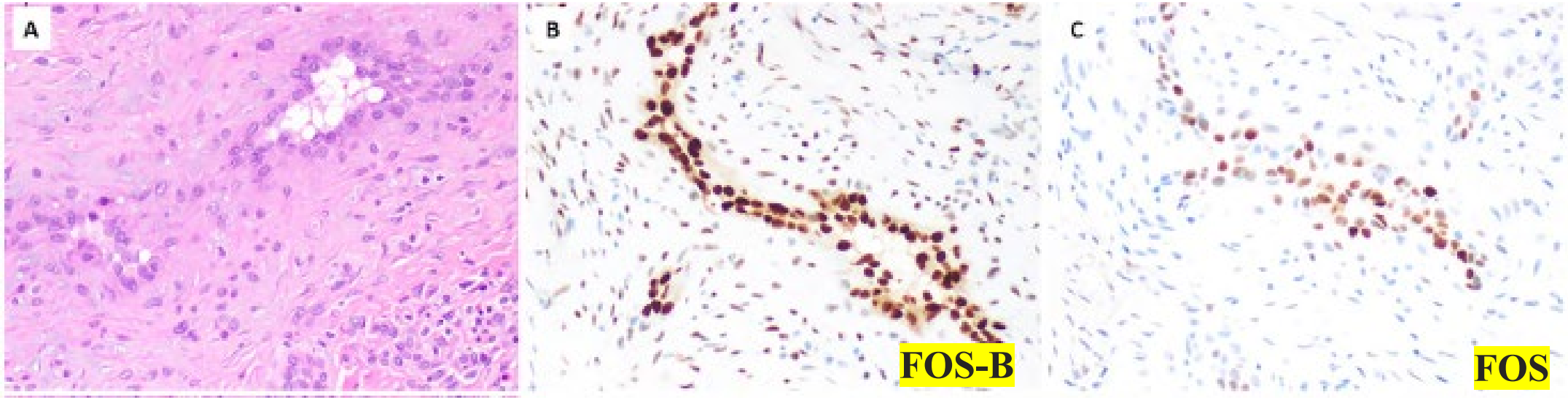

A
B
C
D

Original Article

Immunohistochemistry for FOSB and FOS is a Useful Ancillary Tool in the Diagnosis of Epithelioid Hemangioma but There are Pitfalls in Interpretation Including Expression in Other Vascular Lesions

Kwan Yee Tsui, BMedSci[1], Fiona Maclean, MBBS, FRCPA[1,2,3], Denis Moir, MBBS, FRCPA[1], Alison Cheah, MBBS, FRCPA[1], Fiona Bonar, MBBS, FRCPA[1], Joel Tabot, BSc[1], Anthony J. Gill, MD, FRCPA, AM[2,4,5], and A. Cristina Vargas, MBBS, PhD, FRCPA[1,2,4]

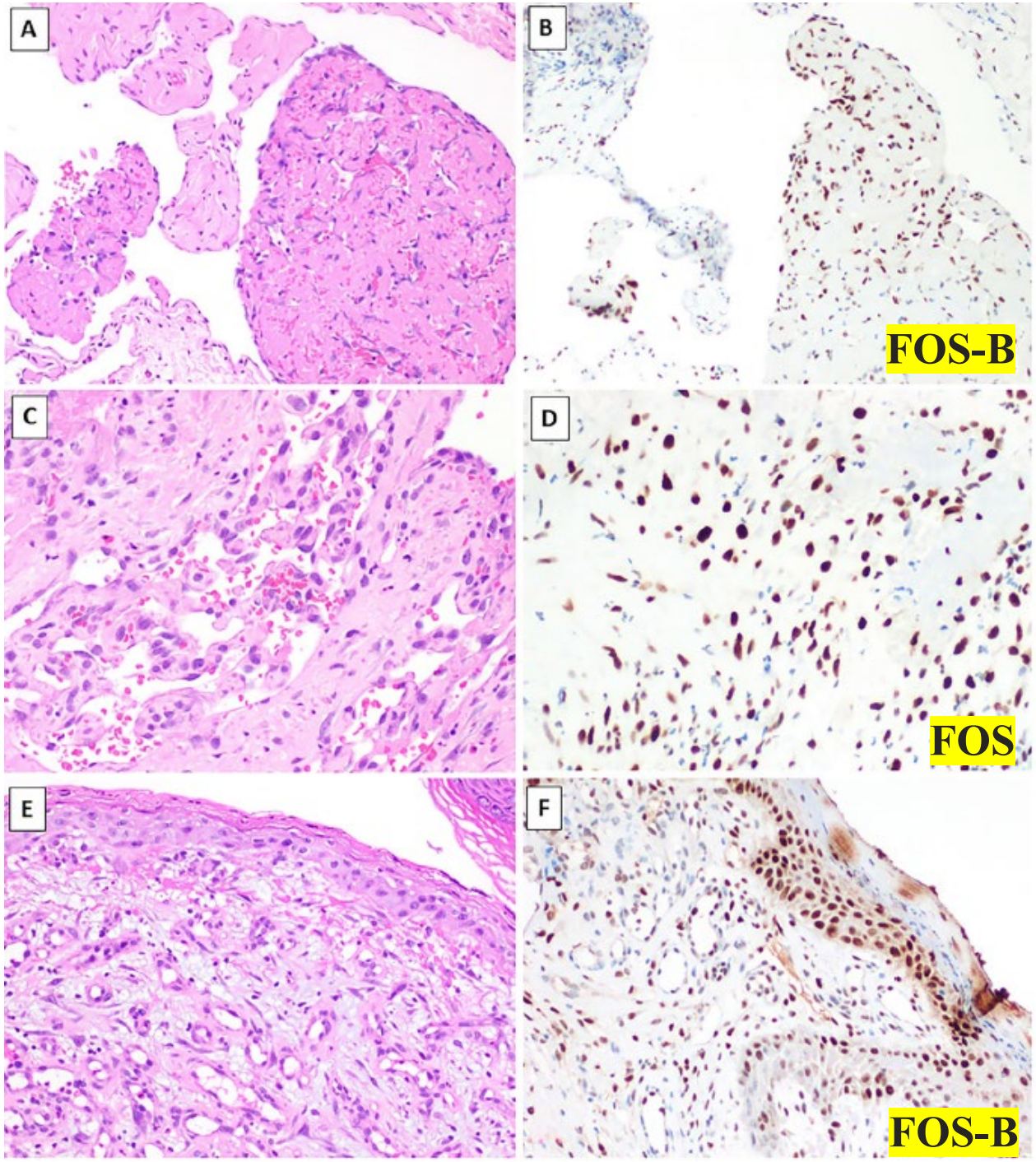
International Journal of Surgical Pathology
2023, Vol. 31(3) 280–288



Papillary endothelial hyperplasia

Papillary endothelial hyperplasia

Lobular capillary hemangioma

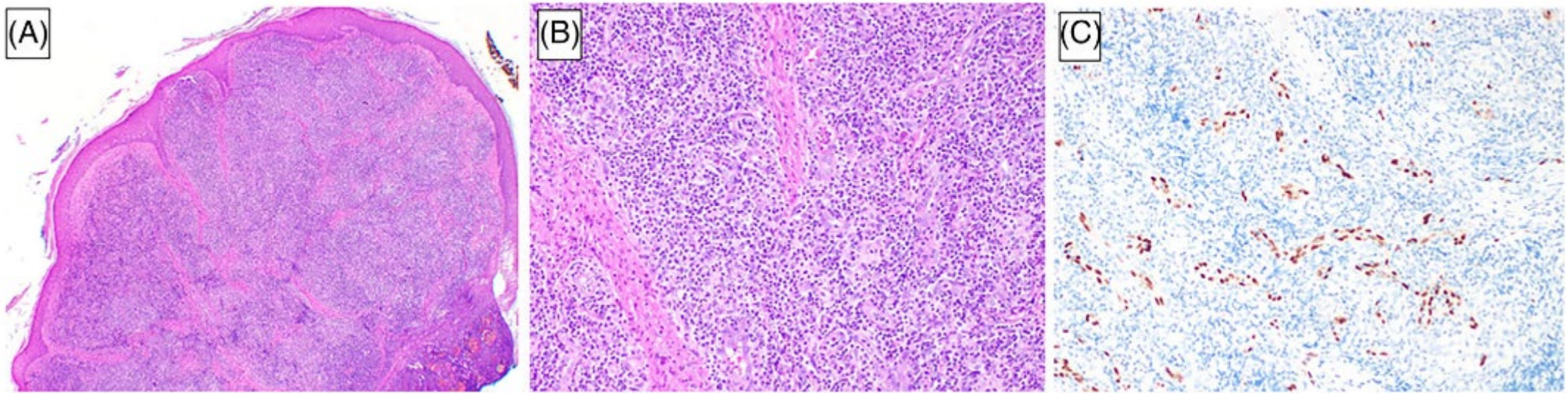


International Journal of Surgical Pathology
2023, Vol. 31(3) 280–288

Inflammatory lobular hemangioma (T-cell-rich angiomatoid polypoid pseudolymphoma)—Assessment of FOS/FOSB and lymphoid markers and comparison with epithelioid hemangioma

Ana Cristina Vargas[1,2,3] | Fiona M. Maclean[1,2,4] | Kwan Yee Tsu[1] | Leanne Ma[1] | Denis Moir[1]

J Cutan Pathol. 2022;49:1067–1073.



Immunohistochemical markers (sensitivity)

FOSB
- 75% conventional subtype
- 100% ALHE subtype
- 10% cellular subtype

Virchows Archiv
https://doi.org/10.1007/s00428-019-02651-4

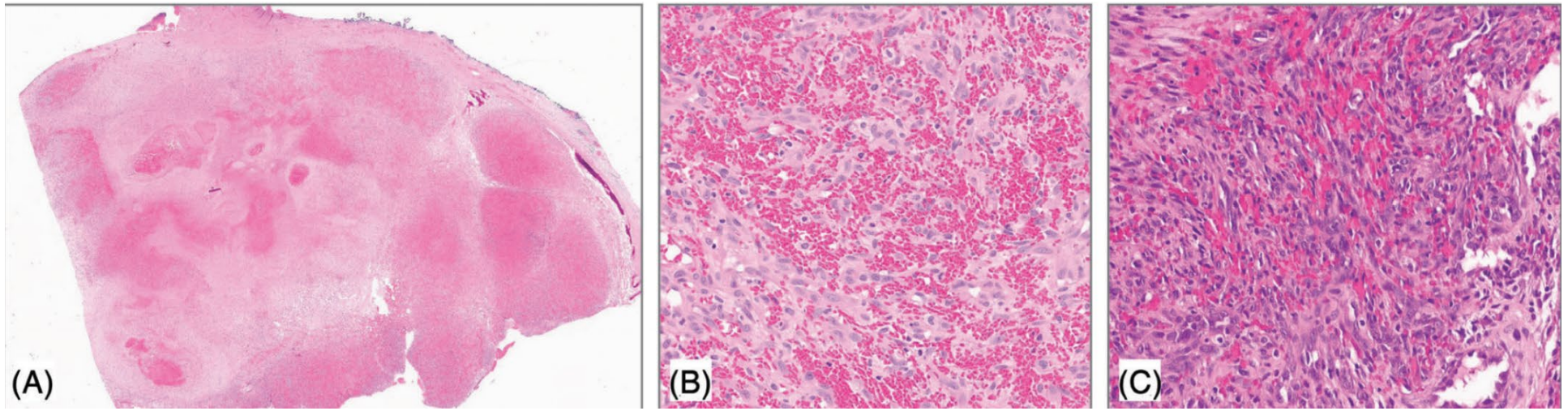
RESEARCH ARTICLE

WILEY

Epithelioid hemangioma of bone harboring *FOS* and *FOSB* gene rearrangements: A clinicopathologic and molecular study

Yusuke Tsuda[1] | Albert J. H. Suurmeijer[2] | Yun-Shao Sung[1] | Lei Zhang[1] | John H. Healey[3] | Cristina R. Antonescu[1]

Genes Chromosomes Cancer. 2021;60:17–25

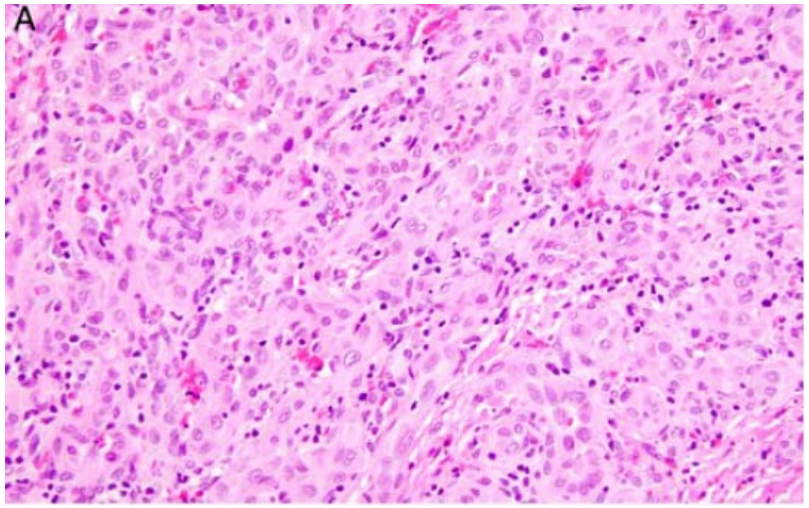


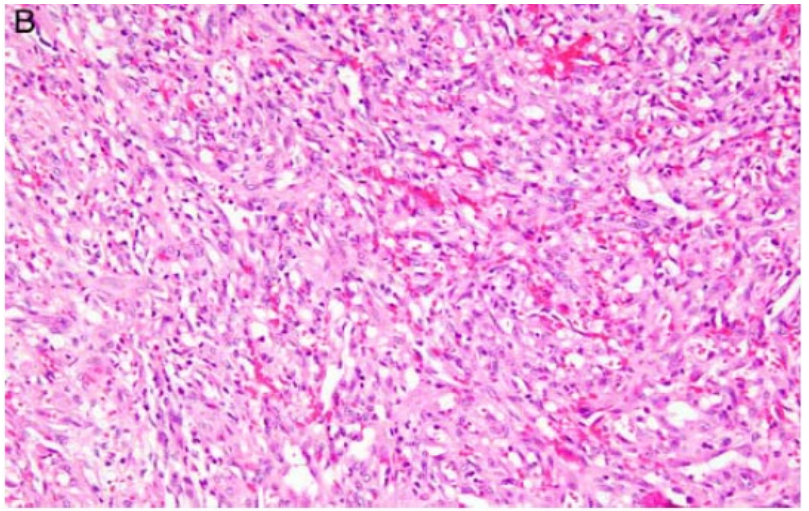
Epithelioid and Spindle Cell Hemangioma

Clinicopathologic Analysis of 18 Primary Bone and Soft Tissue Tumors Highlighting a Predilection for the Hands and Feet, Frequent Multicentricity, and Benign Behavior

David J. Papke Jr, MD, PhD, Jyothi Jagannathan, MD,† Fei Dong, MD,* Brendan C. Dickson, MD, MSc,‡§ Fredrik Mertens, MD, PhD,‖ Jason L. Hornick, MD, PhD,* and Christopher D.M. Fletcher, MD, FRCPath**

Am J Surg Pathol 2022



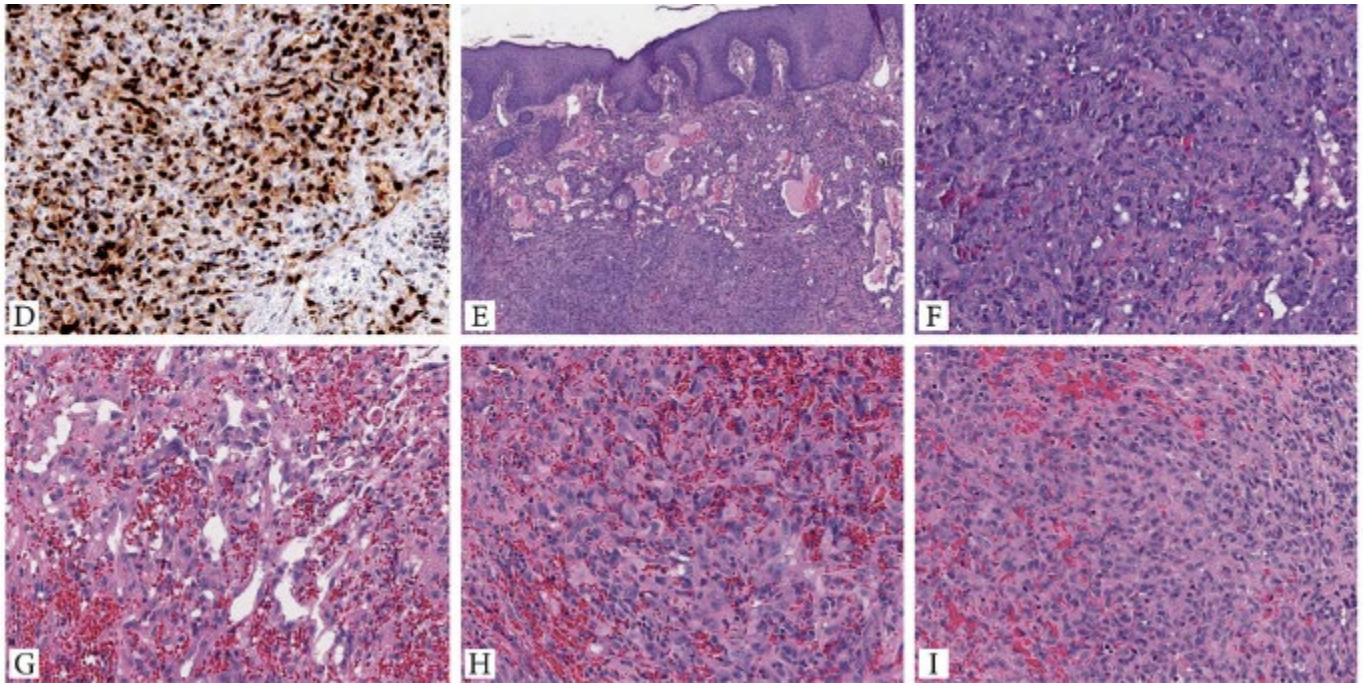


Modern Pathology
https://doi.org/10.1038/s41379-020-00723-4

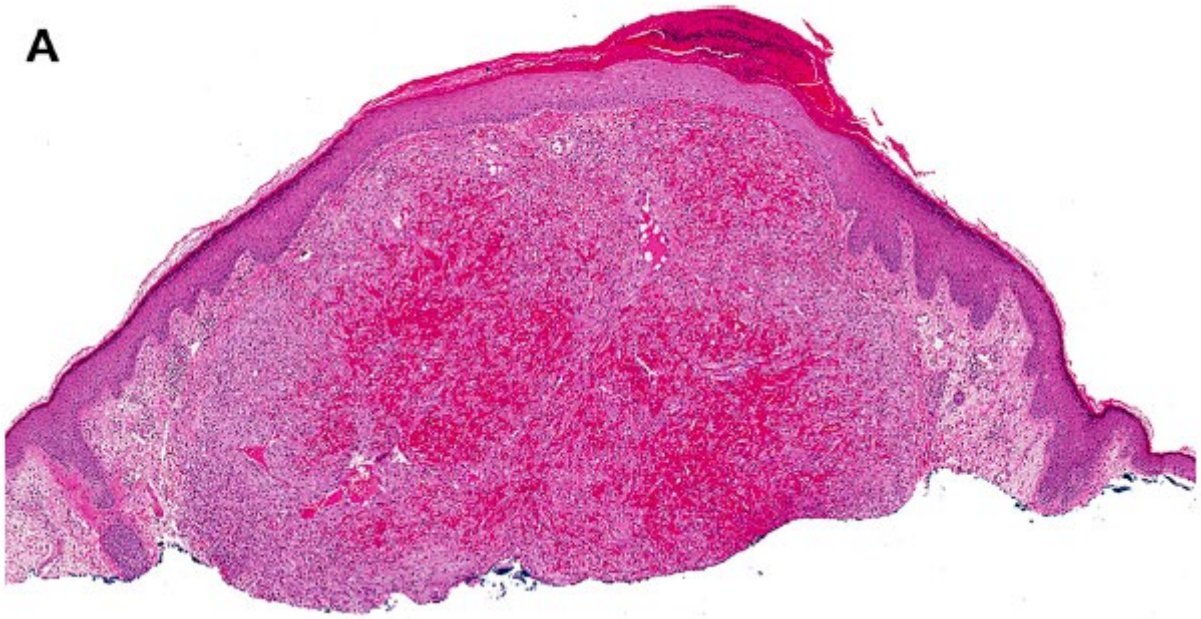
ARTICLE

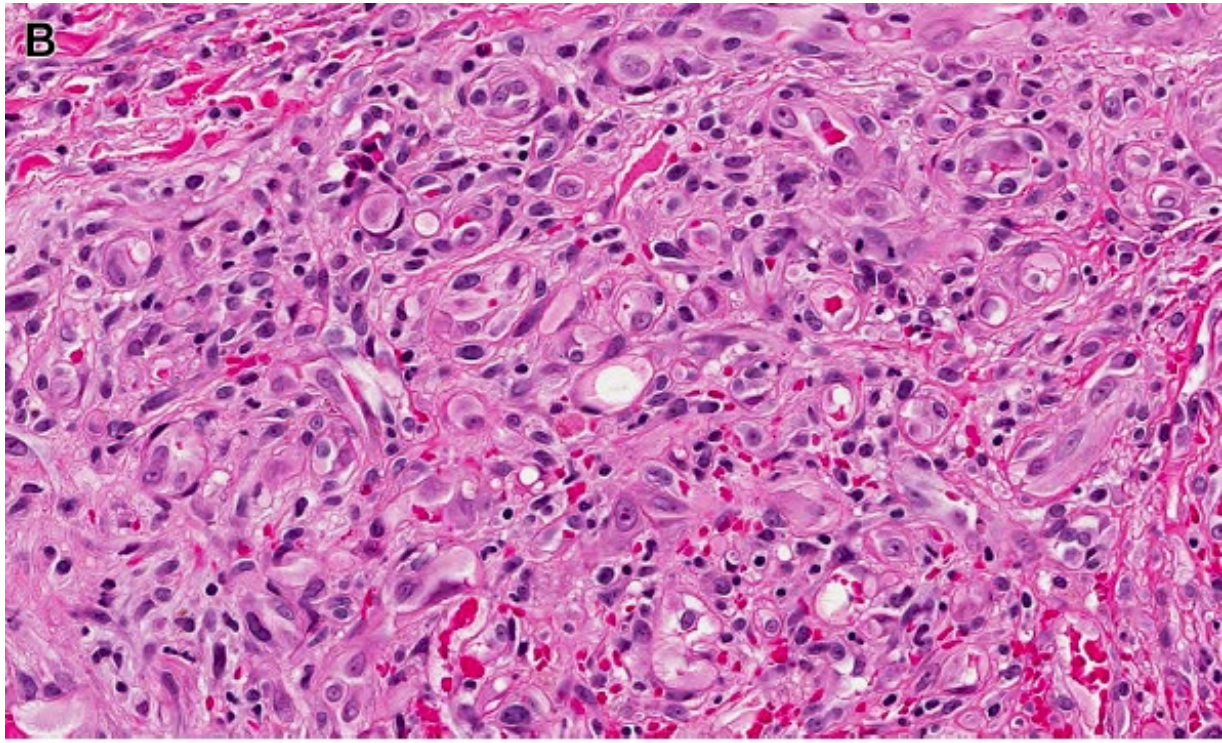
Novel *GATA6-FOXO1* fusions in a subset of epithelioid hemangioma

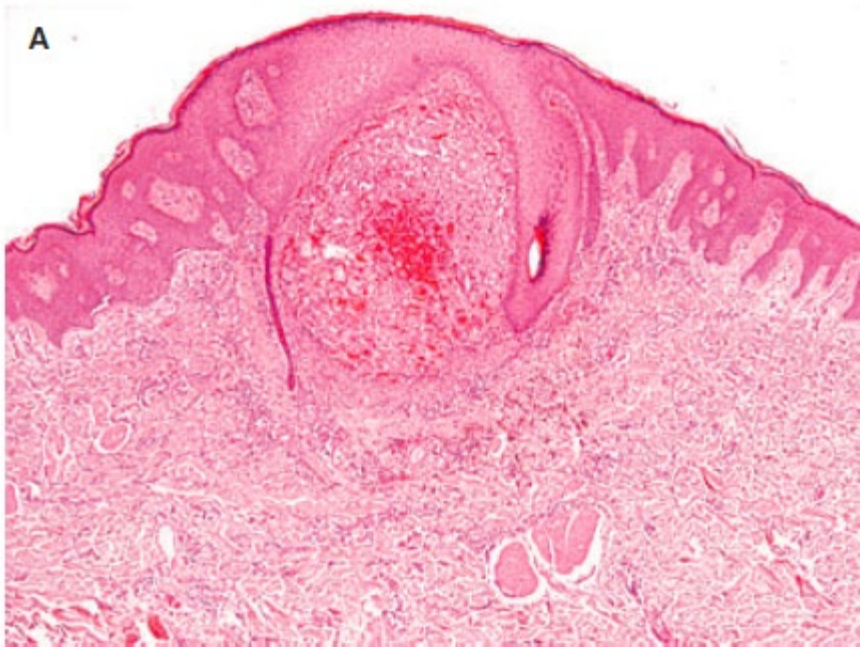
Cristina R. Antonescu[1] · Shih-Chiang Huang[2] · Yun-Shao Sung[1] · Lei Zhang[1] · Burkhard M. Helmke[3] · Martina Kirchner[4] · Albrecht Stenzinger[4] · Gunhild Mechtersheimer[4]

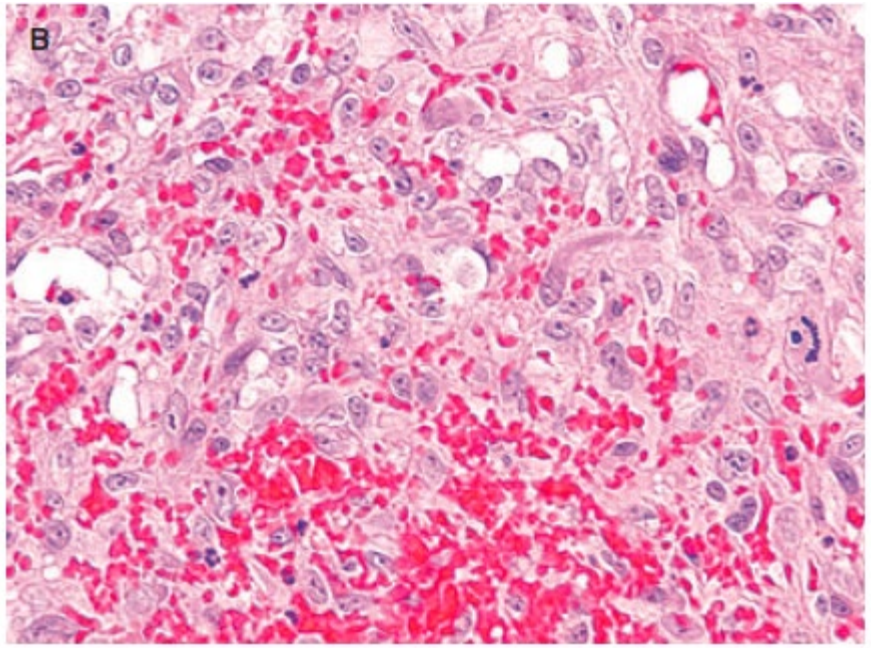


Cutaneous Epithelioid Angiomatous Nodule





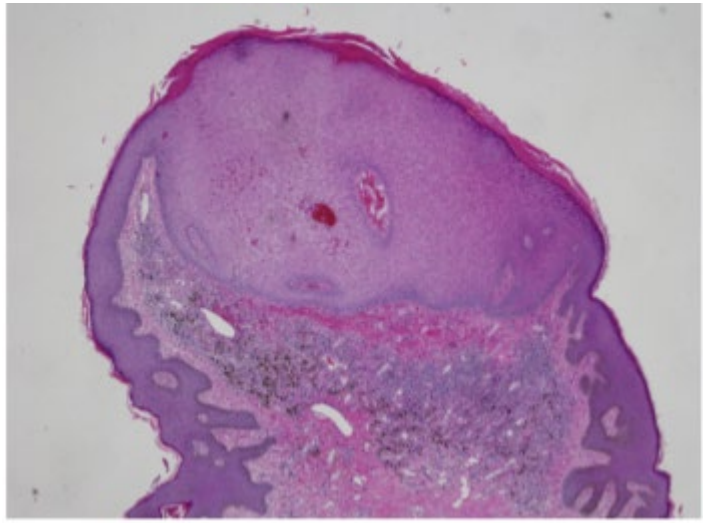




Histopathology 2008, **52**, 661–673.

Multifocal eruptive cutaneous epithelioid angiomatous nodules

Lisa Blackwood, MD,[a] Iona Chapman, MD,[a] Milena Lyon, MD,[a] and Claudia Hernandez, MD[b]
Chicago, Illinois



Cutaneous Epithelioid Angiomatous Nodule: A Case Series and Proposed Classification

Omar P. Sangüeza, MD, Sarah N. Walsh, MD,* Daniel J. Sheehan, MD,**
Almudena Fernández Orland, MD, Beatriz Llombart, MD,† and Luis Requena, MD‡*

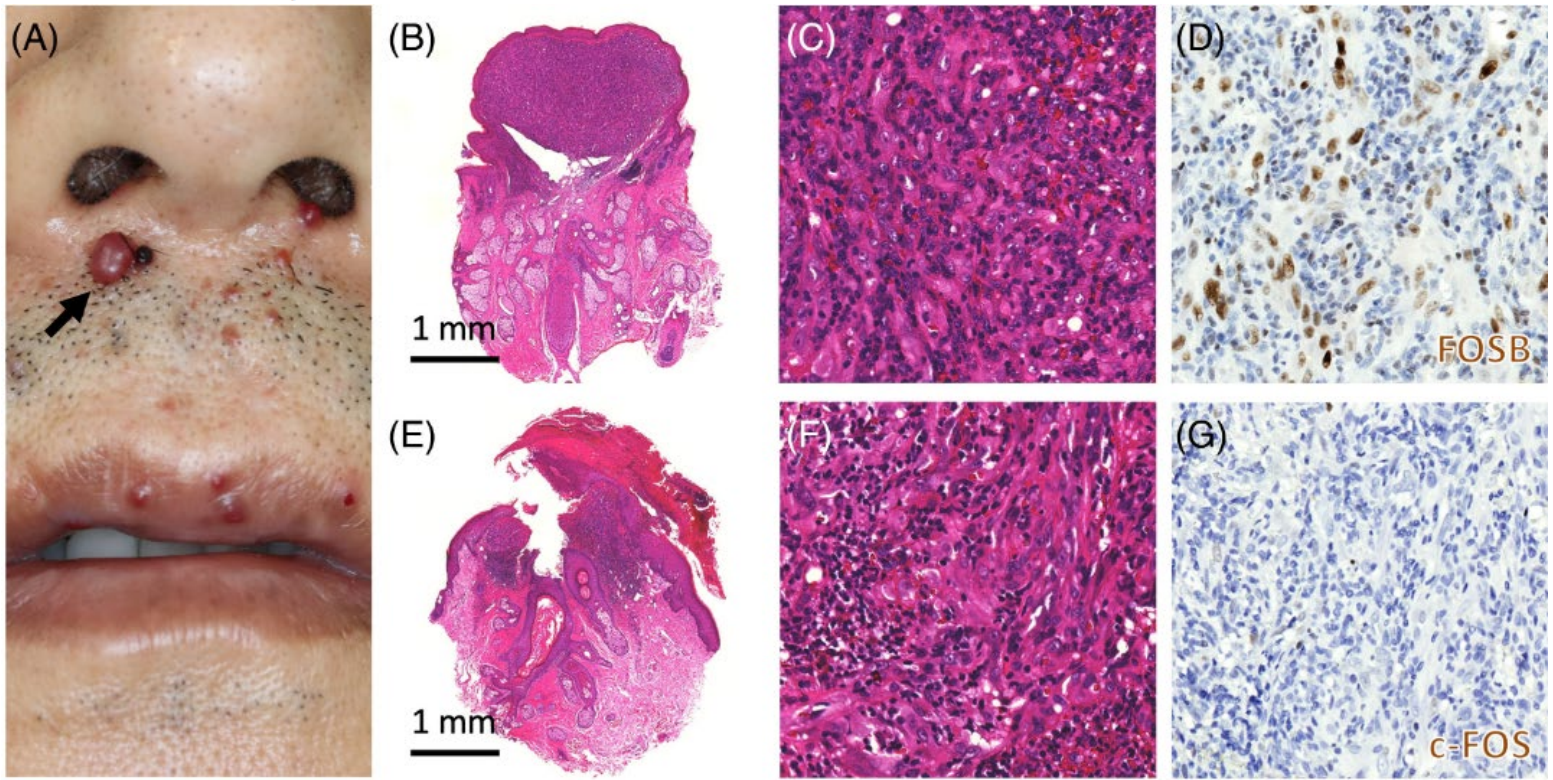
(*Am J Dermatopathol* 2008;30:16–20)

In conclusion, we have reported 10 additional cases of CEAN, a newly described vascular proliferation with prominent epithelioid features. Recognition of this lesion is important, given its uniformly benign behavior and potential for confusion with other malignant vascular neoplasms. Given that the histology is not entirely distinctive and has overlapping features with EH, we feel CEAN is best classified as a variant of EH or at least one manifestation within the same spectrum of benign vascular proliferations.

Categorization of cutaneous epithelioid angiomatous nodule as epithelioid hemangioma or angiolymphoid hyperplasia with eosinophilia: Clinicopathologic, immunohistochemical, and molecular analyses of seven lesions

Keisuke Goto MD[1,2,3,4,5,6,7,8] | Kohei Ogawa MD, PhD[9] |
Tatsuo Fukai MD, PhD[10] | Keiko Miura MD[11] |
Shigeto Yanagihara MD, PhD[12] | Keiichiro Honma MD, PhD[1] |
Toru Motoi MD, PhD[2]

J Cutan Pathol. 2022;49:765–771.

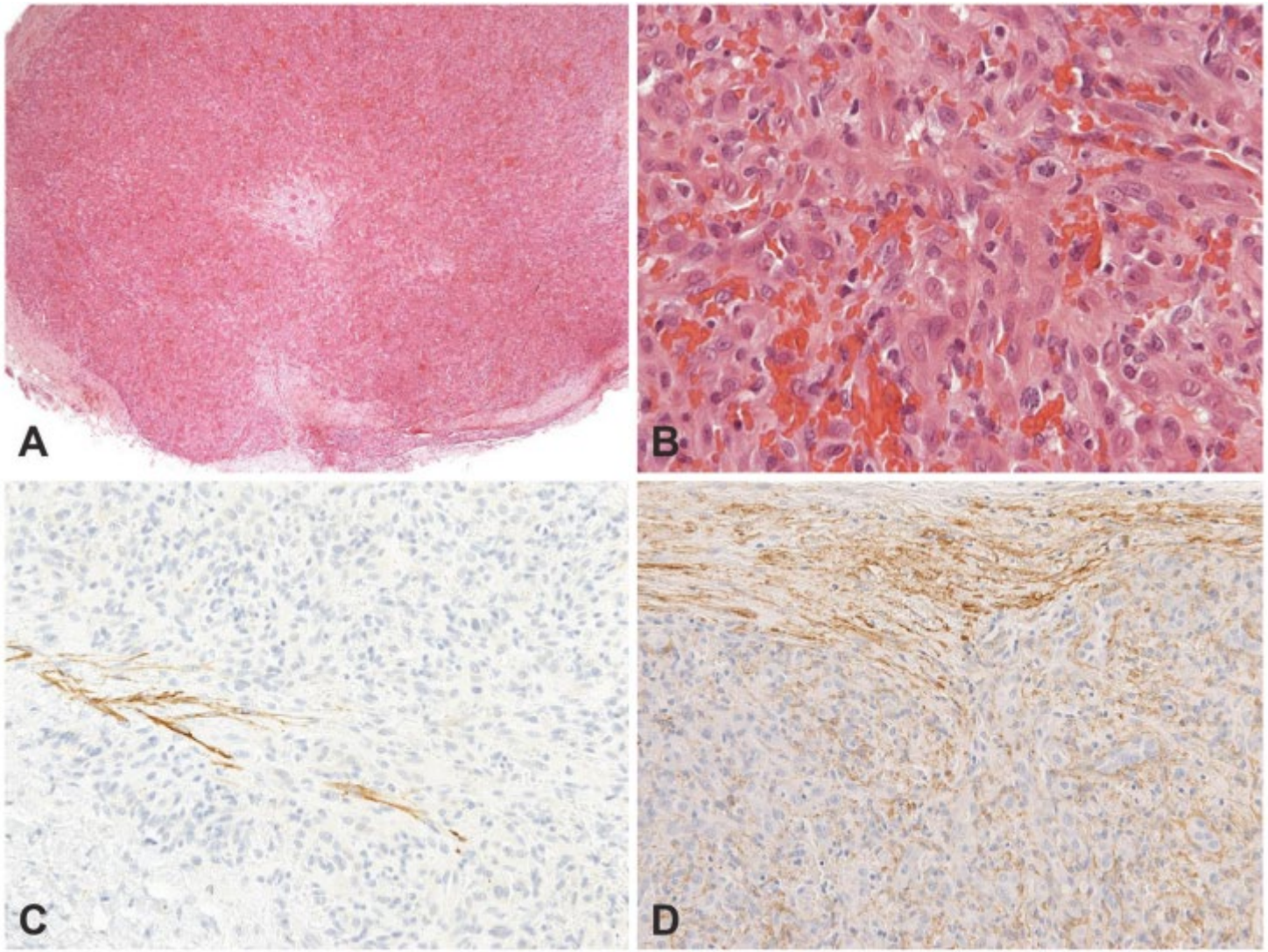


Tumor Type	Total Cases	FOSB Positive (%)*	0	1+	2+	3+	4+
Pseudomyogenic hemangioendothelioma	50	48 (96)	2	0	0	1	47
Epithelioid hemangioma	24	13 (54)	6	4	1	6	7
Conventional	8	6 (75)	0	1	1	4	2
Cellular	10	1 (10)	6	3	0	0	1
Angiolymphoid hyperplasia with eosinophilia	6	6 (100)	0	0	0	2	4
Other endothelial neoplasms and histologic mimics	200	7 (4)	142	42	9	4	3
Epithelioid angiosarcoma	20	1 (5)	11	7	1	0	1
Spindle-cell angiosarcoma	10	1 (10)	9	0	0	1	0
Epithelioid hemangioendothelioma	20	1 (5)	15	4	0	1	0
Epithelioid angiomatous nodule	10	0	9	1	0	0	0
Epithelioid sarcoma	20	0	10	10	0	0	0
Spindle-cell squamous cell carcinoma	20	0	16	4	0	0	0
Spindle-cell rhabdomyosarcoma	20	0	19	1	0	0	0
Leiomyosarcoma	20	0	18	2	0	0	0
Cellular benign fibrous histiocytoma	20	0	12	4	4	0	0
Nodular fasciitis	20	2 (10)	7	7	4	2	0
Proliferative fasciitis	20	2 (10)	16	2	0	0	2

(*Am J Surg Pathol* 2016;00:000–000)

Cutaneous intravascular epithelioid hemangioma. A clinicopathological and molecular study of 21 cases

Boštjan Luzar[1] · Eleni Ieremia[2] · Cristina R. Antonescu[3] · Lei Zhang[3] · Eduardo Calonje[4]

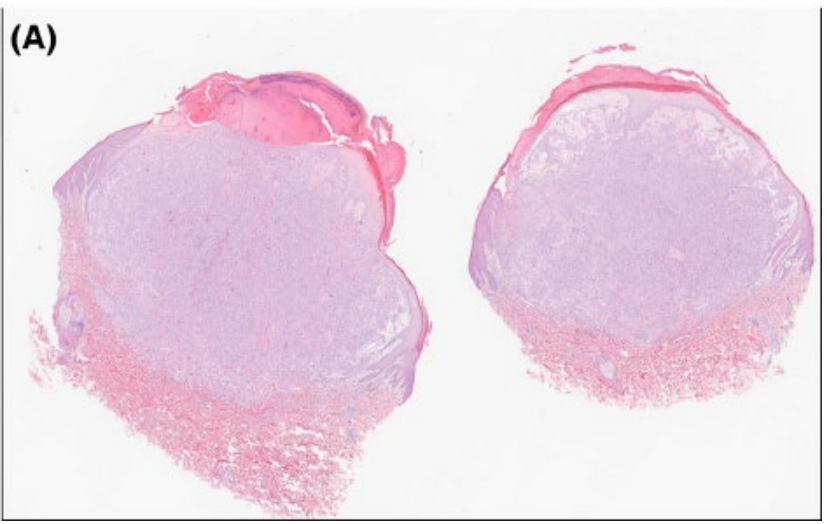


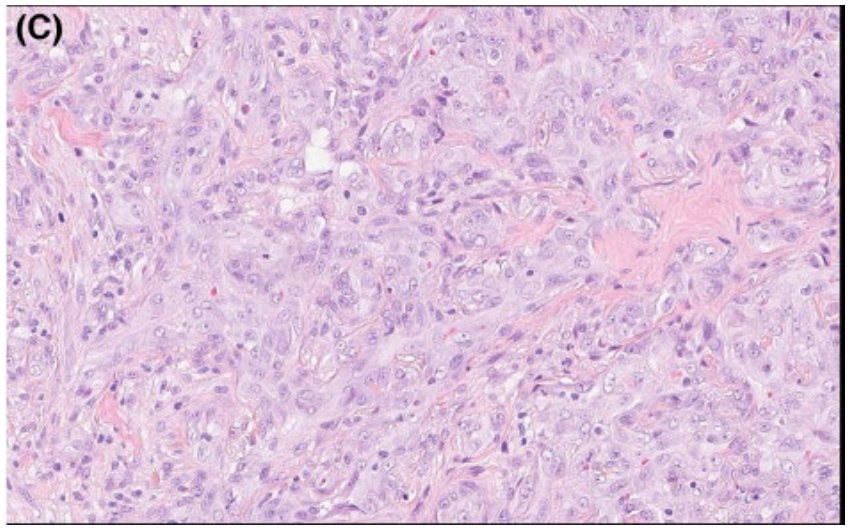
Modern Pathology (2020) 33:1527–1536

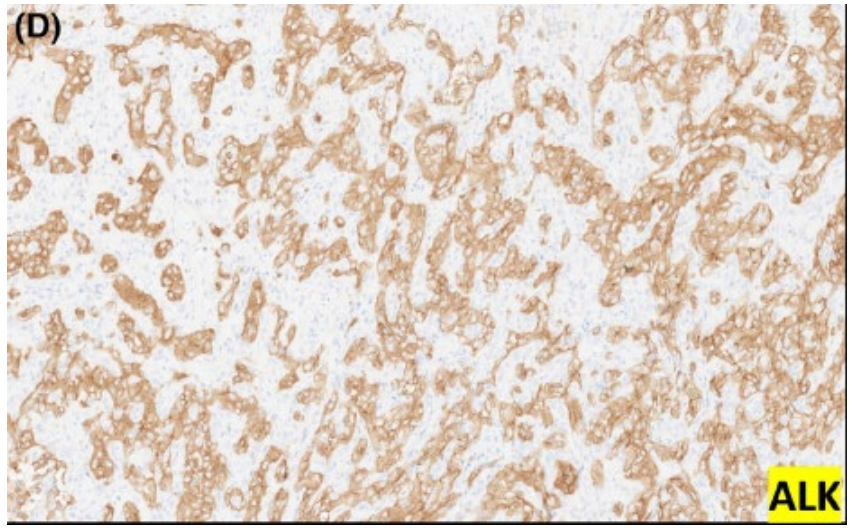
A cutaneous epithelioid vascular tumor harboring a *TPM3::ALK* fusion

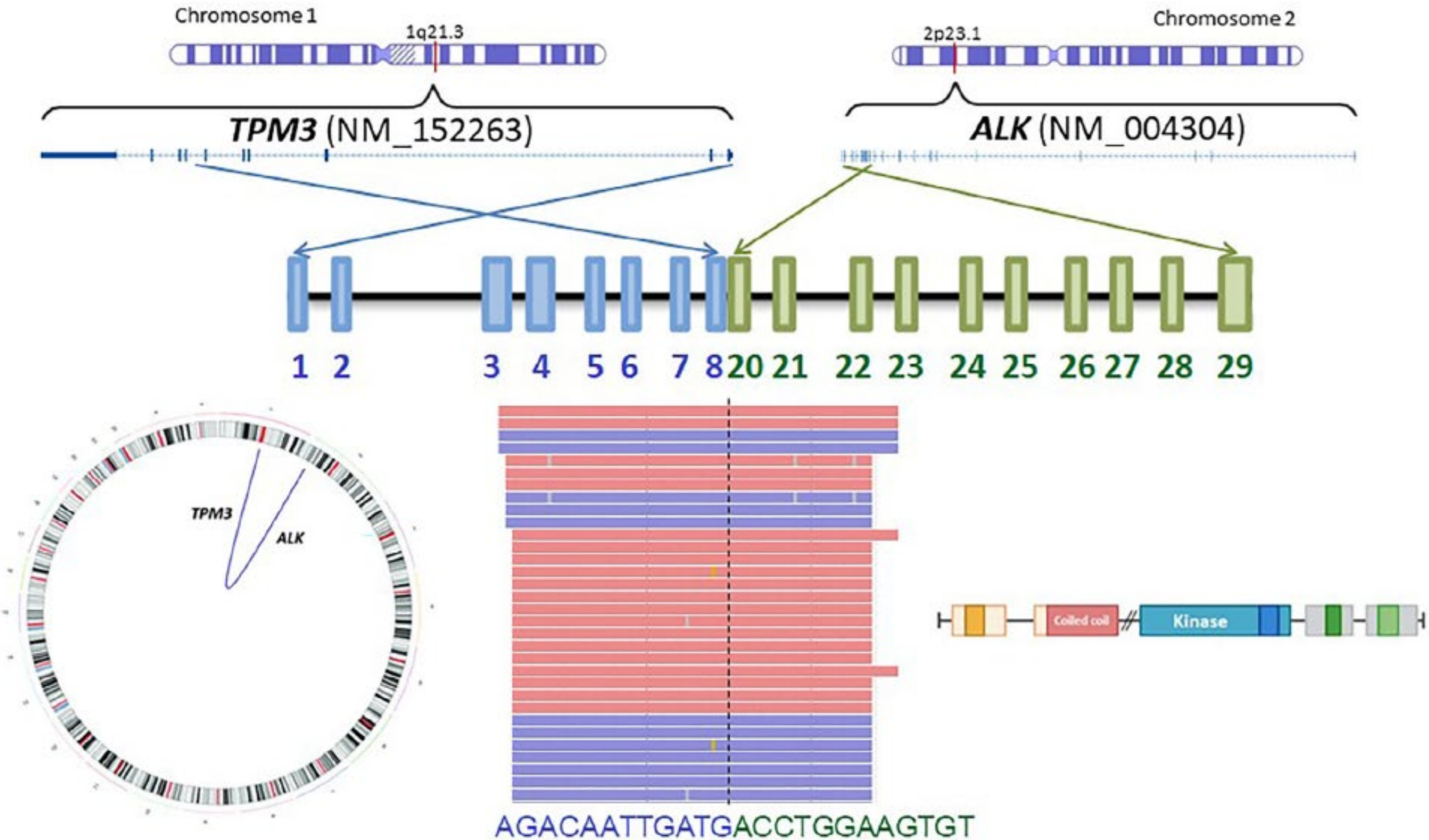
Konstantinos Linos | Jason C. Chang | Klaus J. Busam

Genes Chromosomes Cancer. 2023;1–5.

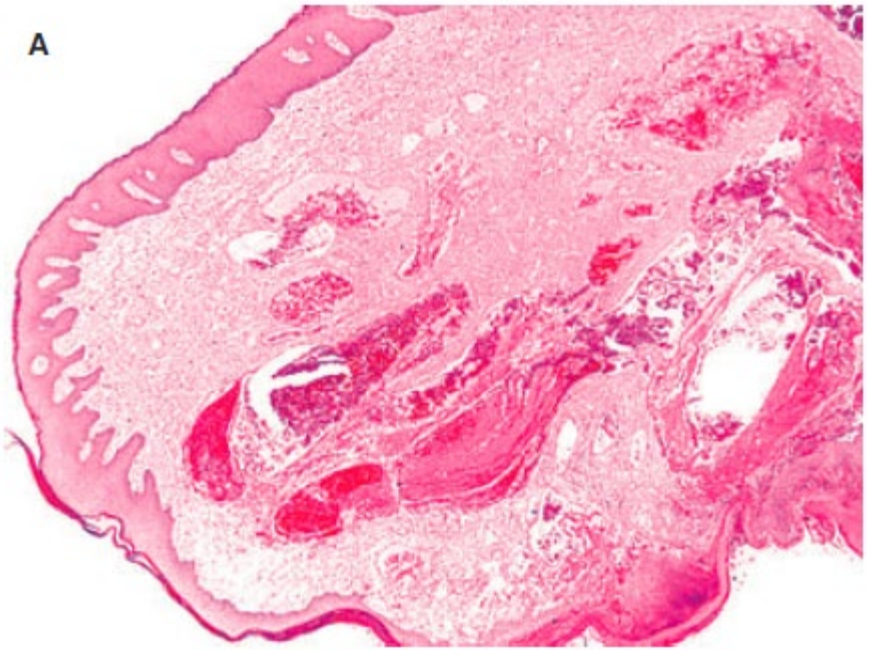


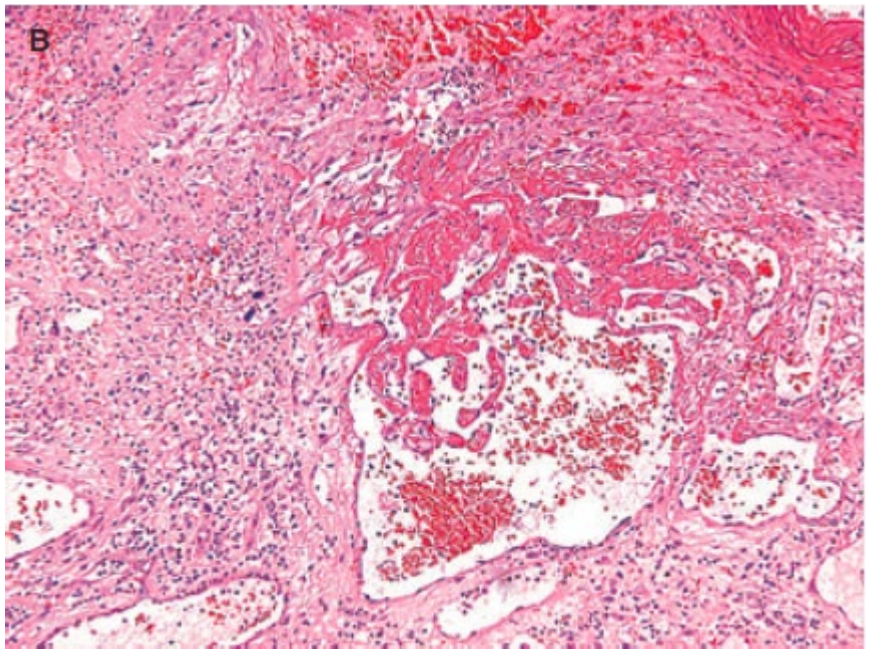


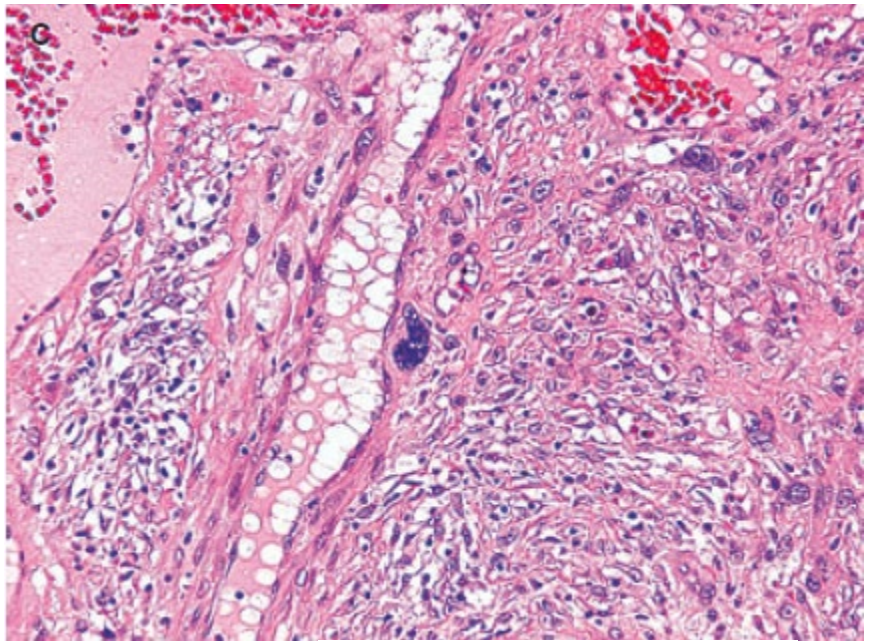



Chromosome 1
1q21.3
Chromosome 2
2p23.1
TPM3 (NM_152263)
ALK (NM_004304)
1 2 3 4 5 6 7 8 20 21 22 23 24 25 26 27 28 29
TPM3
ALK
AGACAATTGATGACCTGGAAGTGT
Coiled coil
Kinase

Symplastic hemangioma







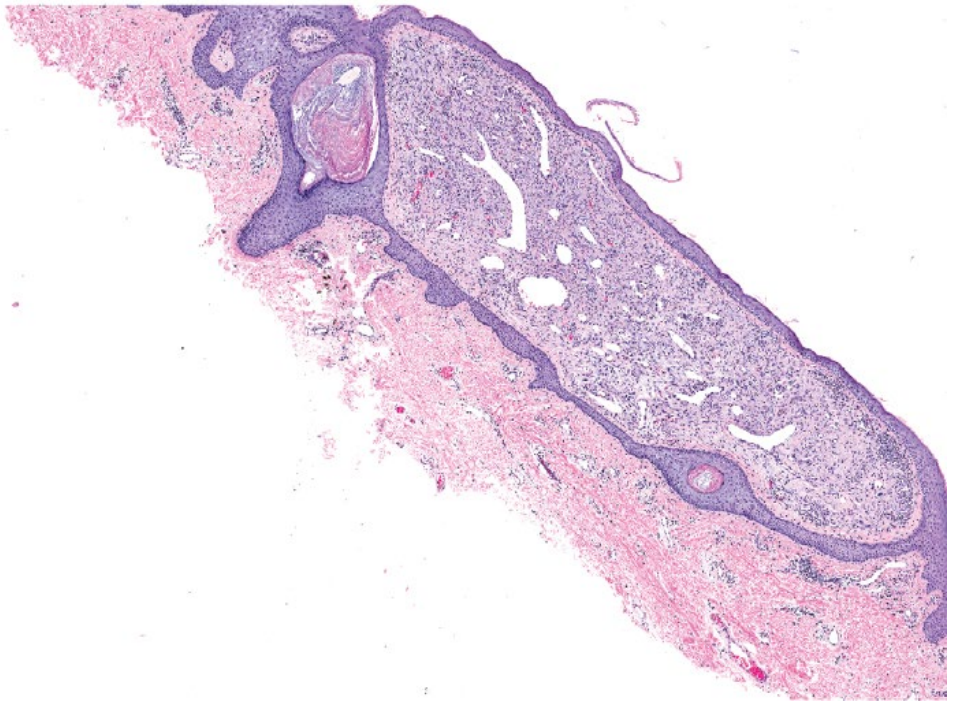
Histopathology 2008, **52**, 661–673.

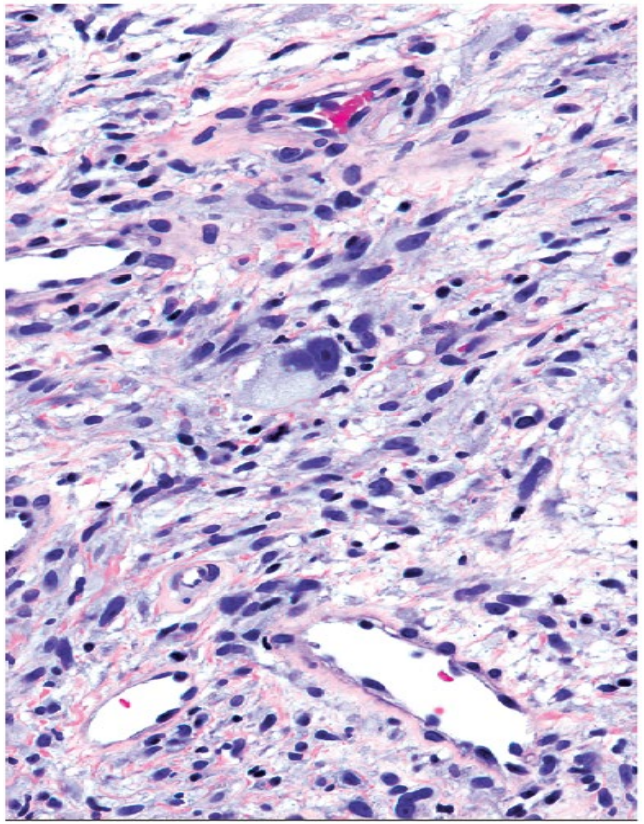
ORIGINAL ARTICLE

JOURNAL OF CUTANEOUS PATHOLOGY WILEY

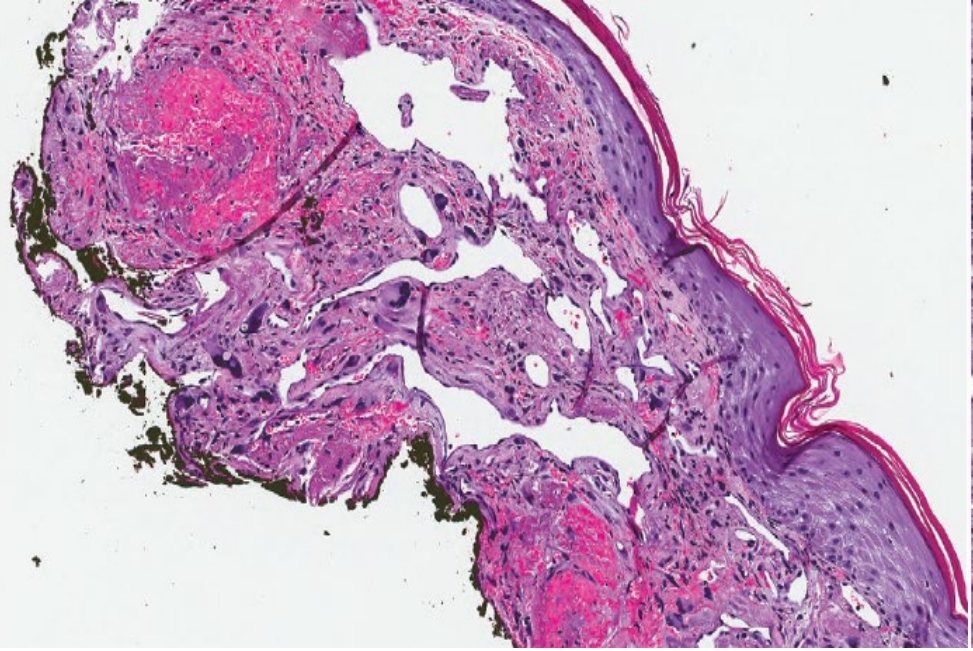
Cutaneous symplastic hemangioma: A series of four cases

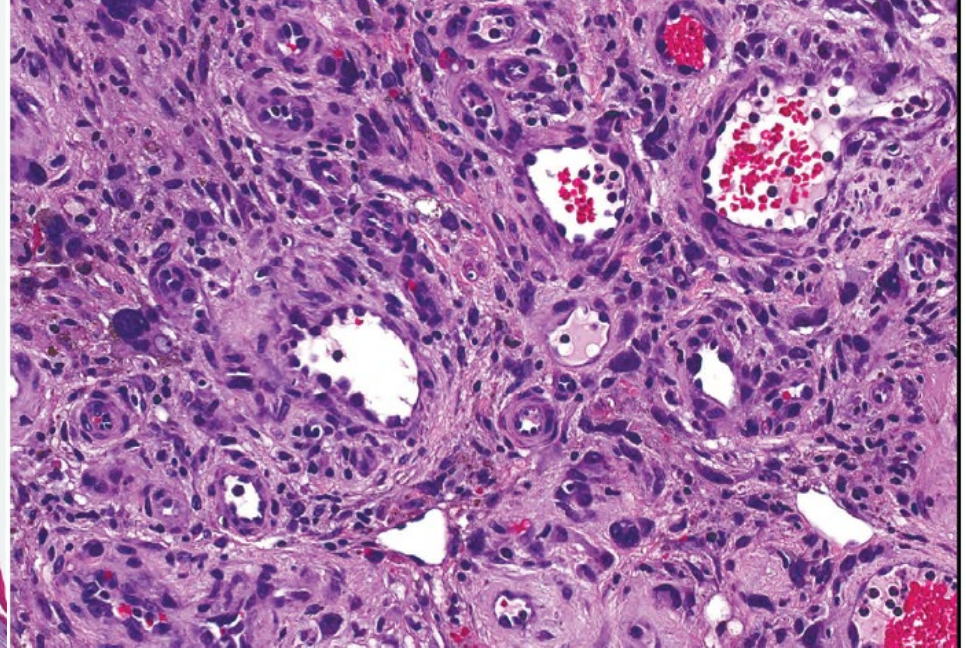
Derek Frew DO | Richard Scarborough DO | Jennifer S. Ko MD, PhD | Steven D. Billings MD

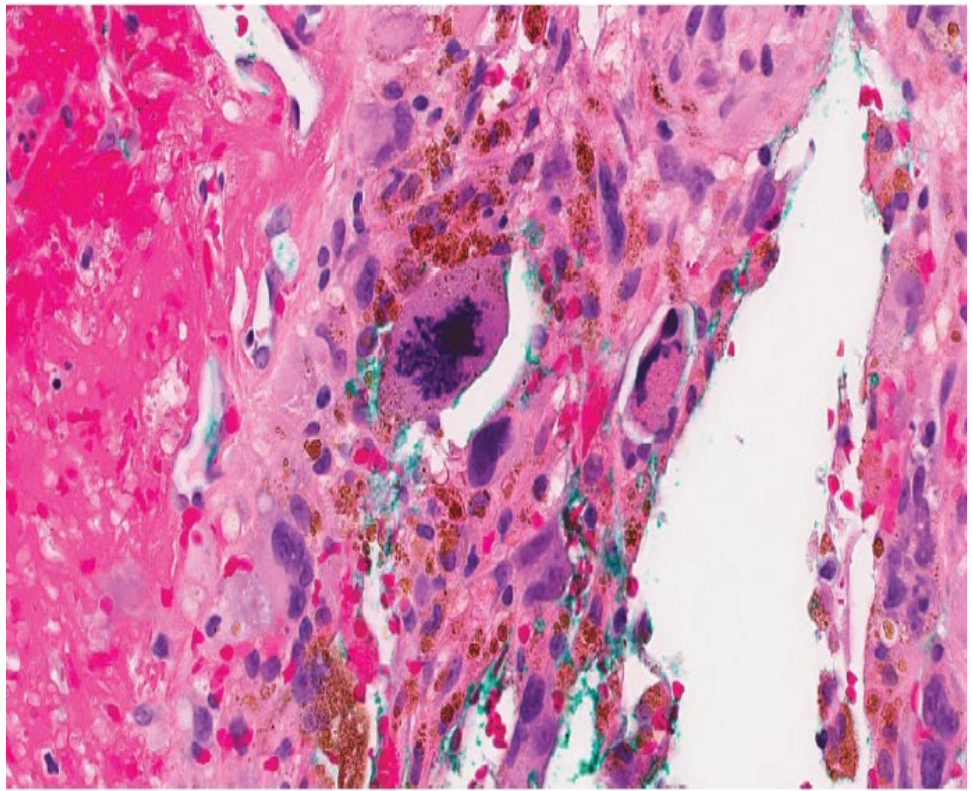


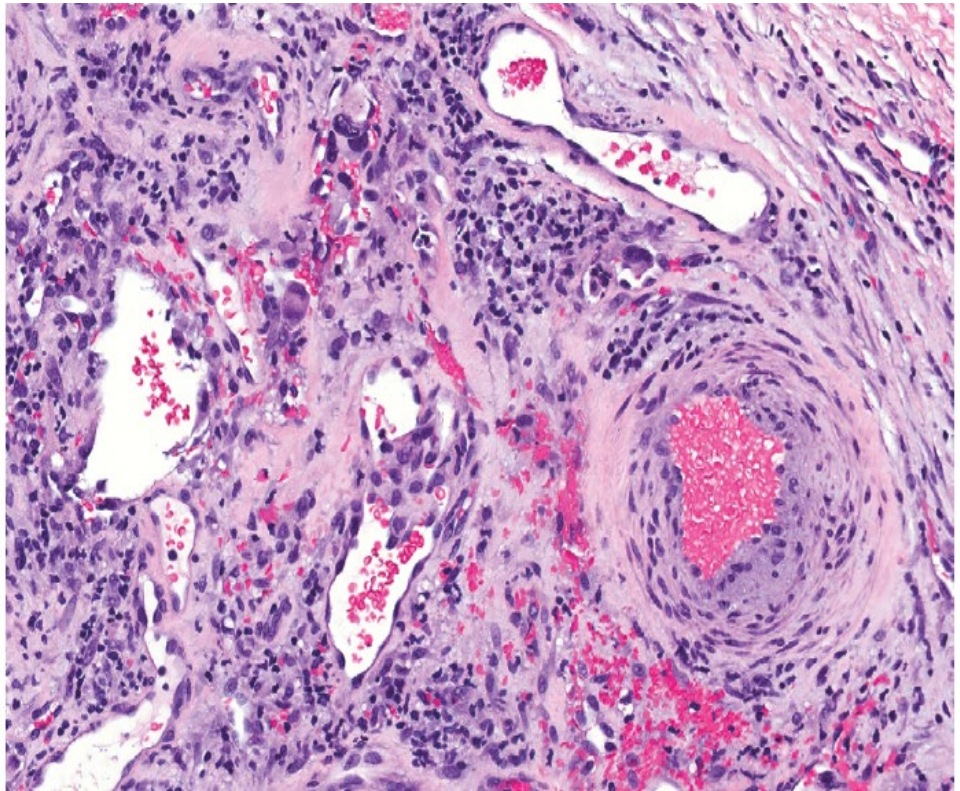


J Cutan Pathol. 2021;1–6.



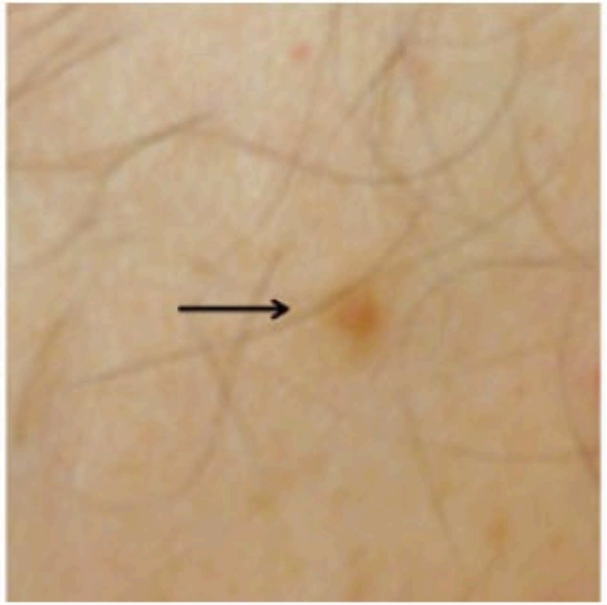






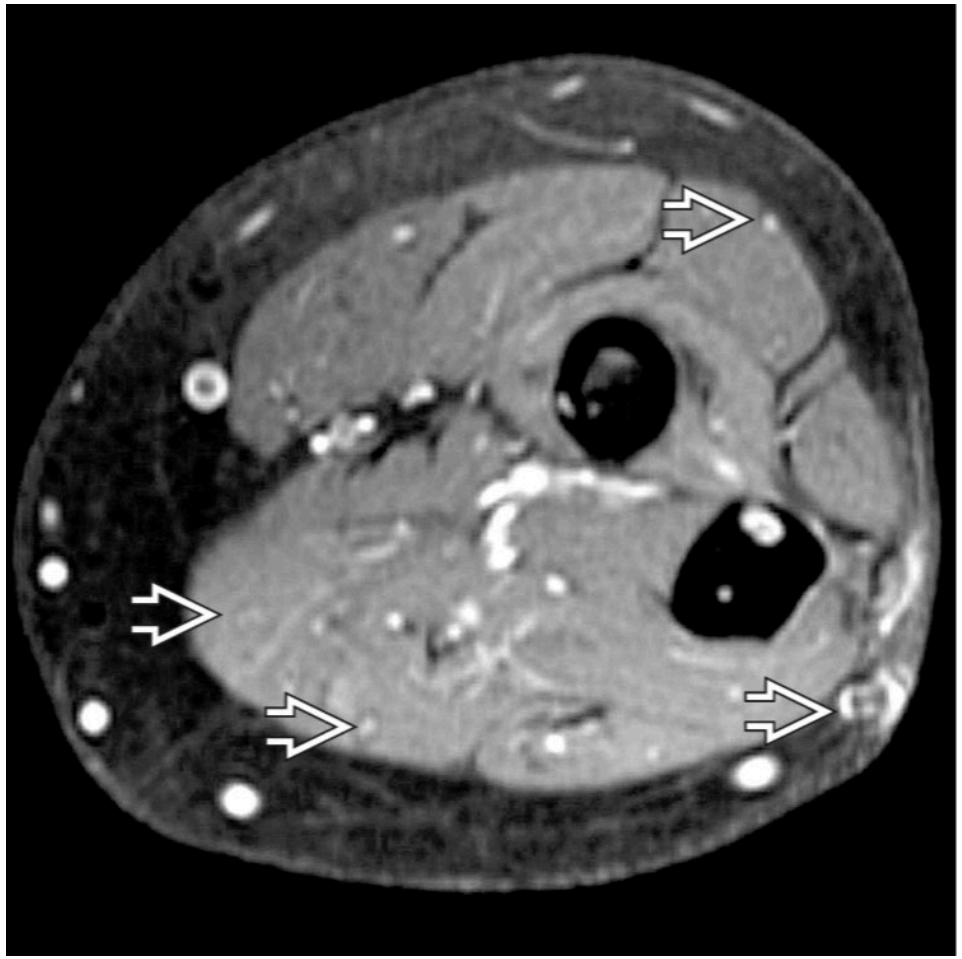
Pseudomyogenic Hemangioendothelioma

- Typically young adults with marked male (4:1) predilection
- Rare soft tissue of **intermediate biological potential**
  - Propensity for local recurrence or frequent (and characteristic) development of additional nodules in the same region
  - Metastasis is rare
- Conservative management is the mainstay of therapy



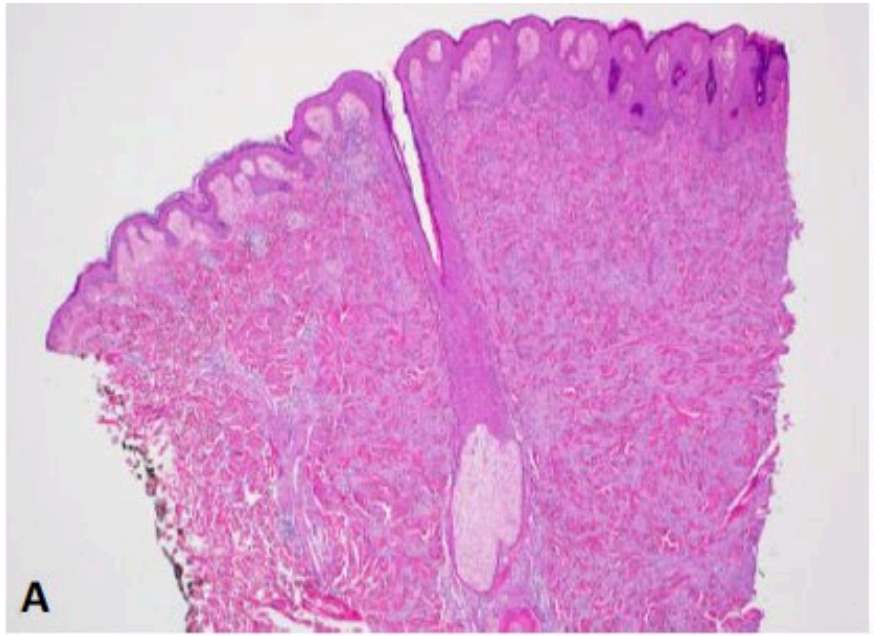
The American Journal of Surgical Pathology *27(1): 48–57, 2003*

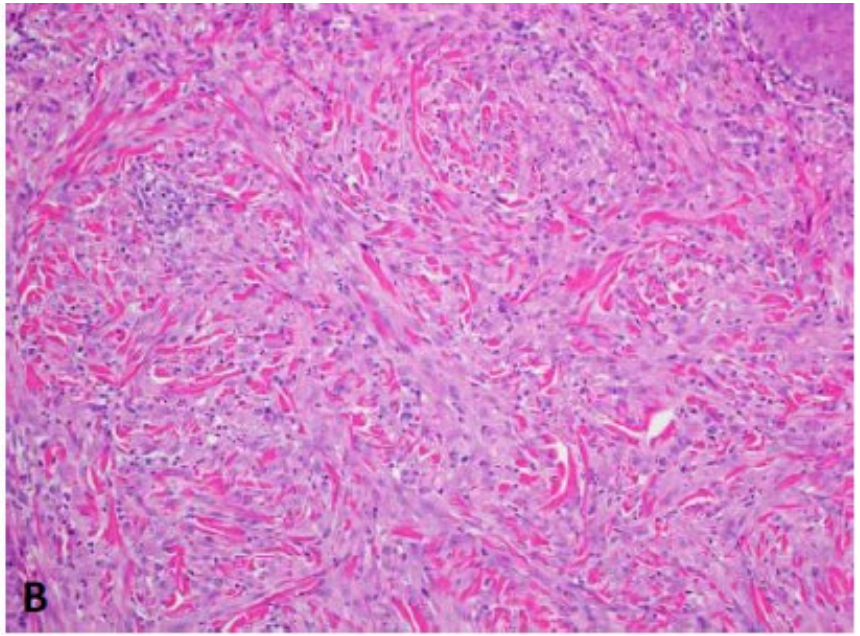
Radiologic findings

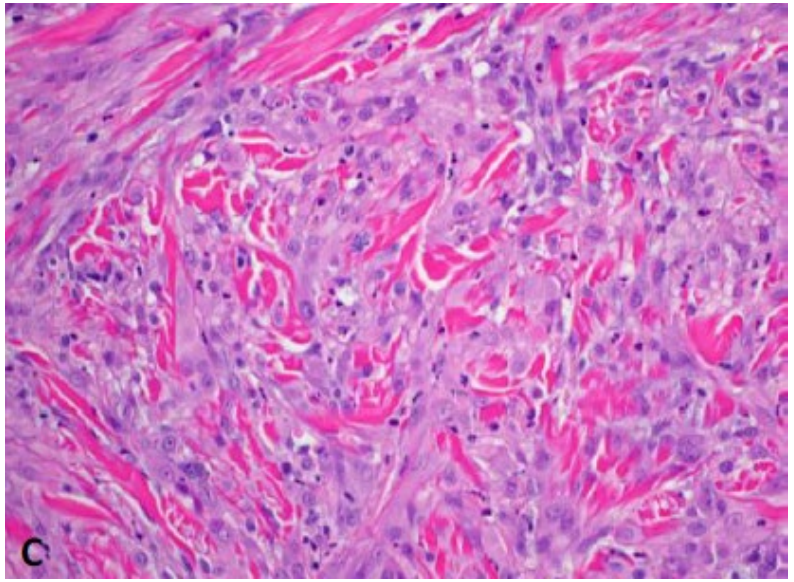


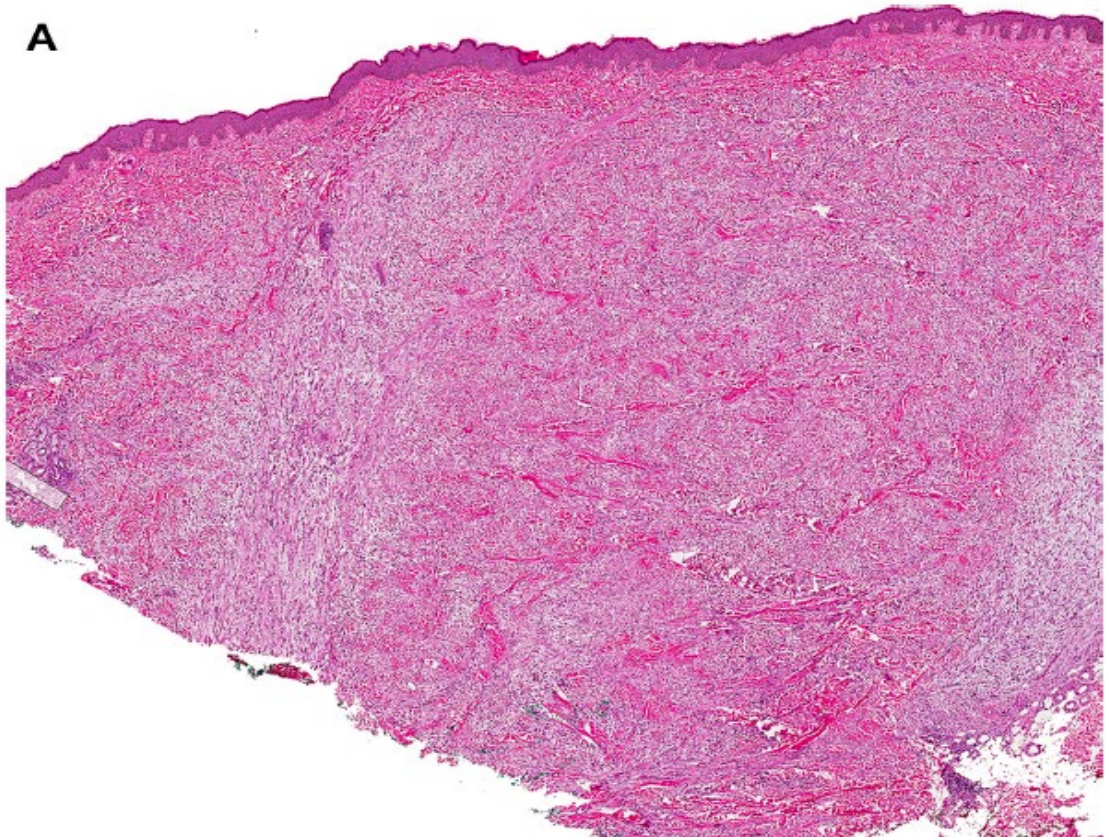
•Diagnostic Pathology: Soft Tissue Tumors 2nd Ed 2015, Elsevier

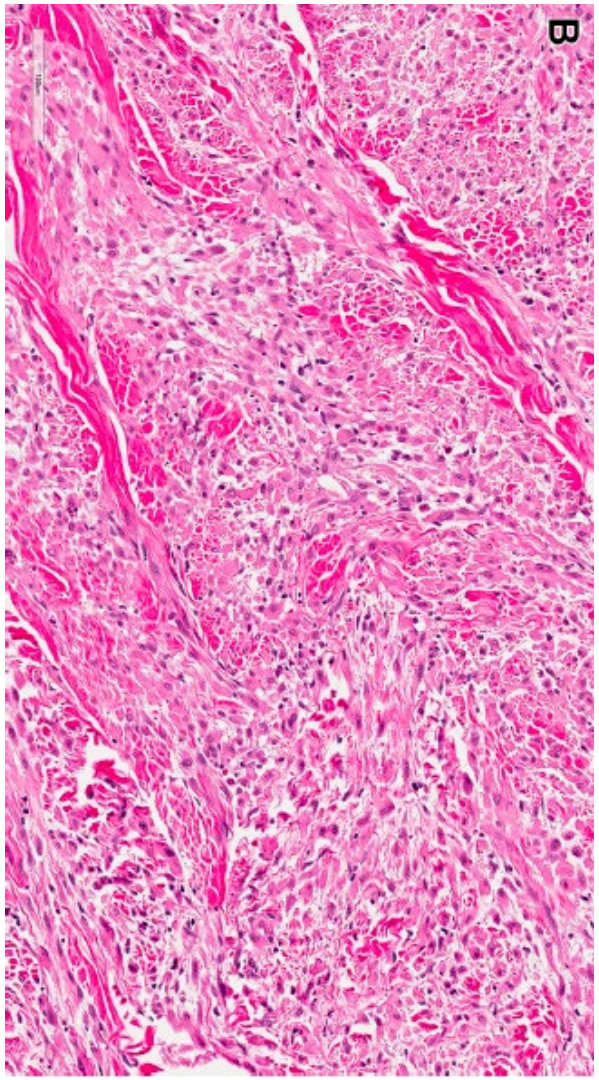
Microscopic findings



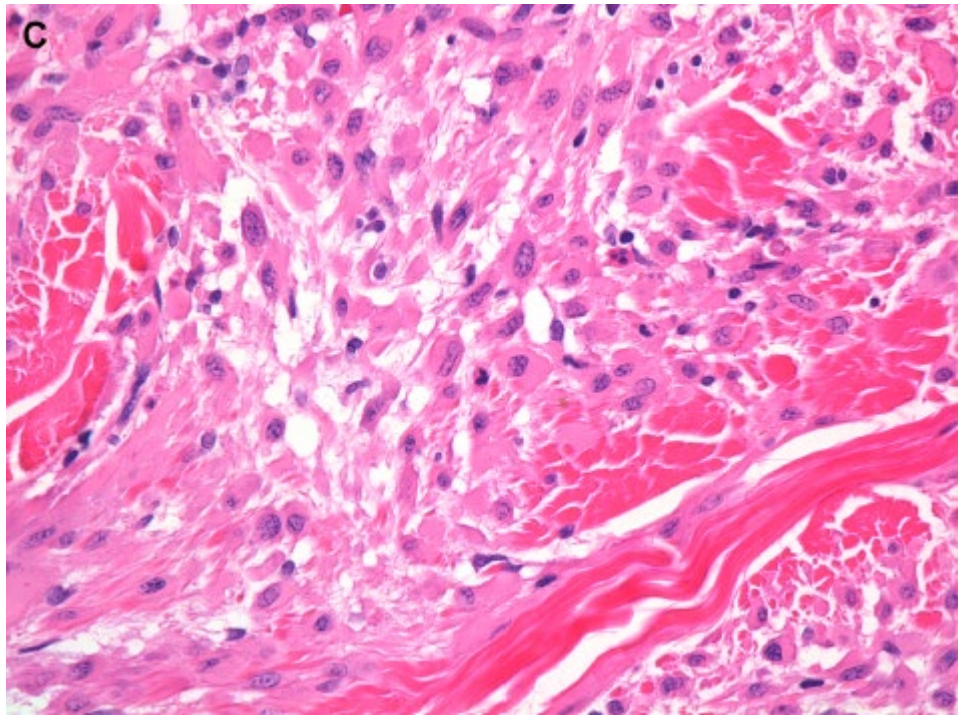


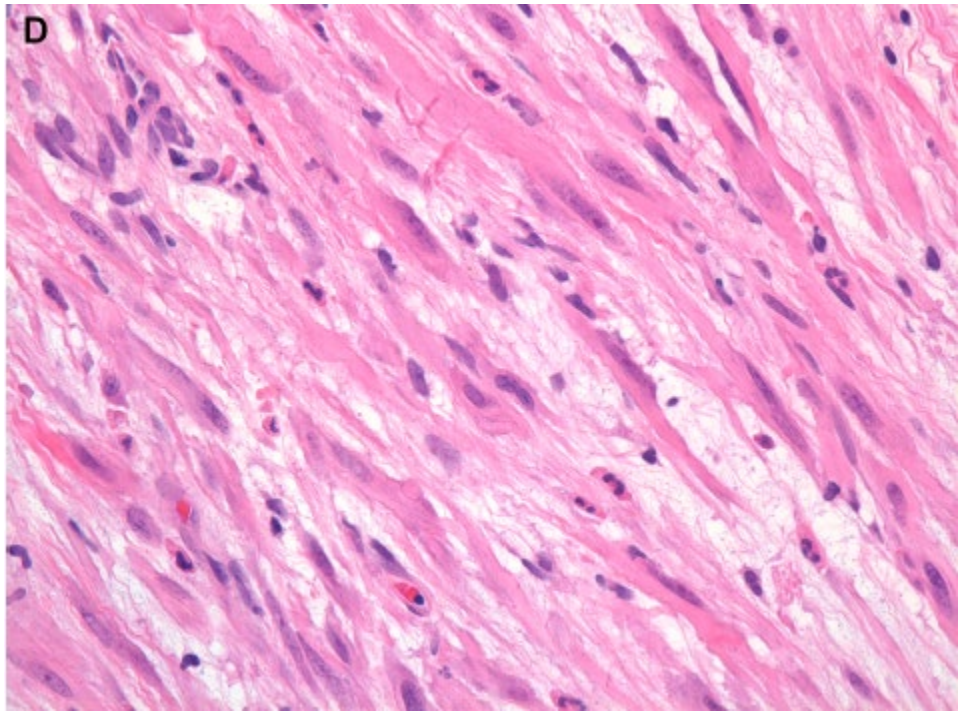






Memorial Sloan Kettering Cancer Center





POSITIVE

CKAE1/3

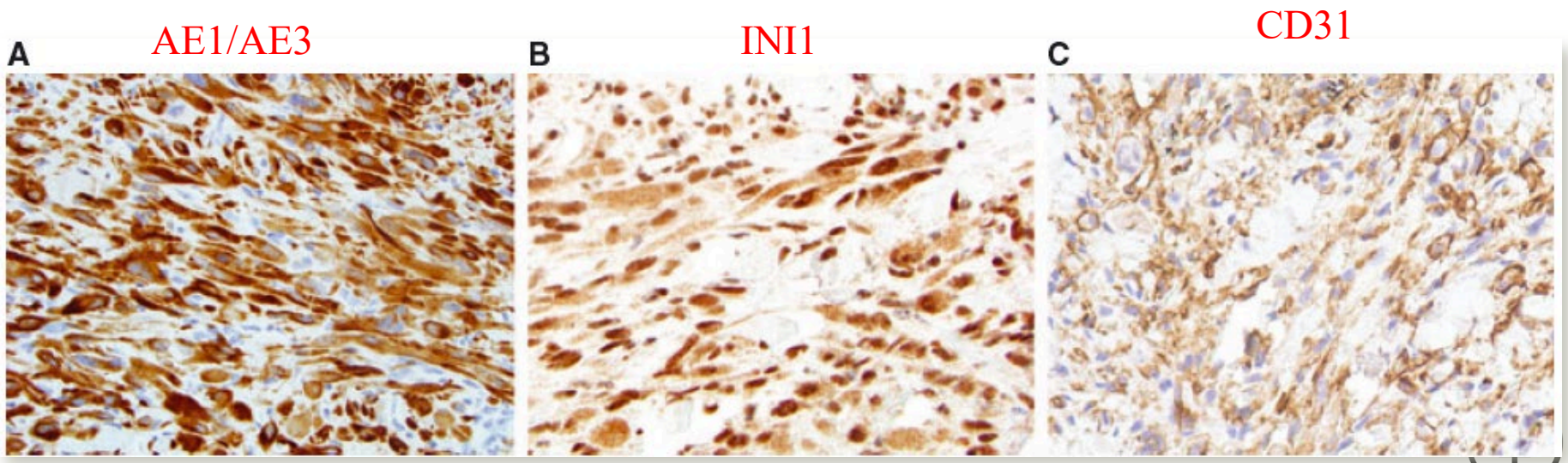
ERG

CD31 (variable)

NEGATIVE

CD34

INI-1 (SMRCB1) is retained



Other Differential Diagnosis

- Spindle cell squamous cell carcinoma
- Cellular benign fibrous histiocytoma
- Smooth muscle neoplasms
- Epithelioid Hemangioendothelioma

Journal of Pathology
J Pathol 2014; **232:** 534–540
Published online 29 January 2014 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.4322

ORIGINAL PAPER

A novel *SERPINE1–FOSB* fusion gene results in transcriptional up-regulation of *FOSB* in pseudomyogenic haemangioendothelioma

Charles Walther,[1,2*] Johnbosco Tayebwa,[1] Henrik Lilljebjörn,[1] Linda Magnusson,[1] Jenny Nilsson,[1] Fredrik Vult von Steyern,[3] Ingrid Øra,[4] Henryk A Domanski,[2] Thoas Fioretos,[1] Karolin H Nord,[1] Christopher DM Fletcher[5] and Fredrik Mertens[1]

Expanding the Spectrum of Genetic Alterations in Pseudomyogenic Hemangioendothelioma With Recurrent Novel *ACTB-FOSB* Gene Fusions

Narasimhan P. Agaram, MBBS, Lei Zhang, MD, Paolo Cotzia, MD, and Cristina R. Antonescu, MD

(*Am J Surg Pathol* 2018;42:1653–1661)

Fusion of the Genes *WWTR1* and *FOSB* in Pseudomyogenic Hemangioendothelioma

IOANNIS PANAGOPOULOS[1], INGVILD LOBMAIER[2], LUDMILA GORUNOVA[1] and SVERRE HEIM[1,3]

CANCER GENOMICS & PROTEOMICS *16*: 293-298 (2019)

A novel *CLTC-FOSB* gene fusion in pseudomyogenic hemangioendothelioma of bone

Julia A. Bridge[1,2] | Janos Sumegi[1] | Thomas Royce[1] | Michael Baker[3] | Konstantinos Linos[3]

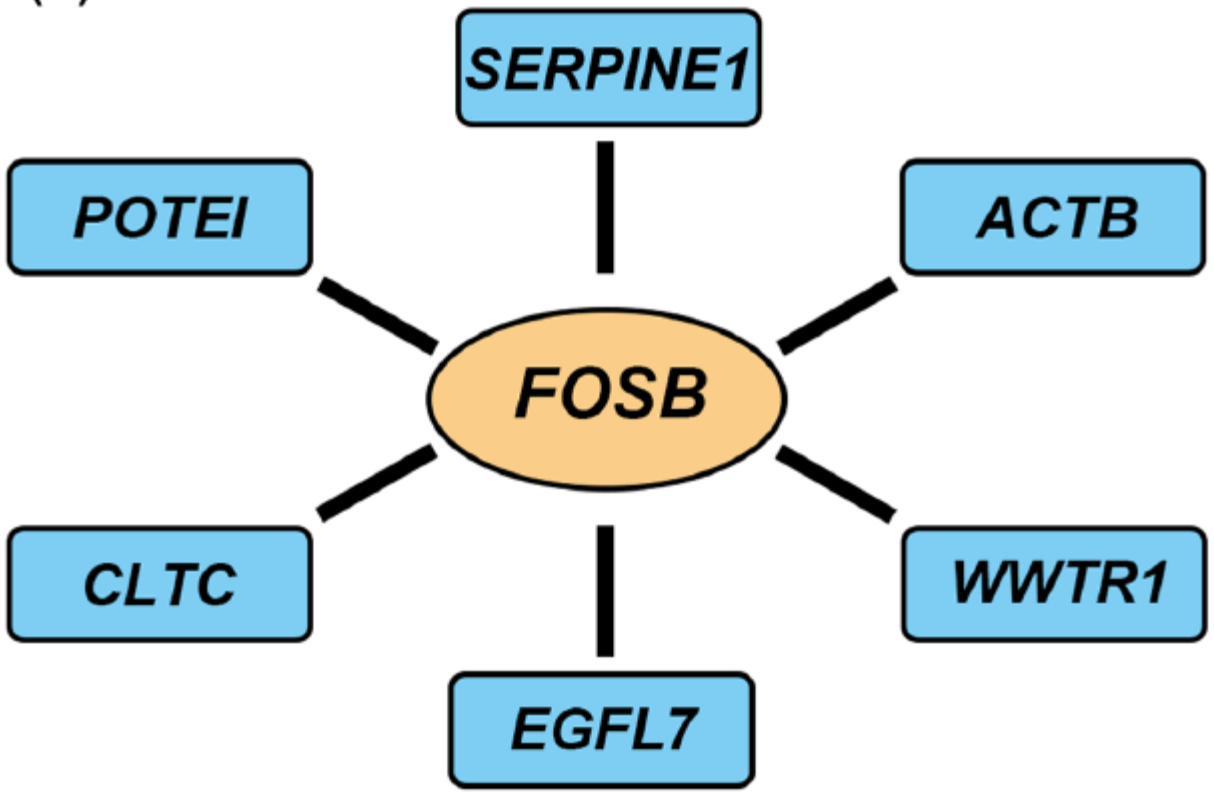
Genes Chromosomes Cancer. 2021;60:38–42

Novel *EGFL7–FOSB* fusion in pseudomyogenic haemangioendothelioma with widely metastatic disease

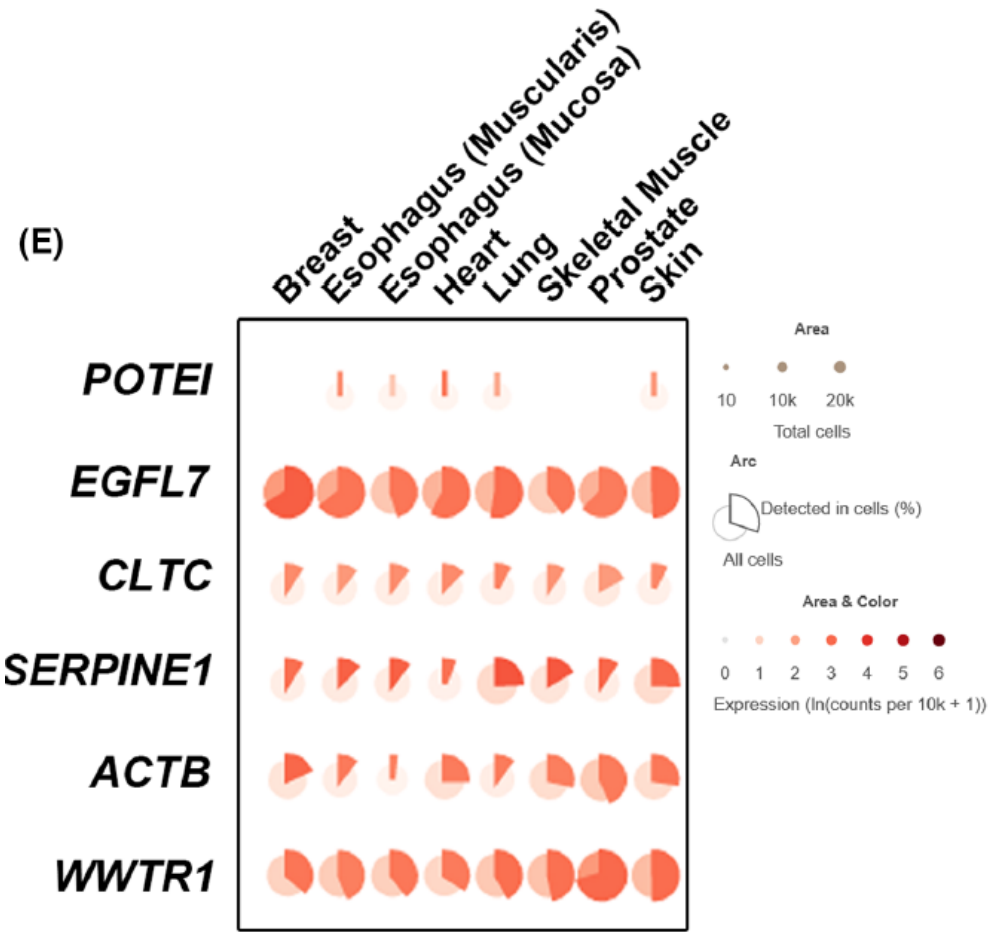
Histopathology 2021

Primary pseudomyogenic haemangioendothelioma of the testis with a novel *POTEI::FOSB* gene fusion

(D)



(E)



Histopathology, 84, 707–718. 2023

Sugita et al. Diagnostic Pathology (2016) 11:75
DOI 10.1186/s13000-016-0530-2

Diagnostic Pathology

RESEARCH Open Access

Diagnostic utility of FOSB immunohistochemistry in pseudomyogenic hemangioendothelioma and its histological mimics

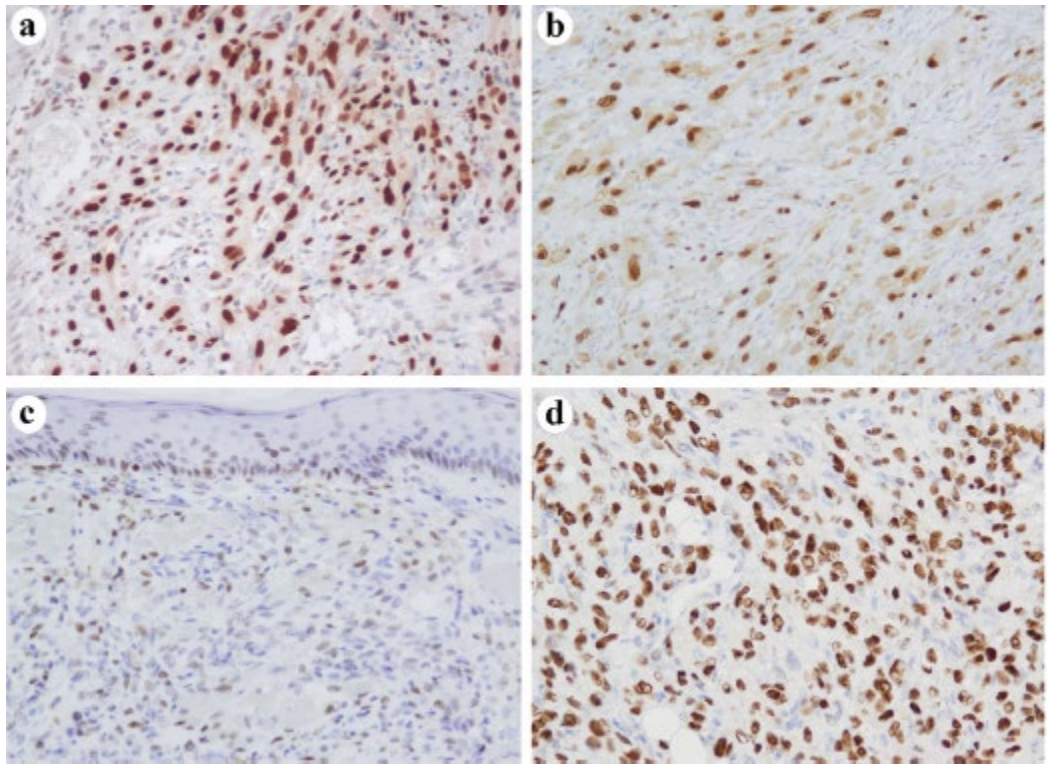
Shintaro Sugita[1], Hiroshi Hirano[1], Noriaki Kikuchi[1], Terufumi Kubo[1], Hiroko Asanuma[1], Tomoyuki Aoyama[1], Makoto Emori[2] and Tadashi Hasegawa[1*]

FOSB is a Useful Diagnostic Marker for Pseudomyogenic Hemangioendothelioma

Yin P. Hung, MD, PhD, Christopher D.M. Fletcher, MD, FRCPath, and Jason L. Hornick, MD, PhD

(*Am J Surg Pathol* 2016;00:000–000)

Case	Age (y)/sex	Histology	Location	FOSB		CAMTA1	
				%	Intensity	%	Intensi
1	20/F	PHE	Bone (mul)[a]	100	Strong	-	-
2	36/M	PHE	Bone (mul)[a]	100	Strong	NA	NA
3	15/F	PHE	Thigh	100	Strong	-	-
4	54/M	PHE	Calcaneus	100	Strong	-	-
5	62/F	EHE	Forehead	-	-	100	Moder
6	71/F	EHE	Femur	10	Weak	100	Moder
7	73/F	EHE	Liver (mul)	-	-	100	Strong
8	86/F	EHE	Upper arm	10	Weak	100	Strong
9	68/F	EHE	Forearm	10	Weak	100	Strong
10	32/M	EHE	Liver (mul)	-	-	100	Strong
11	72/M	AS	Vertebra	10	Weak	-	-
12	48/M	AS	Humerus	10	Weak	10	Weak
13	89/M	AS	Head	-	-	10	Weak
14	62/F	AS	Head	10	Weak	-	-
15	70/M	AS	Head	10	Weak	10	Weak
16	82/F	AS	Head	-	-	-	-
17	74/F	AS	Upper arm	10	Weak	10	Weak
18	77/M	AS	Head	10	Weak	10	Weak
19	89/F	KS	Trunk, limbs (mul)	10	Weak	-	-
20	68/M	KS	Trunk, limbs (mul)	10	Weak	10	Weak
21	76/M	KS	Larynx, limbs (mul)	10	Weak	-	-
22	82/M	KS	Limbs (mul)	10	Weak	-	-
23	75/F	ES	Thigh	10	Weak	-	-
24	73/F	ES	Thigh	10	Weak	-	-
25	55/M	ES	Forearm	-	-	-	-
26	30/M	ES	Thigh	10	Weak	-	-
27	80/F	ES	Genital region	-	-	-	-

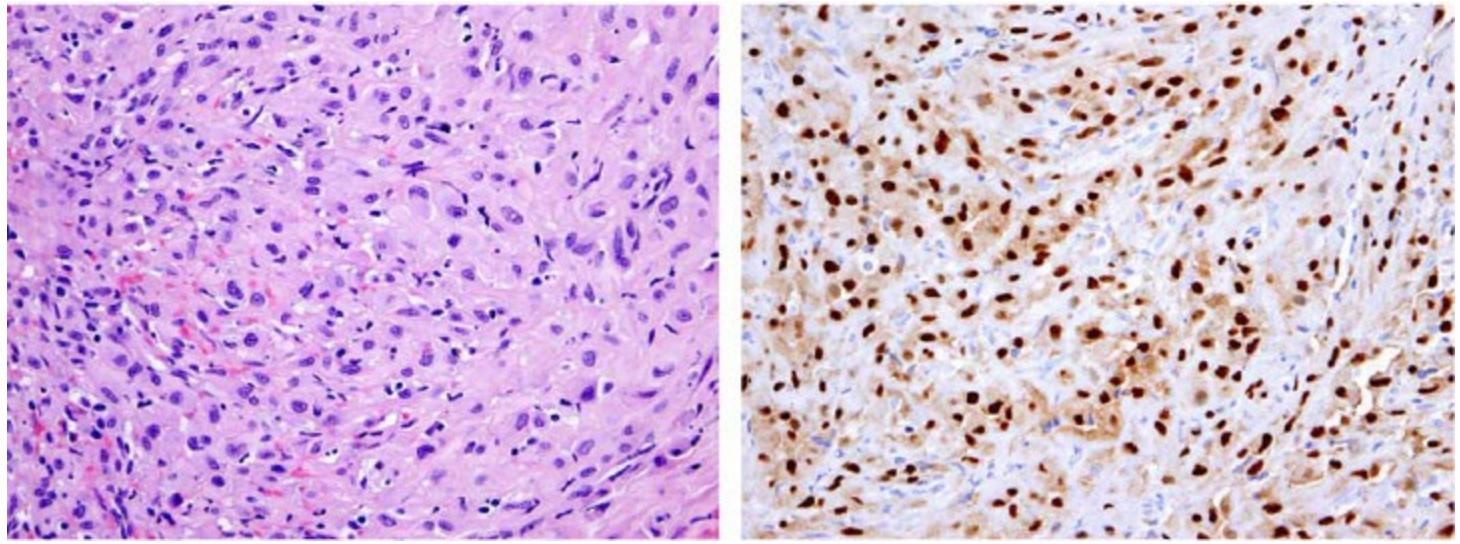


Sugita *et al. Diagnostic Pathology* (2016) 11:75
DOI 10.1186/s13000-016-0530-2

TABLE 1. Summary of Immunohistochemical Staining for FOSB

Tumor Type	Total Cases	FOSB Positive (%)*	0	1+	2+	3+	4+
Pseudomyogenic hemangioendothelioma	50	48 (96)	2	0	0	1	47
Epithelioid hemangioma	24	13 (54)	6	4	1	6	7
Conventional	8	6 (75)	0	1	1	4	2
Cellular	10	1 (10)	6	3	0	0	1
Angiolymphoid hyperplasia with eosinophilia	6	6 (100)	0	0	0	2	4
Other endothelial neoplasms and histologic mimics	200	7 (4)	142	42	9	4	3
Epithelioid angiosarcoma	20	1 (5)	11	7	1	0	1
Spindle-cell angiosarcoma	10	1 (10)	9	0	0	1	0
Epithelioid hemangioendothelioma	20	1 (5)	15	4	0	1	0
Epithelioid angiomatous nodule	10	0	9	1	0	0	0
Epithelioid sarcoma	20	0	10	10	0	0	0
Spindle-cell squamous cell carcinoma	20	0	16	4	0	0	0
Spindle-cell rhabdomyosarcoma	20	0	19	1	0	0	0
Leiomyosarcoma	20	0	18	2	0	0	0
Cellular benign fibrous histiocytoma	20	0	12	4	4	0	0
Nodular fasciitis	20	2 (10)	7	7	4	2	0
Proliferative fasciitis	20	2 (10)	16	2	0	0	2

0, <5%; 1+, 5% to 25%; 2+, 25% to 50%; 3+, 50% to 75%; 4+, 75% to 100%.
*FOSB positivity was defined as moderate-to-strong nuclear staining in at least 50% of cells.



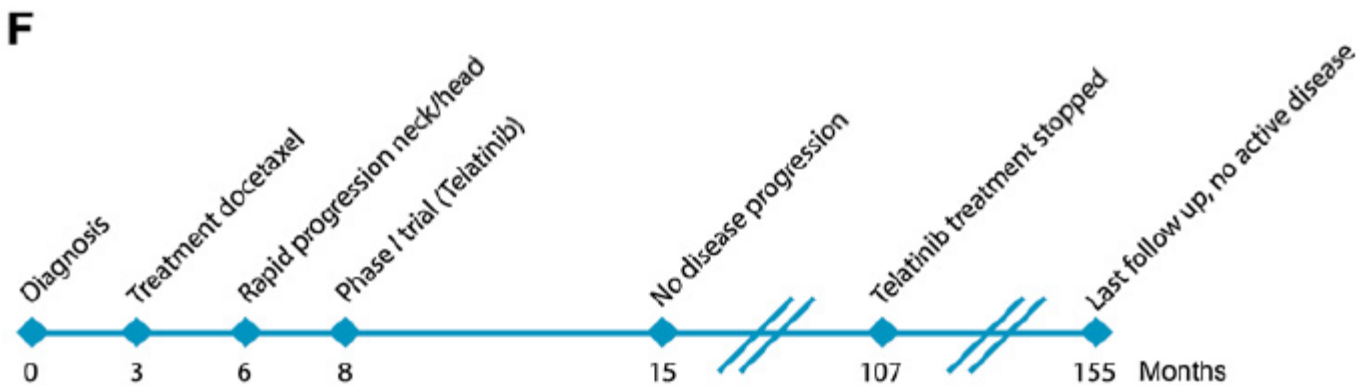
Biology of Human Tumors

Clinical Cancer Research

Telatinib Is an Effective Targeted Therapy for Pseudomyogenic Hemangioendothelioma

David G.P. van IJzendoorn[1], Stefan Sleijfer[2], Hans Gelderblom[3], Ferry A.L.M. Eskens[2], Geert J.L.H. van Leenders[4], Karoly Szuhai[5], and Judith V.M.G. Bovée[1]

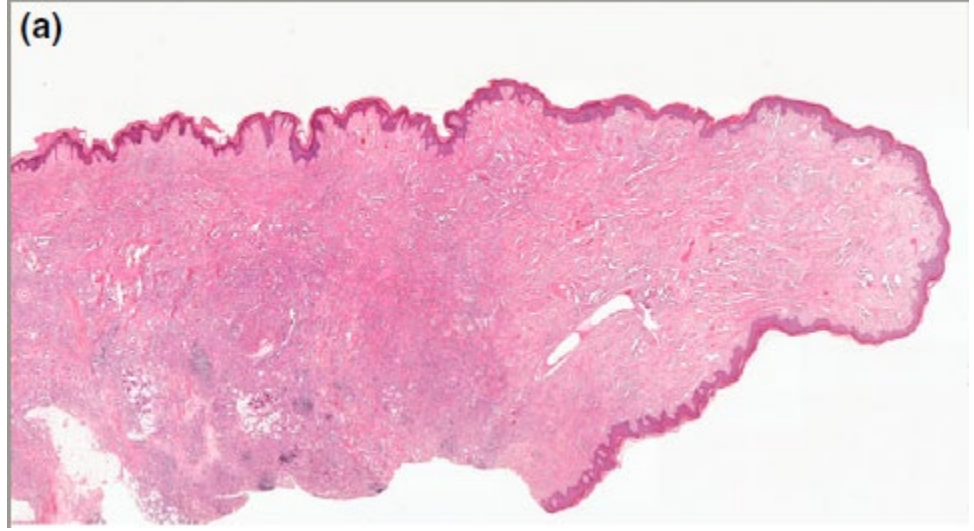
Clin Cancer Res; 24(11) June 1, 2018

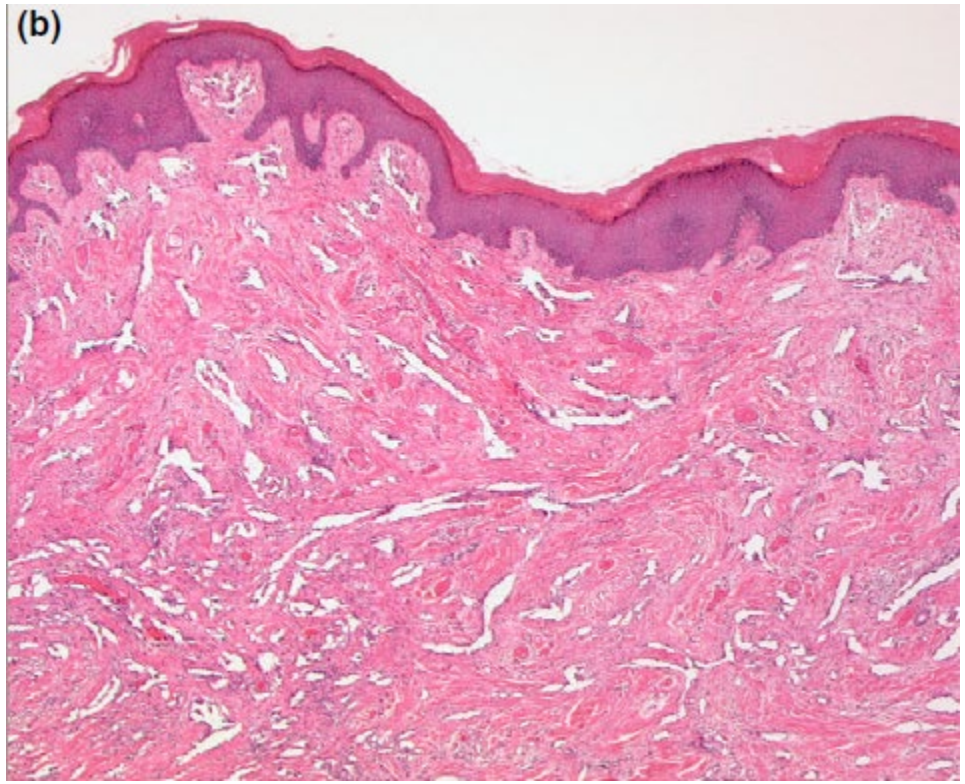


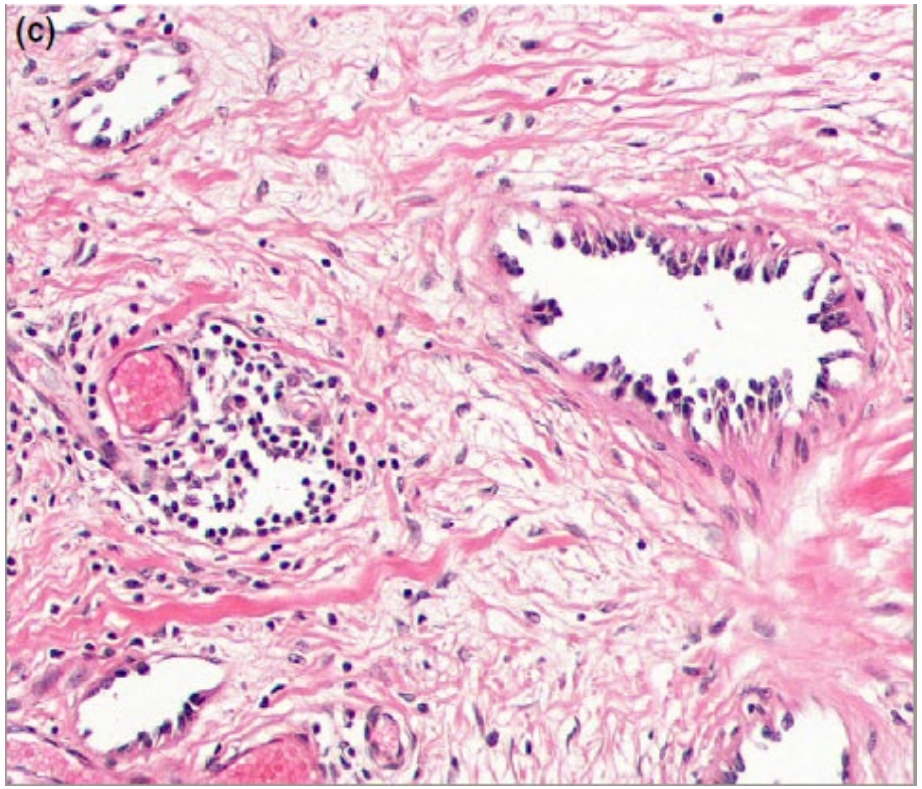
Hobnail Hemangioendotheliomas

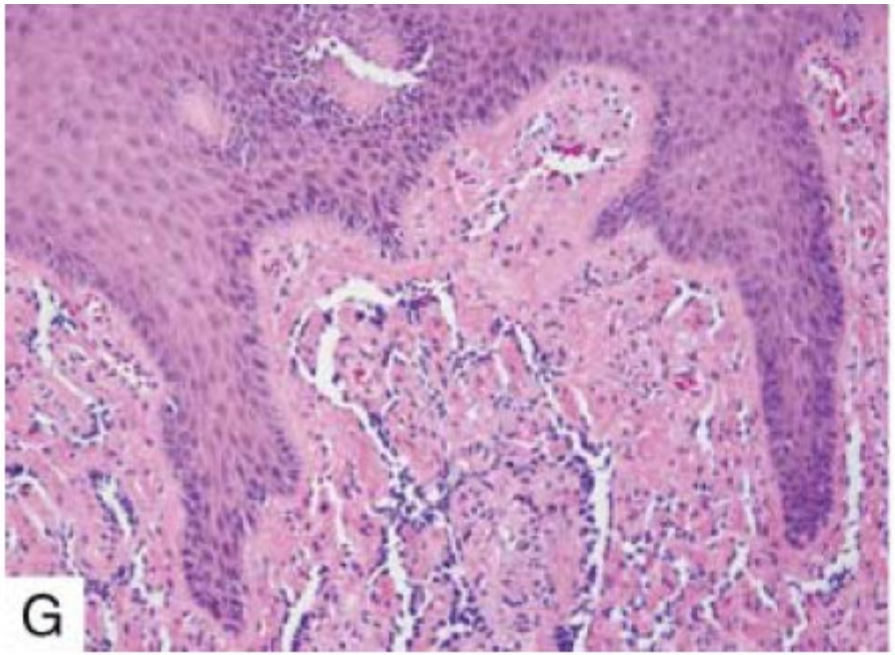
- Locally aggressive; rarely metastasizing
- Composed at least in part of hobnail endothelial proliferations with a lymphatic endothelial phenotype
- Superficially located, mainly occurs in adults
- Preferentially in the **dermis** and **subcutaneous tissue** of distal extremities

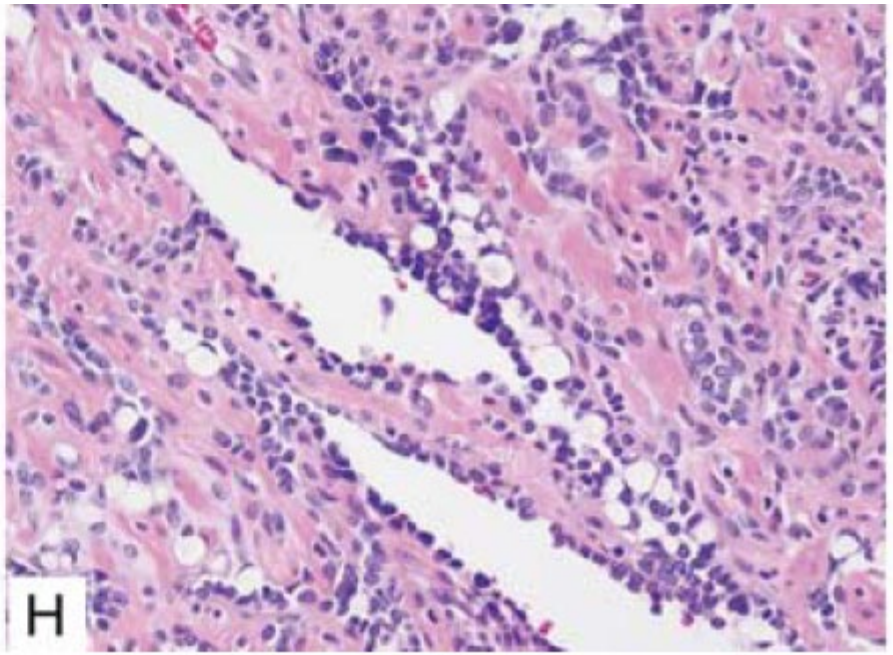
Retiform Hemangioendothelioma



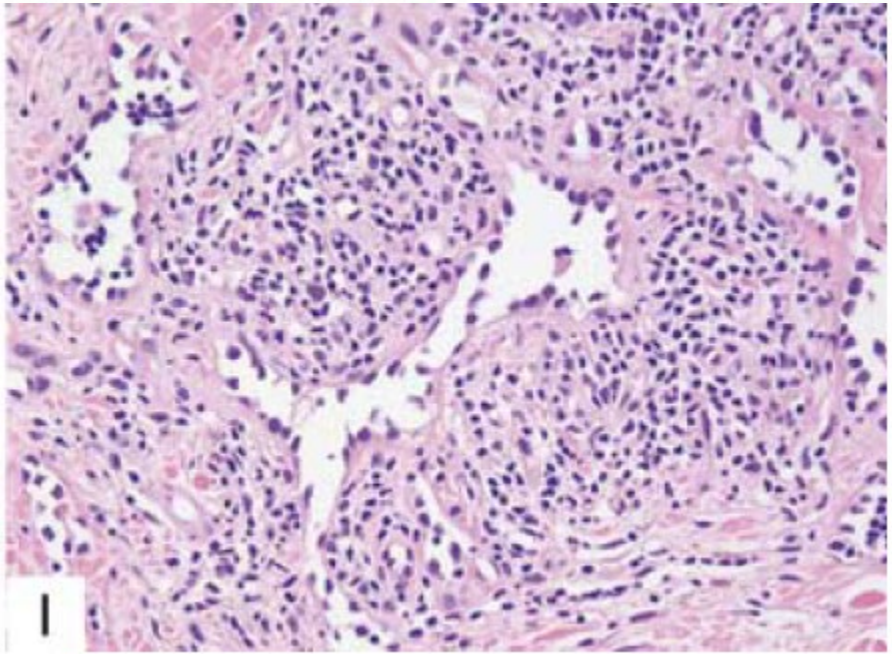


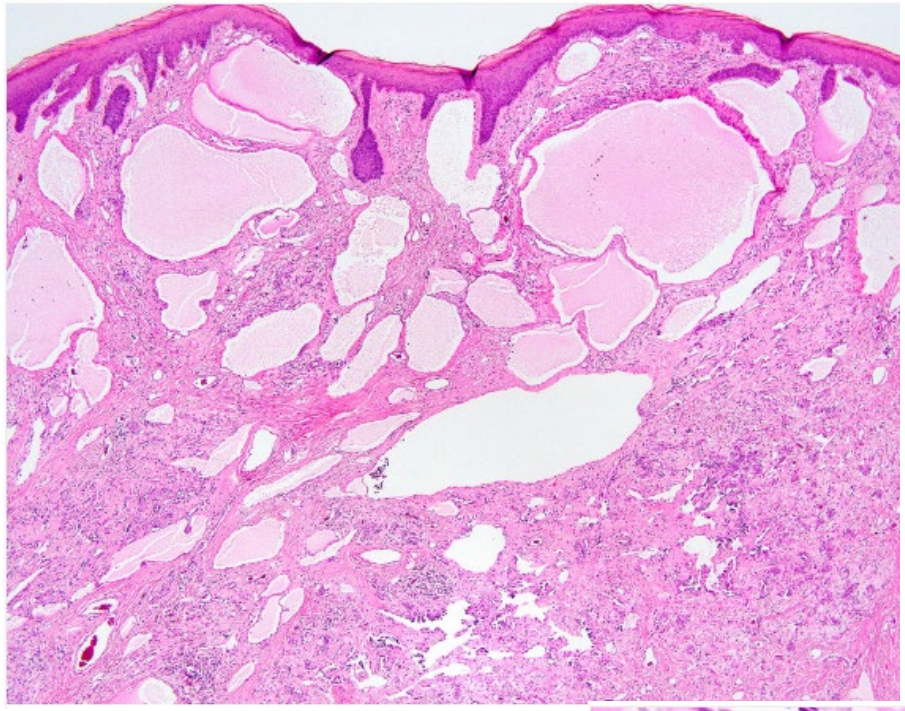


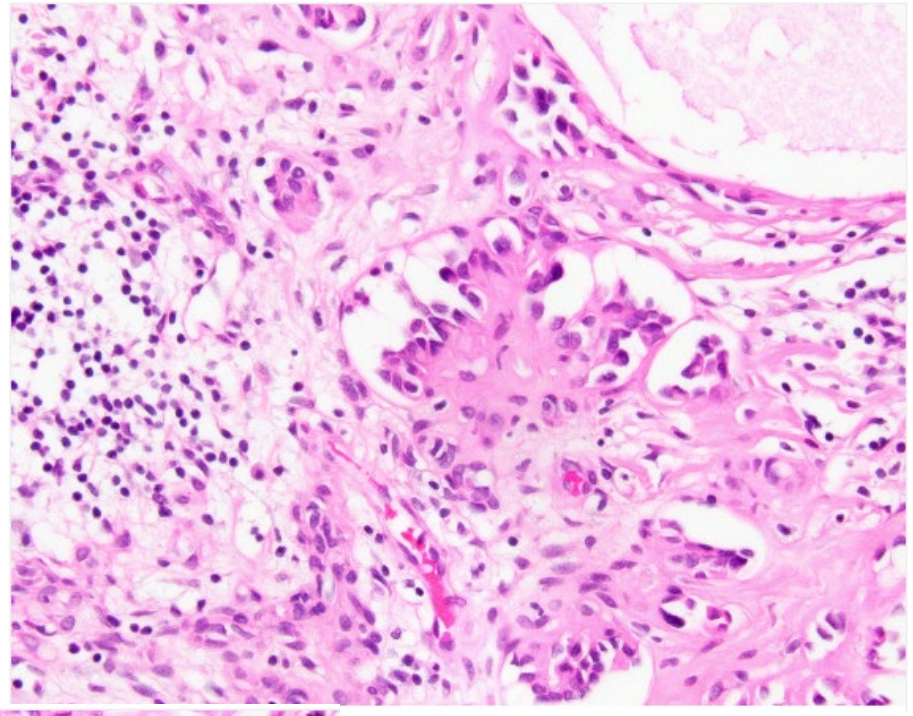


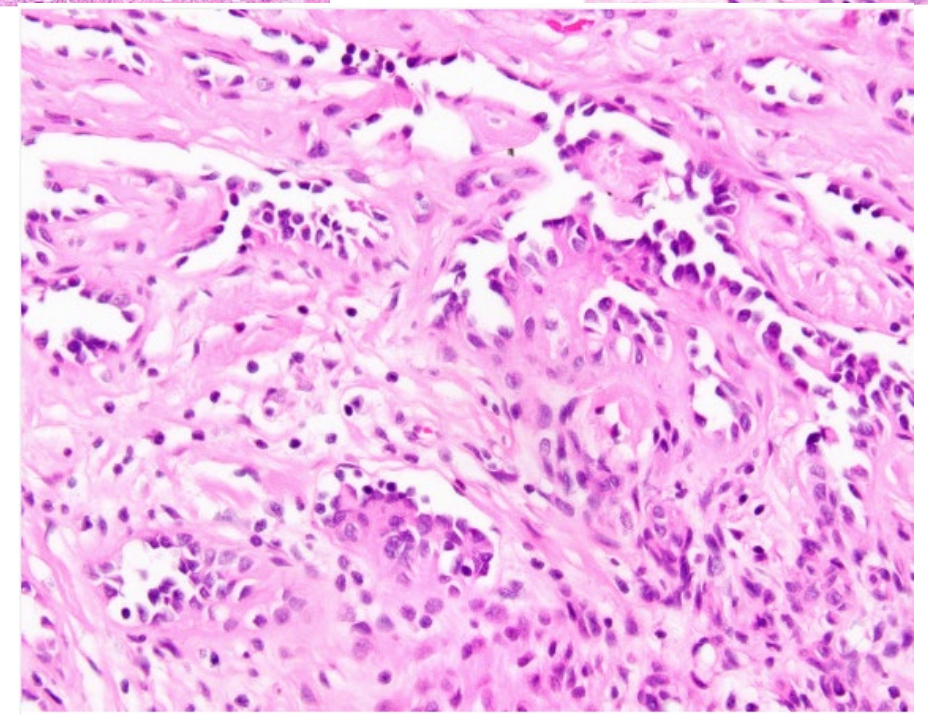


Retiform Hemangioendothelioma









Papillary intralymphatic angioendothelioma

Recurrent *YAP1* and *MAML2* Gene Rearrangements in Retiform and Composite Hemangioendothelioma

Cristina R. Antonescu, MD, Brendan C. Dickson, MD,† Yun-Shao Sung, MSc,* Lei Zhang, MD,* Albert J.H. Suurmeijer, MD,‡ Albrecht Stenzinger, MD,§ Gunhild Mechtersheimer, MD,§ and Christopher D.M. Fletcher, MD||*

Am J Surg Pathol 2020;44:1677–1684

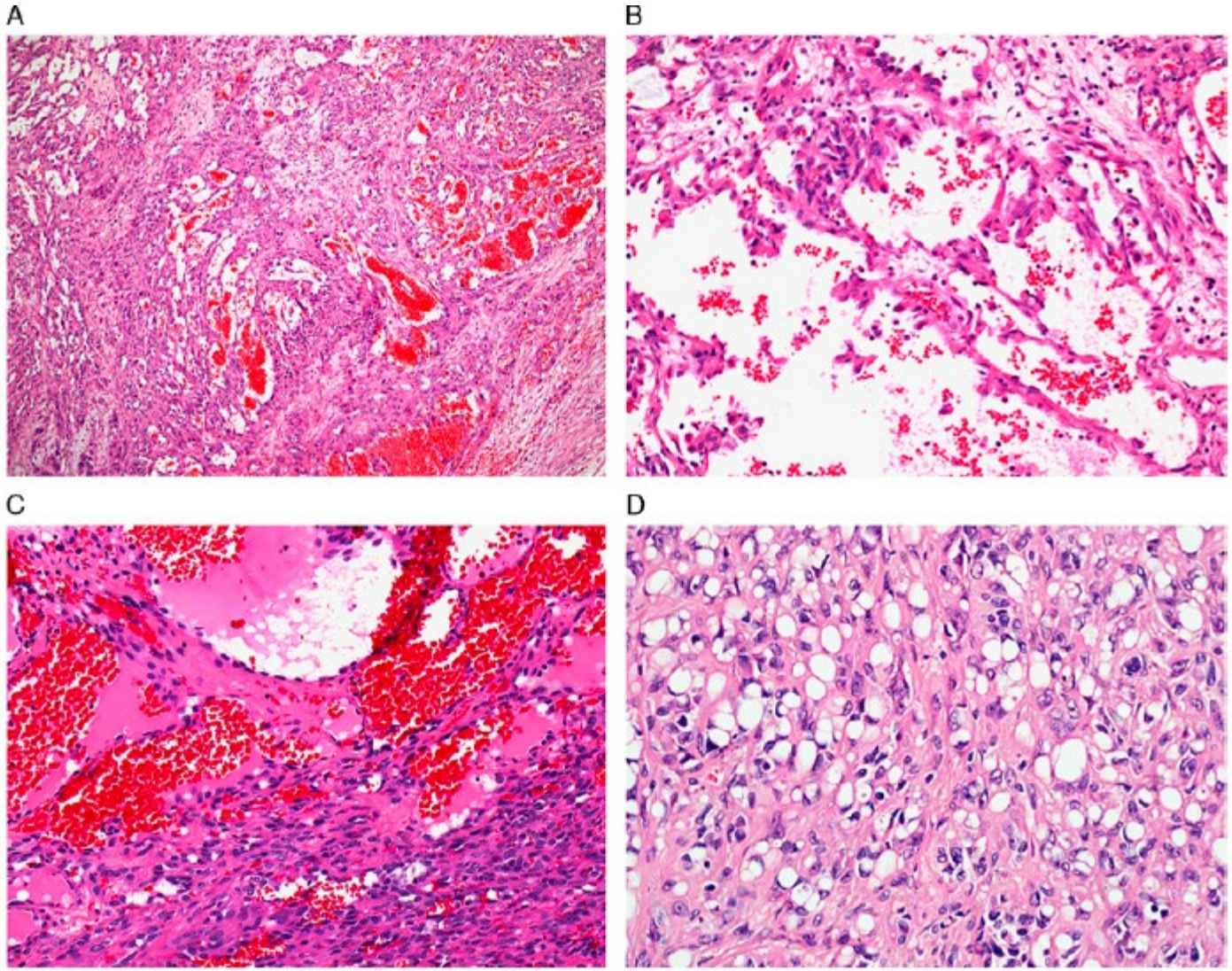
HE #	HE Type	Age/Sex	Site	Genetic Abnormality
1	RHE	10/male	Knee	*YAP1-MAML2**†
2	RHE	31/male	Shoulder	*YAP1*†
3	RHE	23/male	Fourth toe	*YAP1-MAML2*†
4	RHE	10/male	Buttock	*YAP1*†
5	RHE	50/female	Knee	*YAP1*†
6	CHE	9/female	Foot	*YAP1-MAML2*†
7	CHE	9/female	Heel	*YAP1-MAML2*†
8	CHE	7/female	Middle finger	*YAP1-MAML2*†
9	NE-CHE	37/male	Pancreas, liver, and lung lesions	*PTBP1-MAML2**

Composite Hemangioendothelioma (CHE)

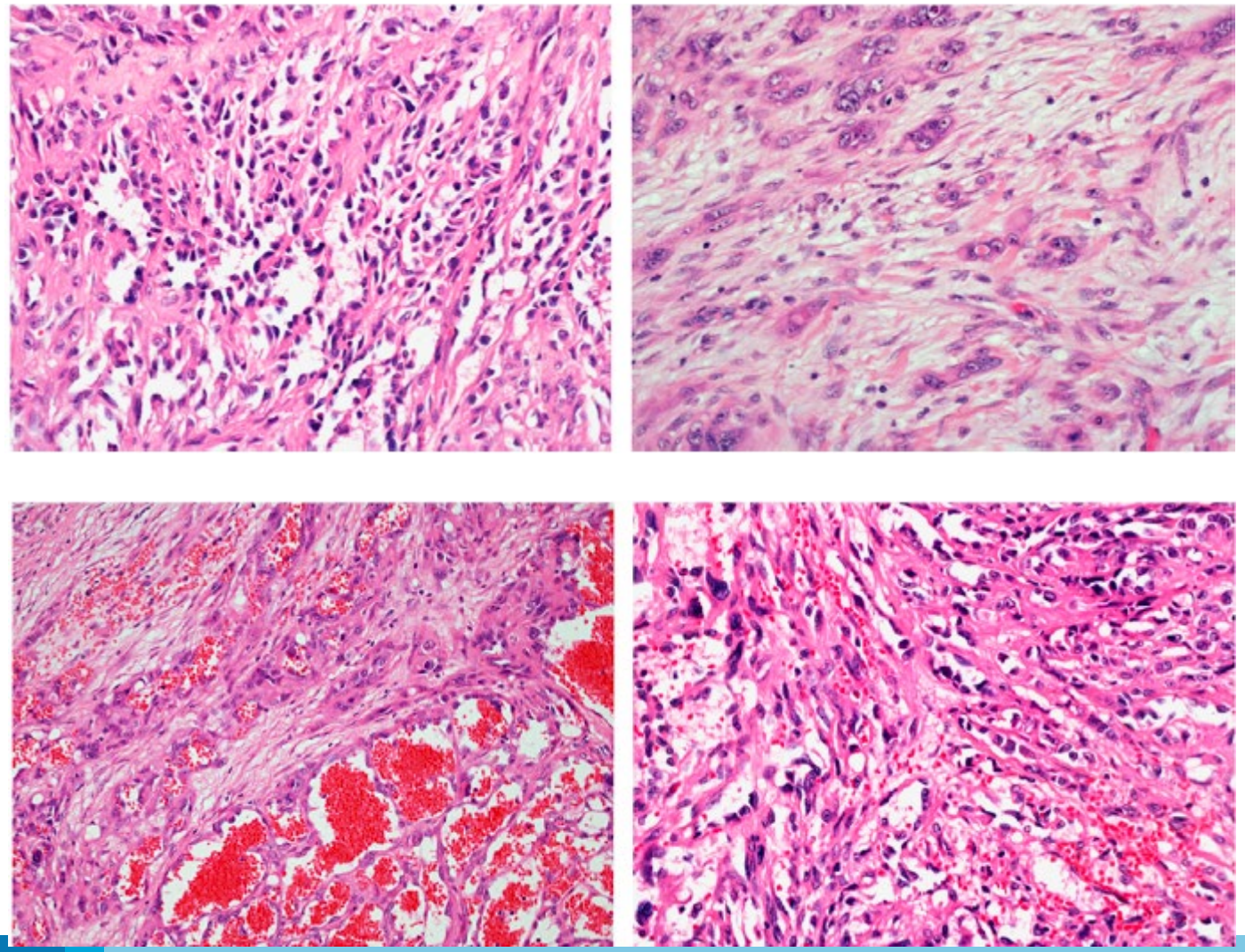
- Locally aggressive, rarely metastasizing endothelial neoplasm with an admixture of vascular components
- Neuroendocrine expression may be present
- Chiefly in young adults
- Very rare pediatric or congenital cases
- Predominantly skin and superficial soft tissues
- High rate of local recurrence (50%)
- Low risk of lymph node (6%) or distant metastases(1%)
- Neuroendocrine CHE appears to be considerably more aggressive

Morphological patterns

- Retiform Hemangioendothelioma-like
- Epithelioid Hemangioendothelioma-like
- Spindle cell Hemangioma-like
- Low-Grade Angiosarcoma-like



(*Adv Anat Pathol* 2015;22:254–259)



(*Adv Anat Pathol* 2015;22:254–259)

Recurrent *YAP1* and *MAML2* Gene Rearrangements in Retiform and Composite Hemangioendothelioma

Cristina R. Antonescu, MD, Brendan C. Dickson, MD,† Yun-Shao Sung, MSc,* Lei Zhang, MD,* Albert J.H. Suurmeijer, MD,‡ Albrecht Stenzinger, MD,§ Gunhild Mechtersheimer, MD,§ and Christopher D.M. Fletcher, MD‖*

Am J Surg Pathol 2020;44:1677–1684

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7	CHE	9/female	Heel	*YAP1-MAML2*†
8	CHE	7/female	Middle finger	*YAP1-MAML2*†
9	NE-CHE	37/male	Pancreas, liver, and lung lesions	*PTBP1-MAML2**

ARTICLE

Check for updates

Loss of expression of YAP1 C-terminus as an ancillary marker for epithelioid hemangioendothelioma variant with *YAP1-TFE3* fusion and other YAP1-related vascular neoplasms

William J. Anderson[1], Christopher D. M. Fletcher[1] and Jason L. Hornick[1]✉

Modern Pathology; https://doi.org/10.1038/s41379-021-00854-2

Tumor type	Total cases	YAP1-CT lost	YAP1-CT retained
Epithelioid hemangioendothelioma with *YAP1-TFE3*	13	10	3
Epithelioid hemangioendothelioma with *WWTR1-CAMTA1*	20	1	19
Retiform hemangioendothelioma	4	4	0
Composite hemangioendothelioma	2	2	0
Pseudomyogenic hemangioendothelioma	10	0	10
Epithelioid hemangioma	19	0	19
Epithelioid angiosarcoma	10	0	10

Untying the Gordian knot of composite hemangioendothelioma: Discovery of novel fusions

Konstantinos Linos[1] | Josephine K. Dermawan[1,2] | Melissa Pulitzer[1]
Meera Hameed[1] | Narasimhan P. Agaram[1] | Abbas Agaimy[3] |
Cristina R. Antonescu[1]

Genes Chromosomes Cancer. 2023;1–10.

Case #	Pertinent IHC	RNA sequencing	DNA sequencing
1	Positive: CD31, CD34, ERG, SMA (pericytes). Negative: Synaptophysin, D2-40, Ki-67 < 5%	*HSPG2::FGFR1* (exon 74-exon 9)	N/A
2	Positive: CD31, ERG, synaptophysin (patchy), D2-40. Negative: HHV8	*YAP1::FOXR1* (exon4-exon 2)	N/A
3	Positive: FVIII, ERG, SMA (pericytes), Ki-67 < 5%. Negative: CAMTA1, TFE3	*ACTB::MAML2* (exon2-exon 2)	N/A
4	Positive: CD31, ERG, CKAE1/AE3 (patchy), synaptophysin (patchy), Ki-67 40%. Negative: D2-40, CD34	*ARID1B::MAML2* (exon6-exon 2)	*TP53* mutation: p.Pro151Ser

MODERN PATHOLOGY (2017) 30, 1589–1602

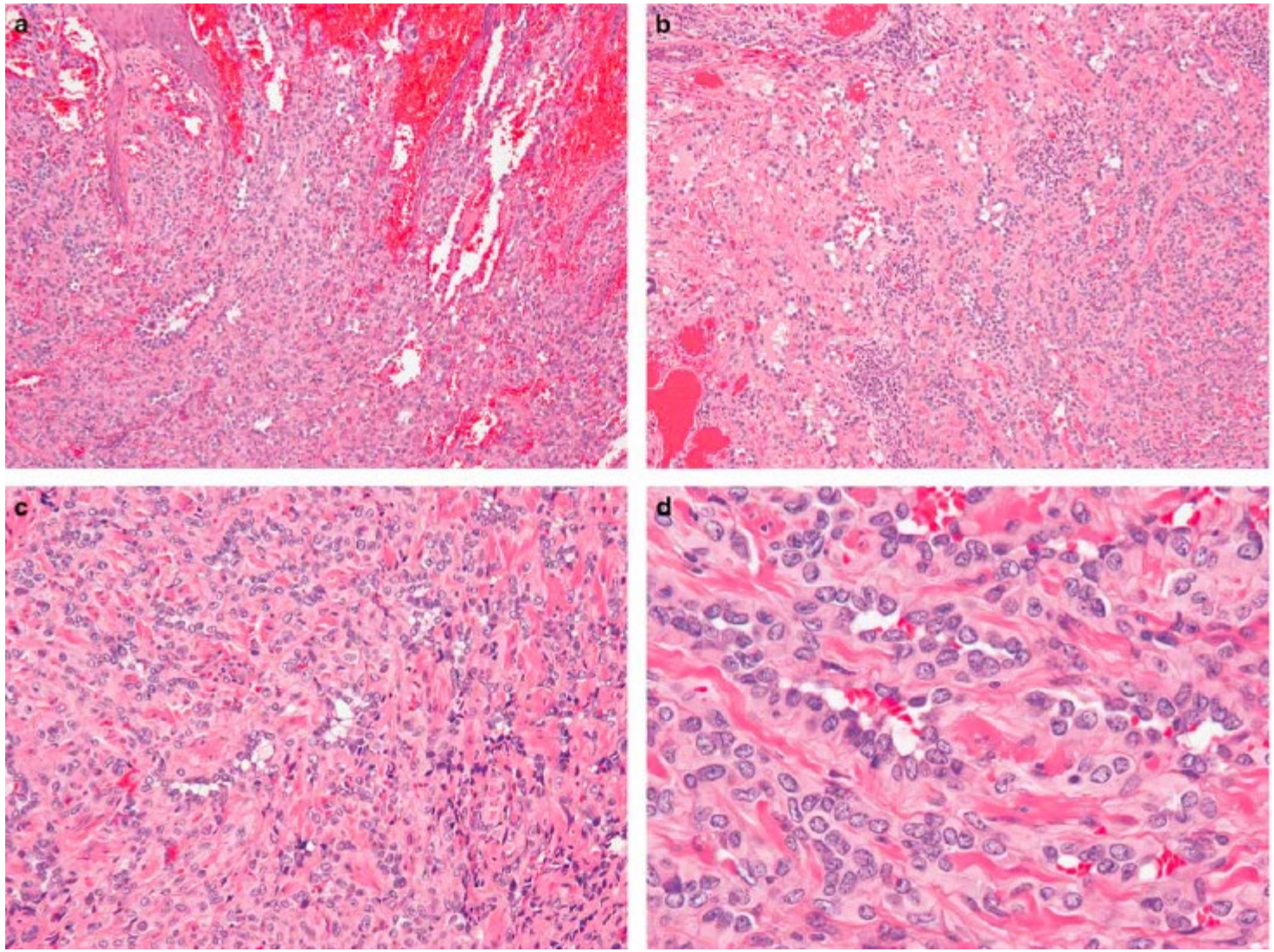
Composite hemangioendothelioma with neuroendocrine marker expression: an aggressive variant

Kyle D Perry[1], Alyaa Al-lbraheemi[2], Brian P Rubin[3], Jin Jen[1,4], Hongzheng Ren[1], Jin Sung Jang[4], Asha Nair[1], Jaime Davila[4], Stefan Pambuccian[5], Andrew Horvai[6], William Sukov[1], Henry D Tazelaar[7] and Andrew L Folpe[1]

[1]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA; [2]Department of Pathology, Boston Children's Hospital, Boston, MA, USA; [3]Robert J Tomsich Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, OH, USA; [4]Genome Analysis Core, Medical Genome Facility, Center for Individualized Medicine, Mayo Clinic, Rochester, MN, USA; [5]Department of Pathology, Loyola University Medical Center, Maywood, IL, USA; [6]Department of Pathology, University of California San Francisco, San Francisco, CA, USA and [7]Department of Laboratory Medicine and Pathology, Mayo Clinic, Scottsdale, AZ, USA

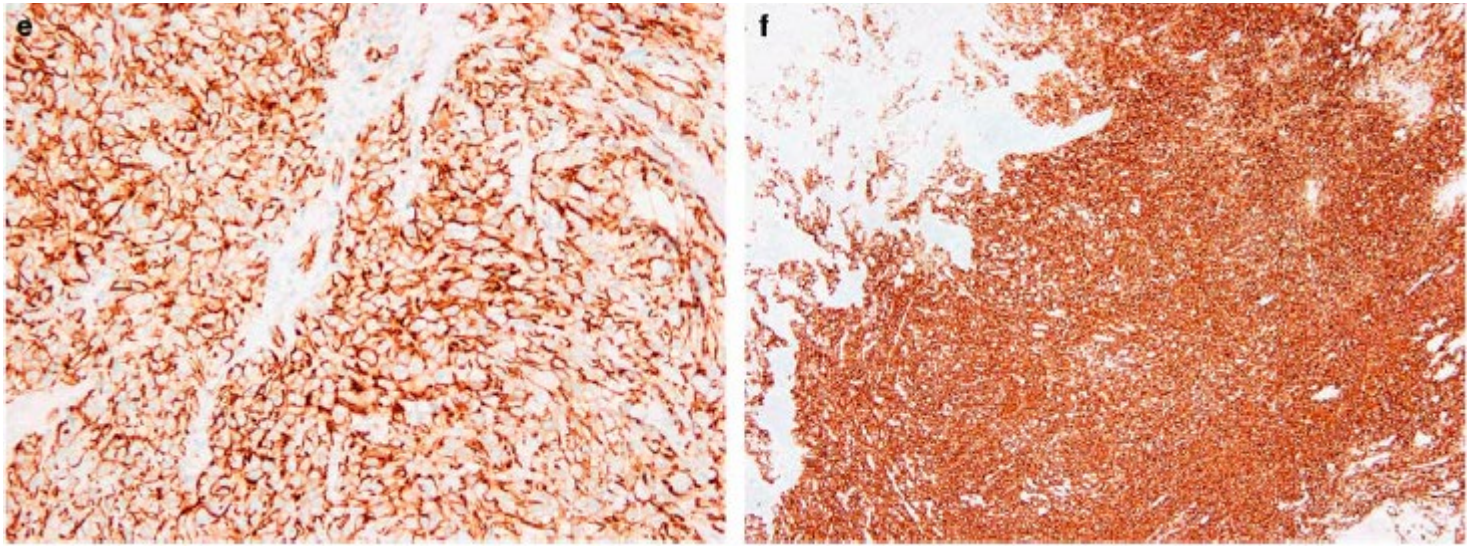
Table 1 Clinicopathological, immunohistochemical, and genetic results

Case	*Sex*	*Age (years)*	*Site*	*Size (cm)*	*LR*	*Met*	*Status*	*CD31*	*ERG*	*FLI-1*	*CD34*	*D2-40*	*SYN*	*CGA*	*CD56*	*CK*	*CAMTA1*	*Genetics*
1	M	47	Wrist	7.7	Yes	Liver/lung/humerus	DOD	+	+	+	–	–	+	–	+	–	–	ND
2	F	48	Right ankle	N/A	Yes	—	AWOD	+	+	+	+	–	+	–	–	–	ND	ND
3	F	36	Periaortic	2.1	—	Sacrum	AWD	+	+	+	–	+	+	–	+	–	–	*PTBP1-MAML2*
4	F	48	Vertebral	N/A	—	Lung	AWD	+	+	+	–	+	+	–	–	–	–	ND
5	M	27	Pulmonary vein	N/A	—	Brain	AWD	+	+	+	–	–	+	+	+	–	–	*EPC1-PHC2*
6	F	14	Ear	3.0	—	—	N/A	+	+	+	+	+	+	–	+	–	–	ND
7	F	55	Superficial hip	0.4	—	—	AWOD	+	+	+	–	+	+	–	–	–	ND	ND
8	M	55	Liver	6.9	—	—	AWOD	ND	ND	ND	ND	ND	+	–	–	–	ND	ND
9	M	15	Foot	1.2	—	—	AWOD	+	ND	+	+	+	+	–	–	–	–	ND
10	F	59	Cheek	9.5	—	—	N/A	+	+	+	+	+	+	–	+	–	ND	ND
11	M	9	Index finger	N/A	—	—	N/A	+	+	+	+	+	+	–	–	–	ND	ND


a
b
c
d

CD31

Synaptophysin



MODERN PATHOLOGY (2017) 30, 1589–1602

Epithelioid Hemangioendothelioma (EHE) and **CAMTA1**

- Rare low-grade, malignant vascular neoplasm that shows endothelial differentiation

- Less aggressive than angiosarcoma
  - Risk of metastasis in ~ 20-30% of cases
  - Death in approximately 15% of cases

J Cutan Pathol 2008: 35: 236–240
doi: 10.1111/j.1600-0560.2007.00790.x
Blackwell Munksgaard. Printed in Singapore

Journal of
Cutaneous Pathology

Cutaneous epithelioid hemangioendothelioma

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor of endothelial cell origin. We describe an EHE arising on the plantar surface of the foot that was treated as verruca vulgaris for several years before a biopsy showed EHE. We discuss the clinical and histopathologic differential diagnoses for these tumors and review additional cases in which EHE has been mistaken for benign entities clinically.

Loren E. Clarke[1], Robert Lee[2], Giuseppe Militello[2], Rosalie Elenitsas[2] and Jacqueline Junkins-Hopkins[2]

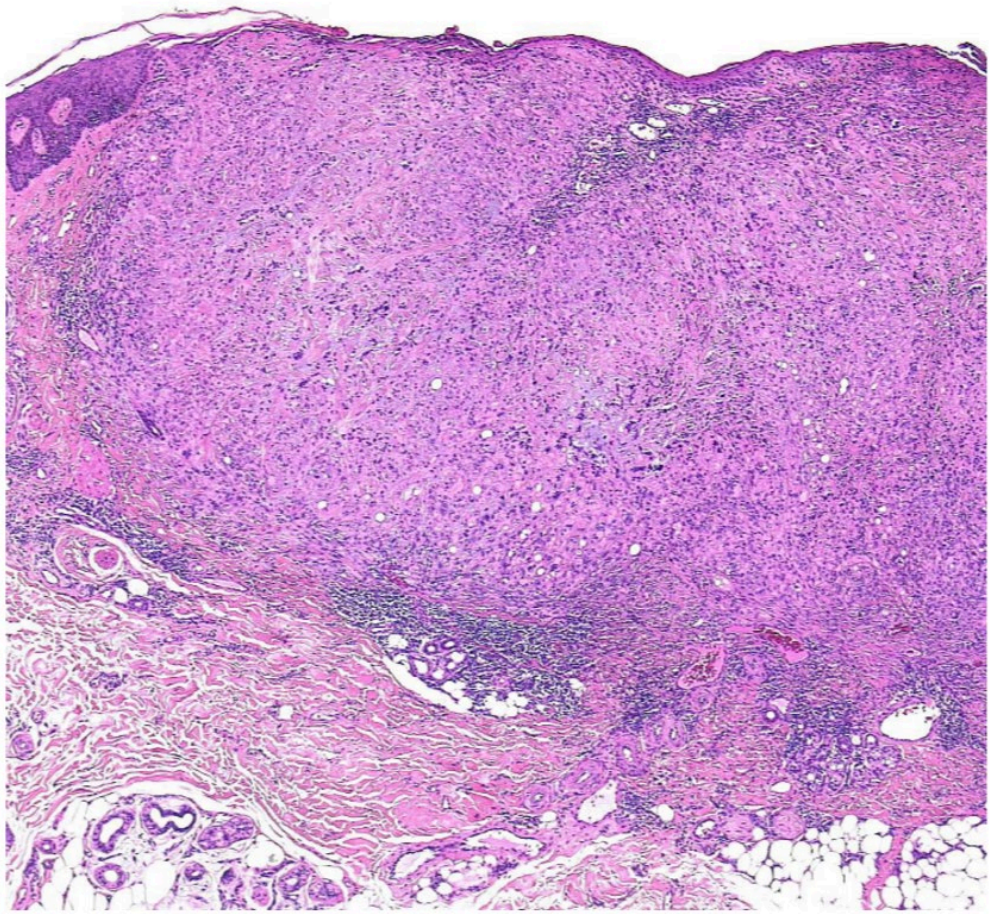
[1]Department of Pathology, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA, and
[2]Department of Dermatology, The Hospital of the University of Pennsylvania, Philadelphia, PA, USA

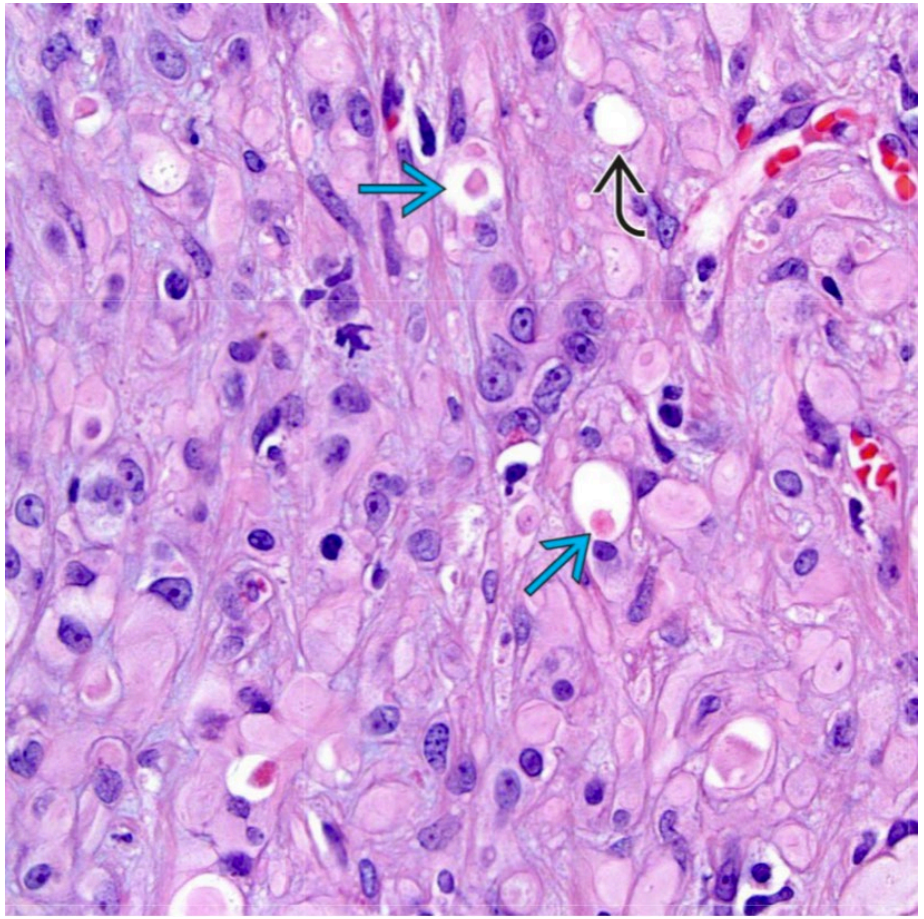
Clinical Features

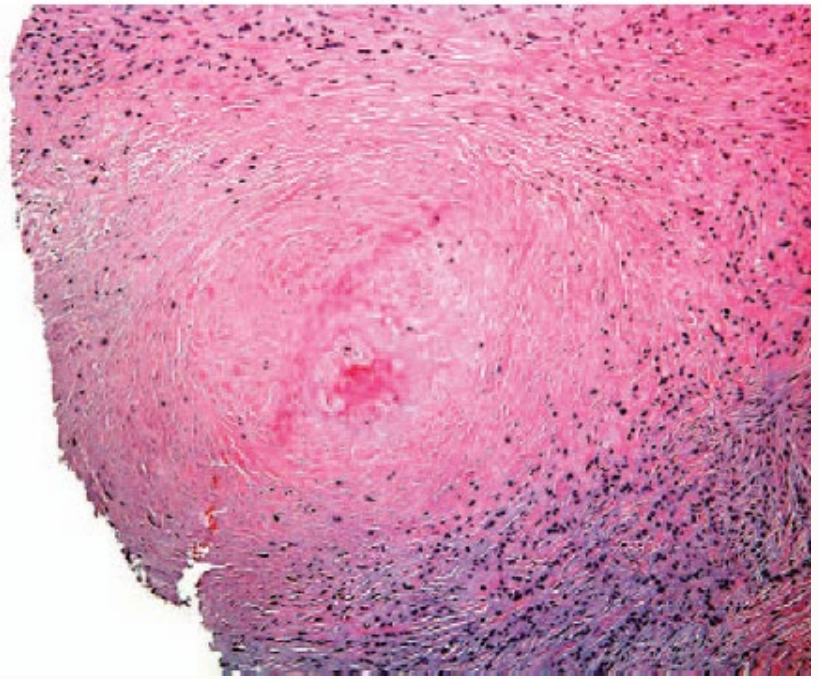
- Affects patients of all ages but rare during childhood
- Typically solitary lesion on the extremities
- Can involve larger preexisting vessels

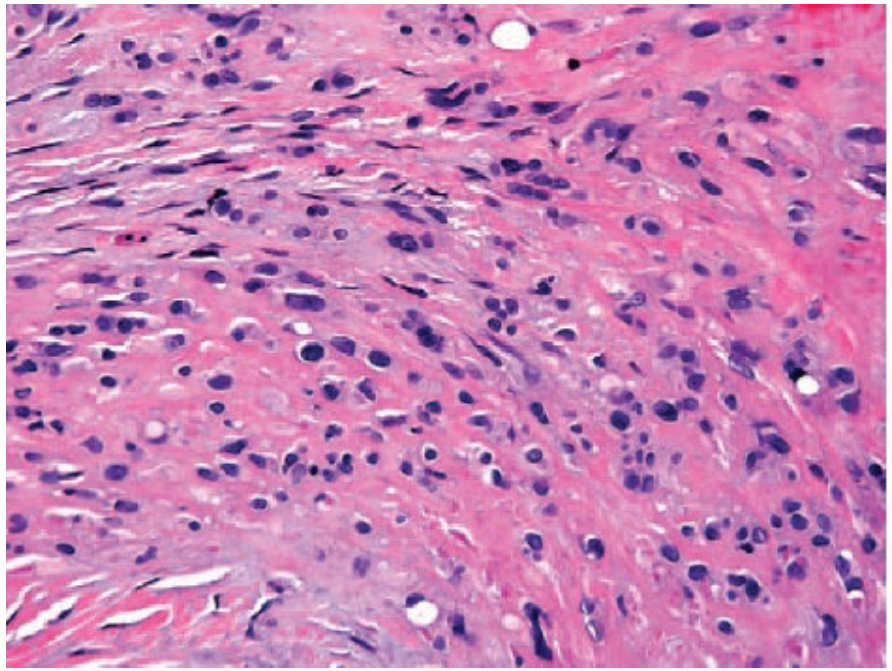
<u>Multiple cutaneous nodules</u>

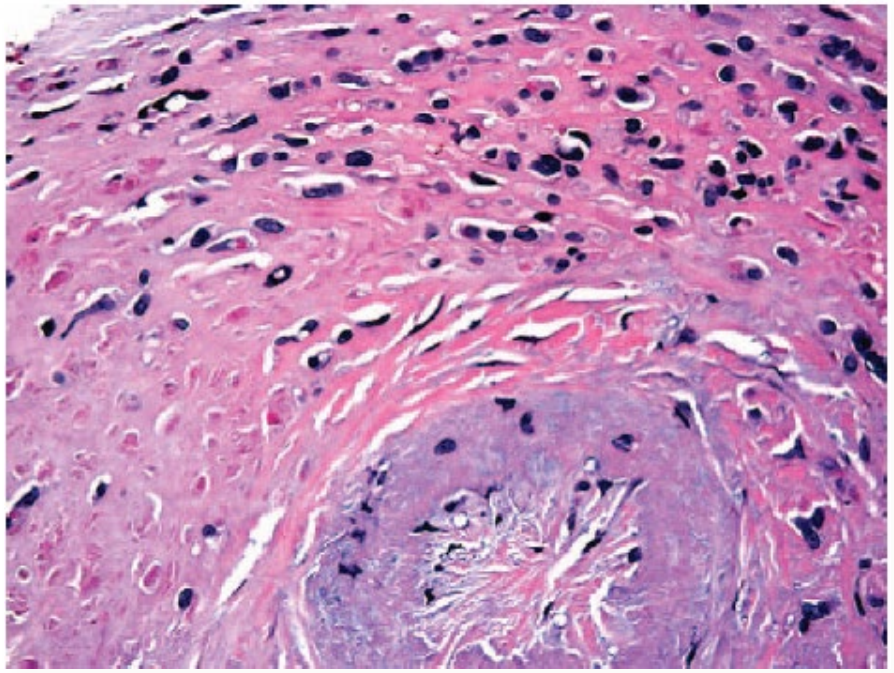
- !!!!**Metastasizing deep soft tissue or osseous EHE should be ruled out**!!!!

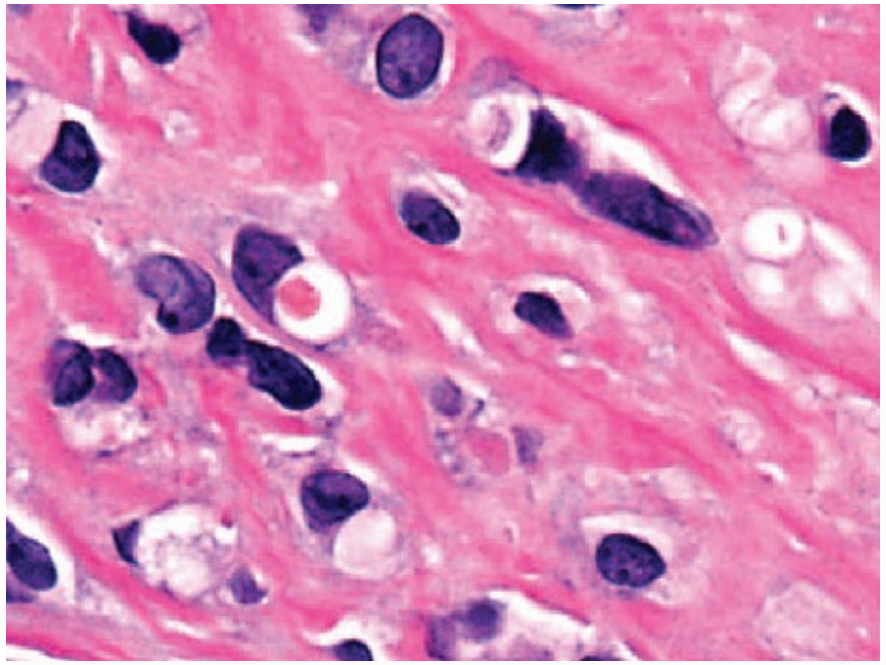


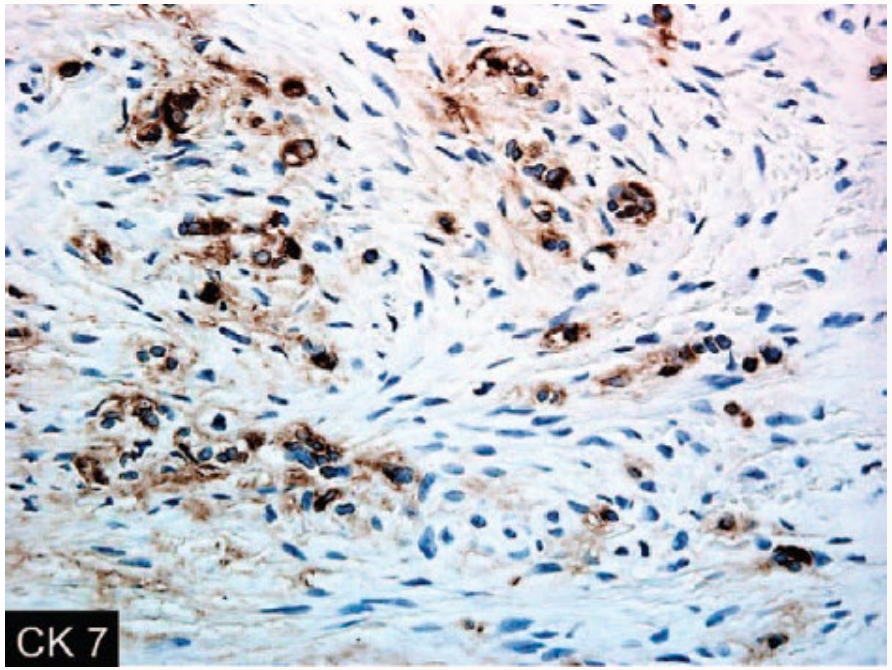


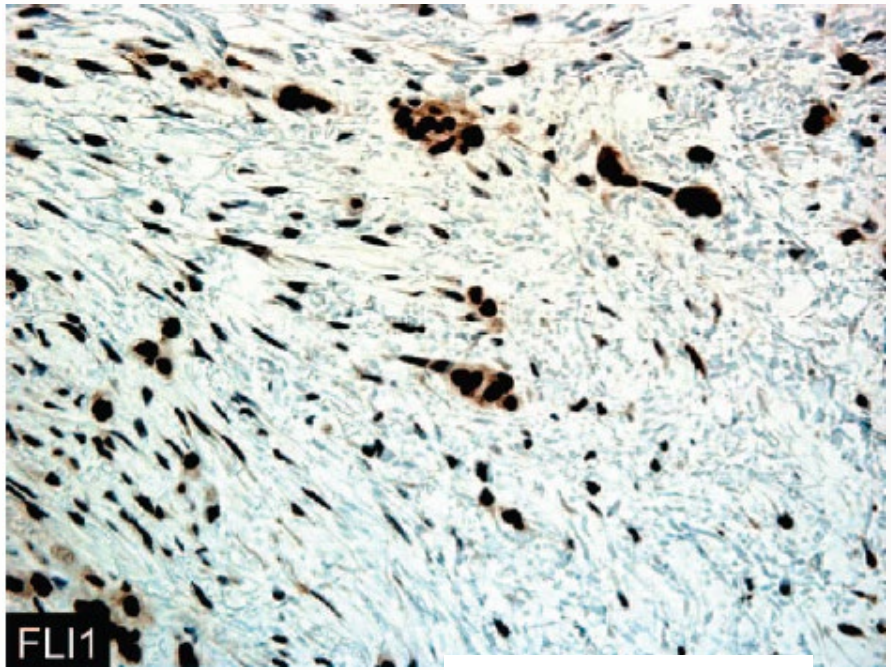









CK 7


FLI1

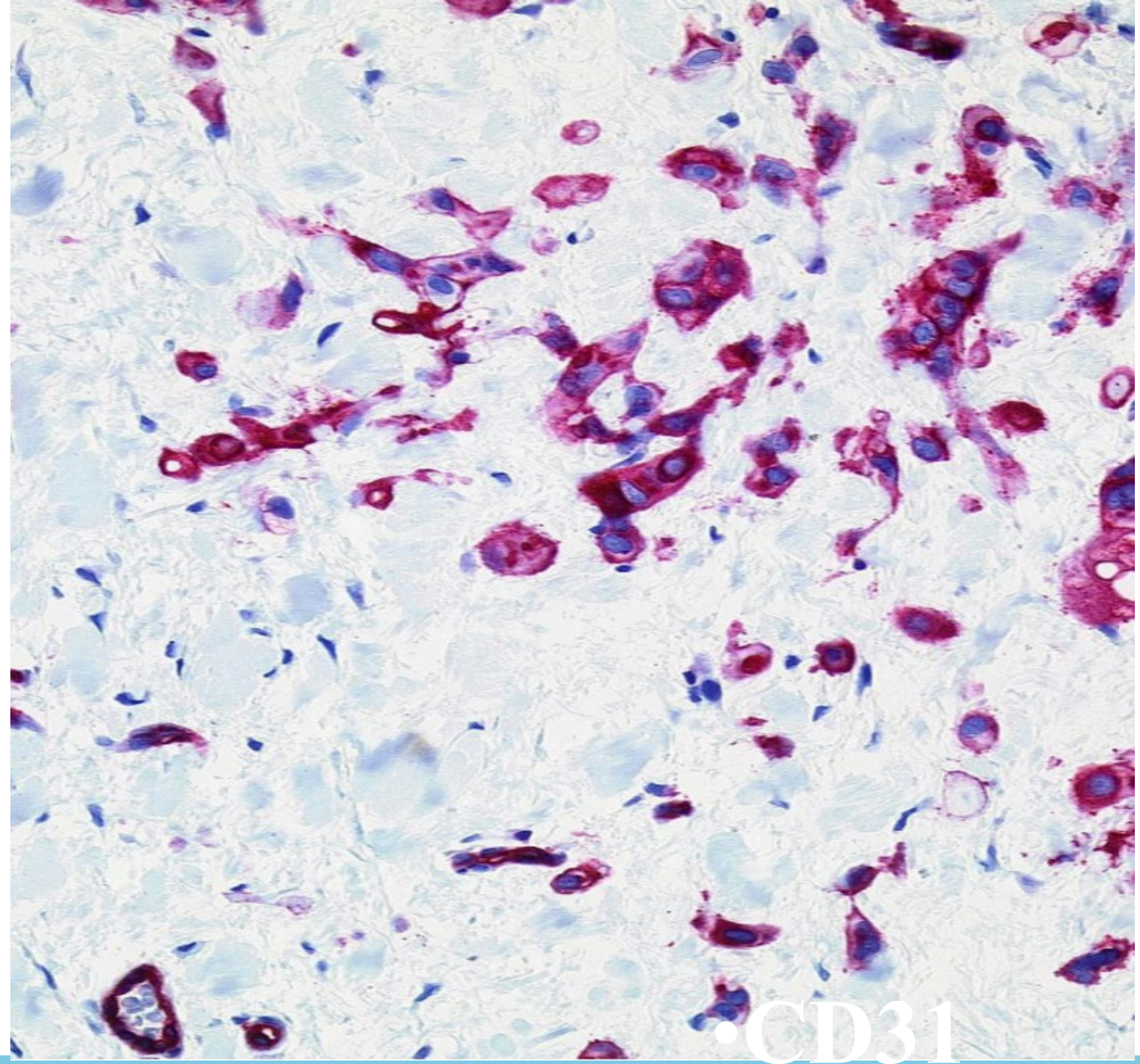
Immunohistochemistry

POSITIVE

- CD31
- CD34
- ERG
- AE1/AE3 in 25% of cases

NEGATIVE

- S100 protein
- Desmin
- EMA



Molecular

- Recurrent translocation t(1;3)(p36;q25) involving **WWTR1** (3q25) and **CAMTA1** (1p36)
  - Approximately 90% of EHE with classic morphology and not identified in histologic mimics

- A subset shown to harbor **YAP1-TFE3**

CAMTA1 is a useful immunohistochemical marker for diagnosing epithelioid haemangioendothelioma

Ryo Shibuya, Atsuji Matsuyama, Eisuke Shiba, Hiroshi Harada, Kei Yabuki & Masanori Hisaoka

Department of Pathology and Oncology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

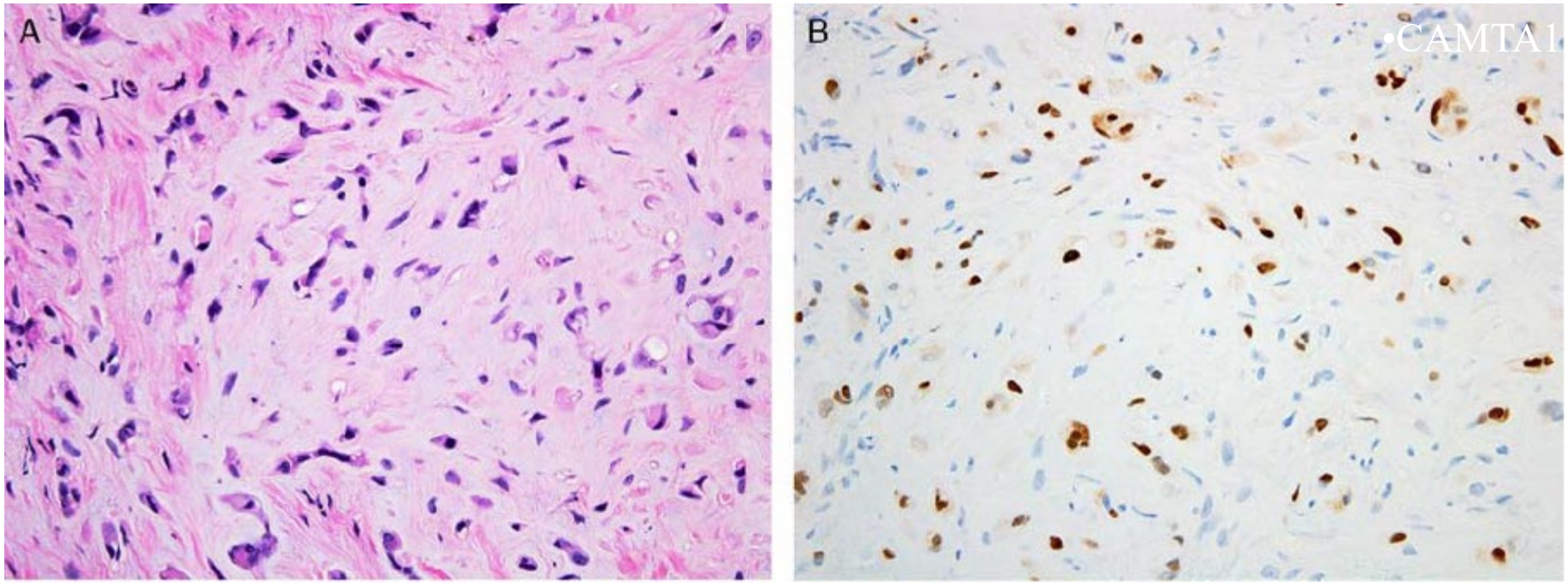
Histopathology 2015, 67, 827–835.

Nuclear Expression of CAMTA1 Distinguishes Epithelioid Hemangioendothelioma From Histologic Mimics

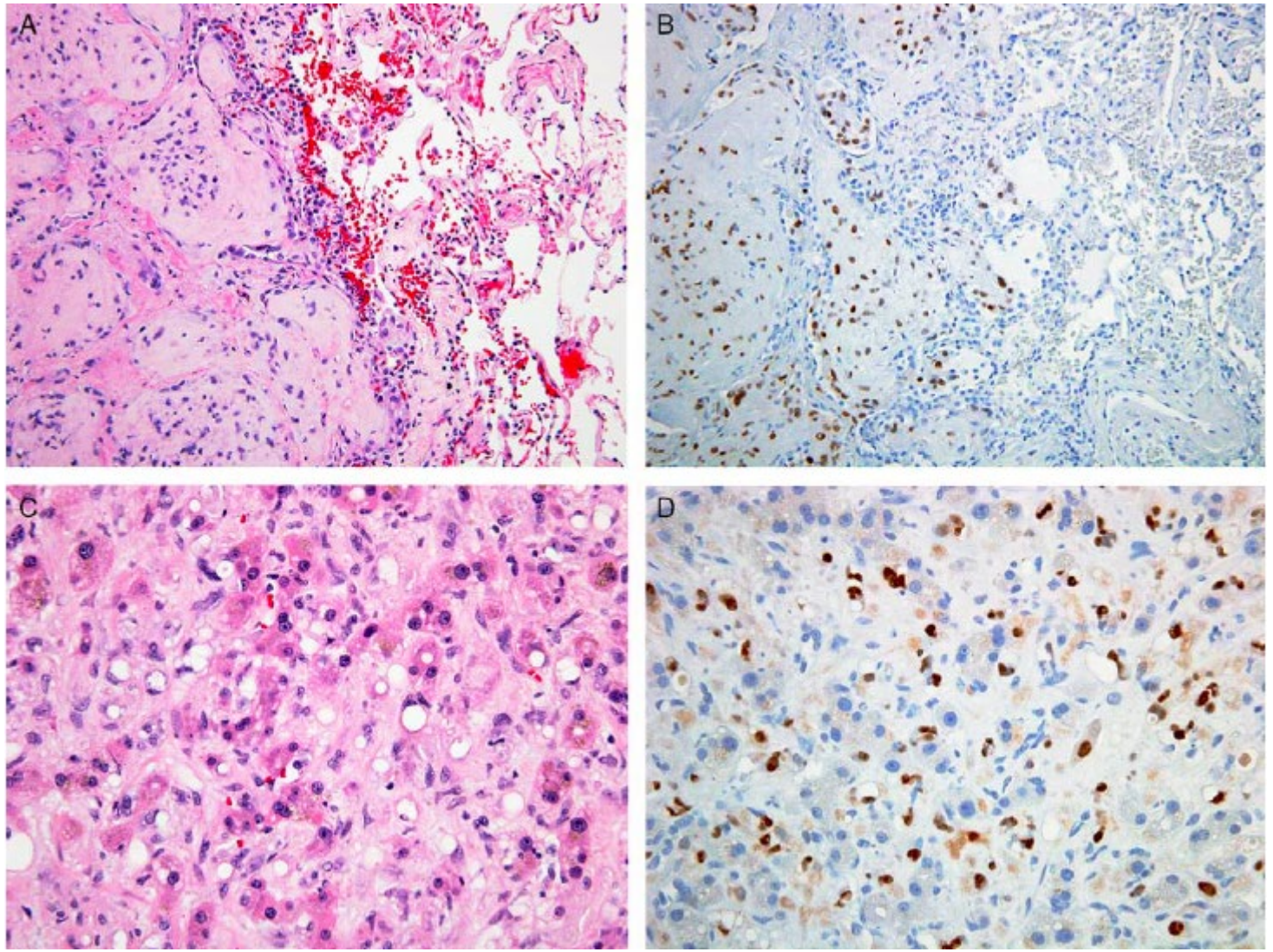
Leona A. Doyle, MD, Christopher D.M. Fletcher, MD, FRCPath, and Jason L. Hornick, MD, PhD

(*Am J Surg Pathol* 2016;40:94–102)

Tumor Type	Total Cases	CAMTA1 Positive (%)
EHE	59	51 (86)*
Epithelioid hemangioma	20	0 (0)
Epithelioid angiomatous nodule	10	0 (0)
Epithelioid angiosarcoma	25	1 (4)
Composite hemangioendothelioma	5	0 (0)
Pseudomyogenic hemangioendothelioma	10	0 (0)
Epithelioid sarcoma	25	0 (0)
Sclerosing epithelioid fibrosarcoma	10	0 (0)
Myoepithelial neoplasms of soft tissue	10	0 (0)
PEComa	10	0 (0)
Alveolar soft part sarcoma	10	0 (0)
Ossifying fibromyxoid tumor	10	0 (0)



(*Am J Surg Pathol* 2016;40:94–102)



(*Am J Surg Pathol* 2016;40:94–102)

Tumour type	CAMTA1 positivity
Carcinomas	1/169
Adenocarcinoma, bile duct	0/5
Adenocarcinoma, colon	0/24
Adenocarcinoma, ductal, breast	1/37
Adenocarcinoma, endometrium	0/5
Adenocarcinoma, lobular, breast	0/9
Adenocarcinoma, lung	0/6
Adenocarcinoma, ovary	0/6
Adenocarcinoma, prostate	0/6
Adenocarcinoma, stomach (7 signet ring cell)	0/12
Basal cell carcinoma, skin	0/7
Carcinoma of thyroid (4 papillary, 1 follicular, 1 medurally)	0/6
Hepatocellular carcinoma	0/6
Renal cell carcinoma	0/7
Squamous cell carcinoma, oesophagus	0/7
Squamous cell carcinoma, lung	0/6
Squamous cell carcinoma, skin	0/7
Squamous cell carcinoma, uterine cervix	0/6
Urothelial carcinoma	0/7

Tumour type	CAMTA1 positivity
Epithelioid haemangioendothelioma (EHE)	14/16
Non-EHE tumours	1/276
Non-epithelial tumours other than EHE	0/107
Alveolar soft part sarcoma (*ASPL–TFE3* fusion +)	0/4
Anaplastic large cell lymphoma	0/4
Angiomatoid fibrous histiocytoma	0/3
Angiosarcoma (2 epithelioid)	0/12
Clear cell sarcoma	0/5
Composite haemangioendothelioma	0/1
Desmoplastic small round cell tumour	0/2
Epithelioid angiomyolipoma	0/5
Epithelioid haemangioma	0/6
Epithelioid neurofibroma	0/2
Epithelioid sarcoma	0/8
Epithelioid schwannoma	0/1
Extraskeletal myxoid chondrosarcoma	0/6
Gastrointestinal stromal tumour (epithelioid)	0/2
Leiomyosarcoma (epithelioid)	0/2
Malignant melanoma	0/13
Malignant mesothelioma (epithelioid)	0/6
Malignant peripheral nerve sheath tumour (epithelioid)	0/3
Malignant perivascular epithelioid cell tumour (PEComa)	0/2
Myoepithelioma of soft tissue	0/4
Ossifying fibromyxoid tumour	0/2
Pseudomyogenic haemangioendothelioma	0/4
Sclerosing epithelioid fibrosarcoma	0/2
Solitary fibrous tumour (epithelioid)	0/2
Synovial sarcoma (biphasic type)	0/6

Variant *WWTR1* gene fusions in epithelioid hemangioendothelioma—A genetic subset associated with cardiac involvement

Albert J. H. Suurmeijer[1] | Brendan C. Dickson[2] | David Swanson[2] | Yun S. Sung[3] | Lei Zhang[3] | Cristina R. Antonescu[3]

Genes Chromosomes Cancer. 2020;59:389–395.

Case 1[a]	WWTR1-MAML2	EHE	76/F	Heart, left atrium	N/A
Case 2	*WWTR1-MAML2*	EHE	21/M	Bone, vertebra T11	NED, 70 months (s/p resection)
Case 3[a]	*WWTR1-ACTL6A*	Malignant EHE	73/F	Heart, right ventricle	DOD, 9 months
Case 4[a]	*WWTR1* rearrangement	EHE	72/F	Heart, left atrium	DOD, 15 months (s/p chemo Adriamycin +DTIC), soft tissue metastases
Case 5[a]	*WWTR1* rearrangement	EHE	67/M	Heart, left atrium	Lung metastases at diagnosis
Case 6	*WWTR1* rearrangement	Malignant EHE	65/M	Pelvic mass	Recent case

Virchows Arch. 2021 Jul 6. doi: 10.1007/s00428-021-03143-0. Online ahead of print.

Novel detection of the CAMTA1-WWTR1 fusion gene in extra-adrenal myelolipoma-like lesion: a case report

Hirofumi Watanabe [1], Kazuhiro Murakami [2], Toru Motoi [3], Keigo Murakami [2], Yayoi Aoyama [4], Hideki Mitomo [5], Naoya Ishibashi [5], Takashi Sugawara [5], Toshiharu Tabata [5], Tomonori Matsuura [6], Hironobu Sasano [4], Yasuhiro Nakamura [2]

Int J Surg Pathol. 2019 Sep;27(6):664-668. doi: 10.1177/1066896919837611. Epub 2019 Apr 3.

Epithelioid Hemangioendothelioma Arising Within Mediastinal Myelolipoma: A WWTR1-Driven Composite Neoplasm

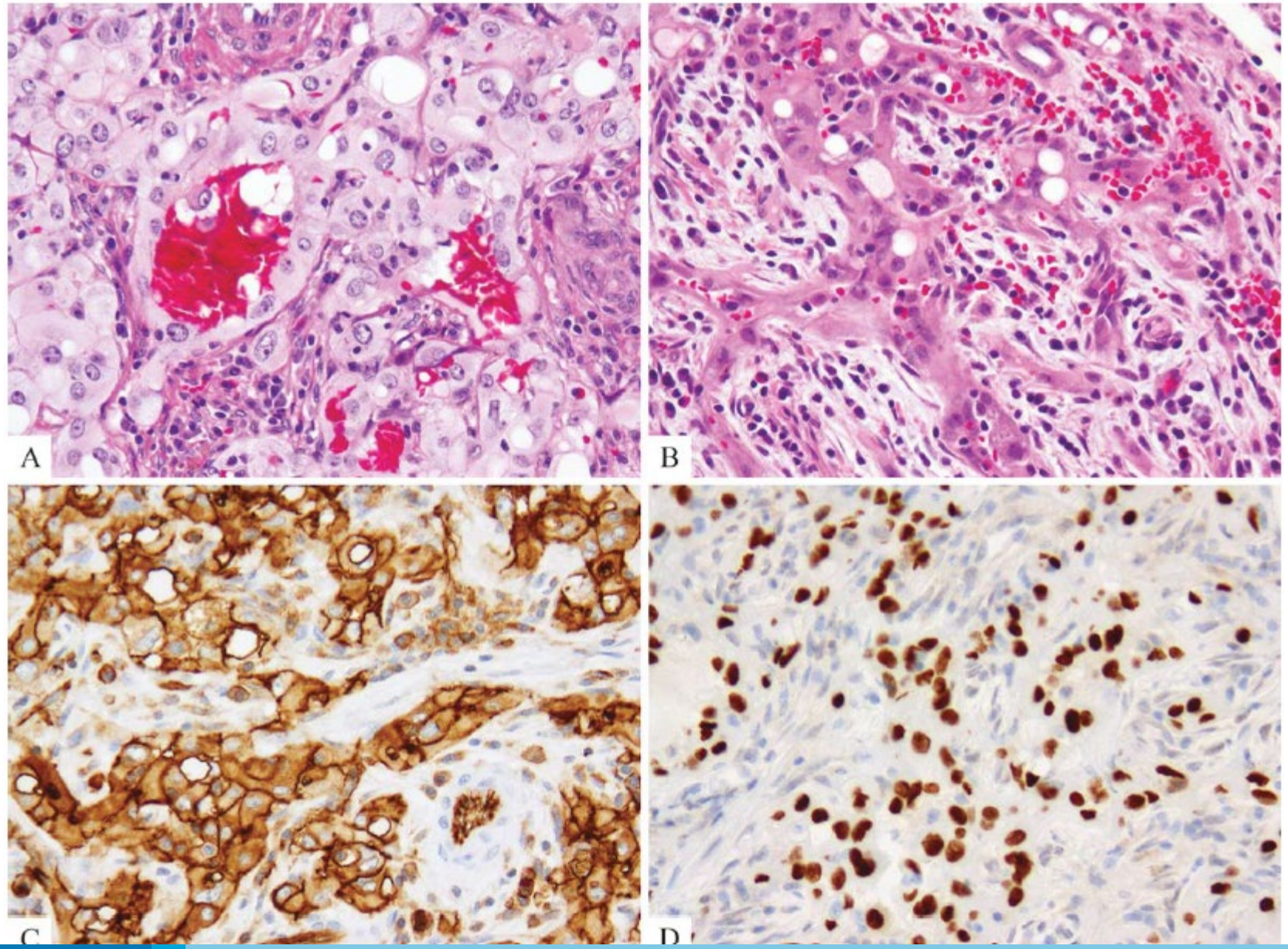
Julio A Diaz-Perez [1], Jaylou Velez-Torres [1], Oleksii Iakymenko [1], Nestor Villamizar [2], Andrew E Rosenberg [1]

Novel *YAP1-TFE3* Fusion Defines a Distinct Subset of Epithelioid Hemangioendothelioma

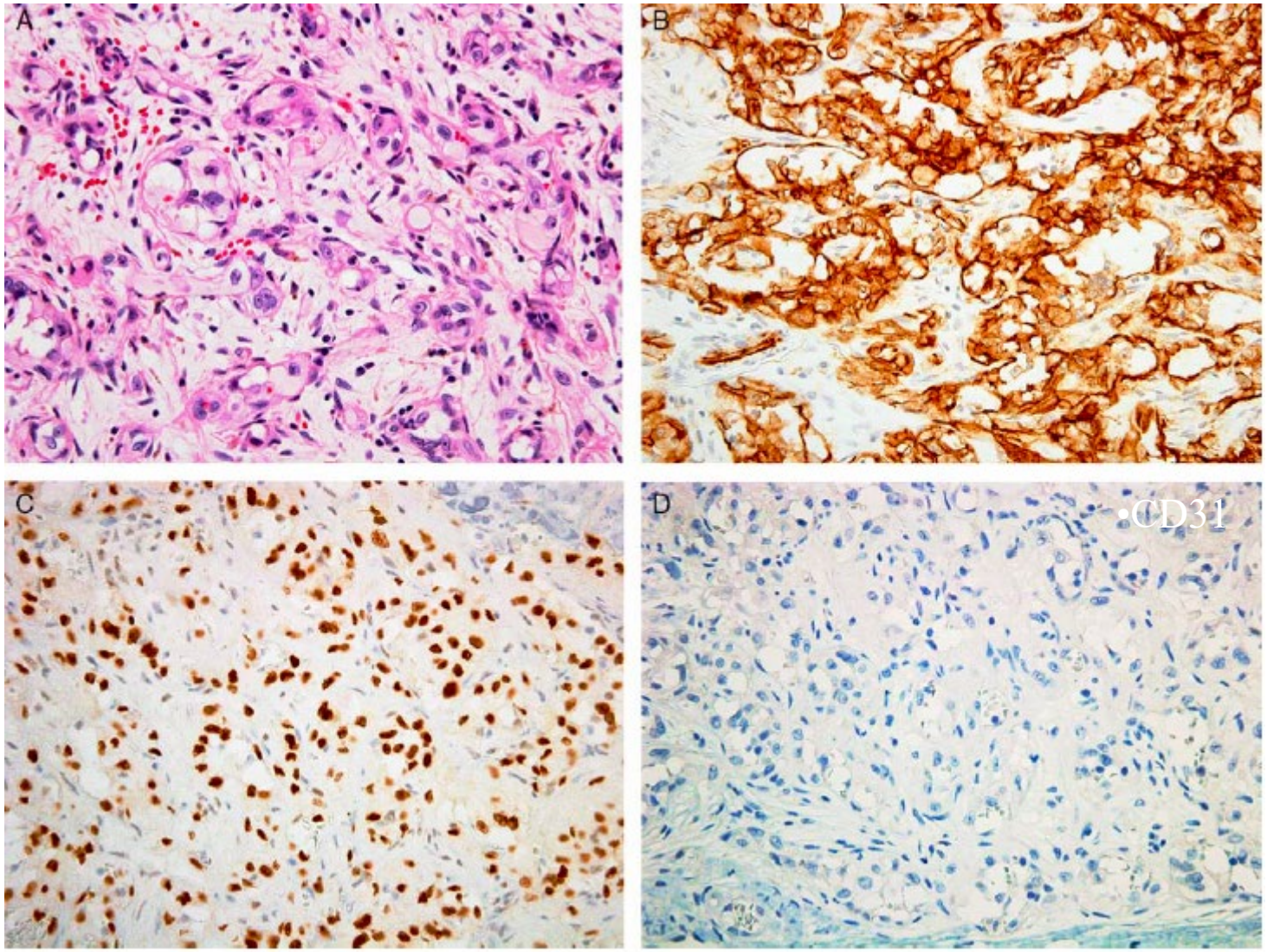
Cristina R. Antonescu,[1]* Francois Le Loarer,[1] Juan-Miguel Mosquera,[2] Andrea Sboner,[2,3] Lei Zhang,[1] Chun-Liang Chen,[1] Hsiao-Wei Chen,[1] Nursat Pathan,[4] Thomas Krausz,[5] Brendan C. Dickson,[6] Ilan Weinreb,[7] Mark A. Rubin,[2] Meera Hameed,[1] and Christopher D. M. Fletcher[8]*

[1]Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY
[2]Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY
[3]Institute for Computational Biomedicine, Weill Medical College of Cornell University, New York, NY
[4]Department of Pathology, Raritan Bay Medical Center, Raritan Bay, NJ
[5]Department of Pathology, University of Chicago, Chicago, IL
[6]Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada
[7]Department of Pathology, University Health Network and Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada
[8]Department of Pathology, Brigham & Women's Hospital and Harvard Medical School, Boston, MA

GENES, CHROMOSOMES & CANCER 52:775–784 (2013)



Antonescu et al, Genes, Chromosomes and Cancer 52, 772-784, 2013



(*Am J Surg Pathol* 2016;40:94–102)

ARTICLE

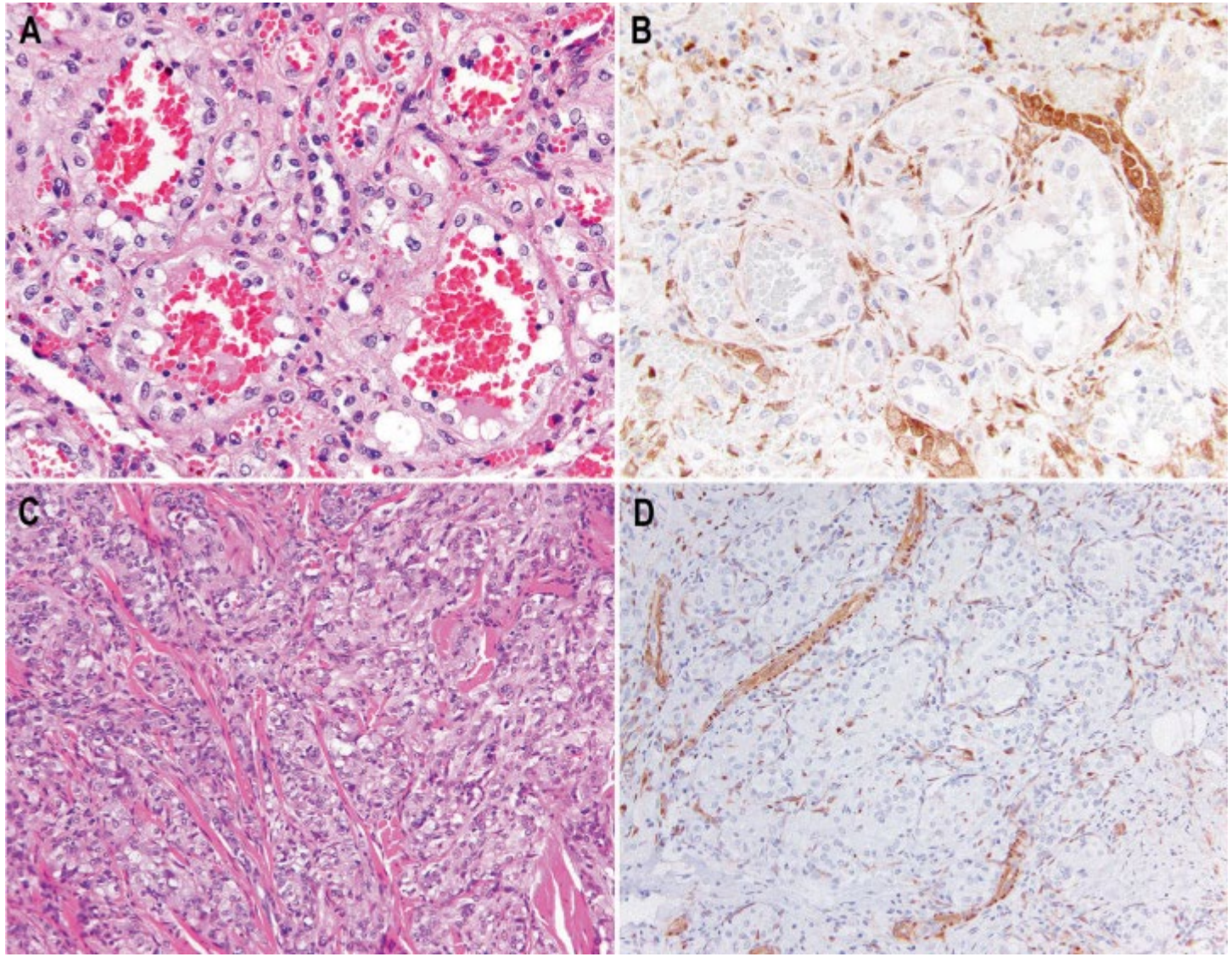
Check for updates

Loss of expression of YAP1 C-terminus as an ancillary marker for epithelioid hemangioendothelioma variant with *YAP1-TFE3* fusion and other YAP1-related vascular neoplasms

William J. Anderson[1], Christopher D. M. Fletcher[1] and Jason L. Hornick[1]✉

Modern Pathology; https://doi.org/10.1038/s41379-021-00854-2

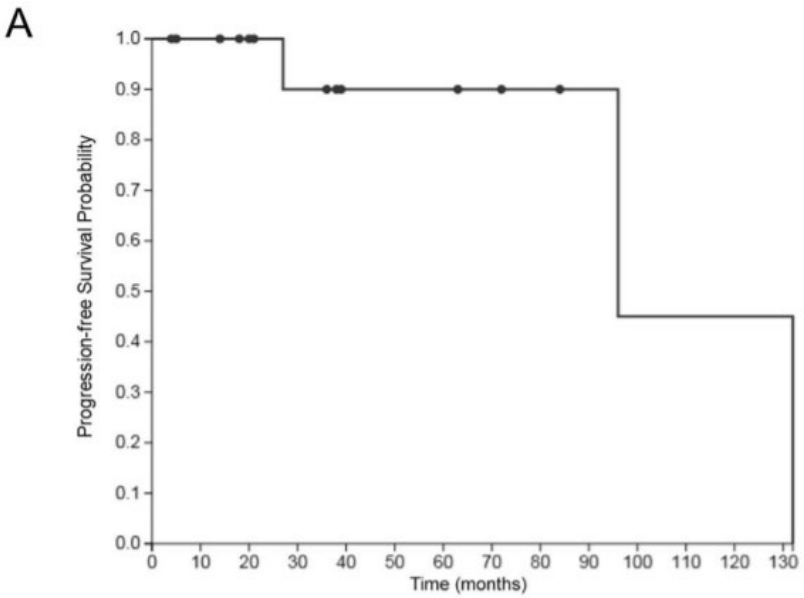
Tumor type	Total cases	YAP1-CT lost	YAP1-CT retained
Epithelioid hemangioendothelioma with *YAP1-TFE3*	13	10	3
Epithelioid hemangioendothelioma with *WWTR1-CAMTA1*	20	1	19
Retiform hemangioendothelioma	4	4	0
Composite hemangioendothelioma	2	2	0
Pseudomyogenic hemangioendothelioma	10	0	10
Epithelioid hemangioma	19	0	19
Epithelioid angiosarcoma	10	0	10

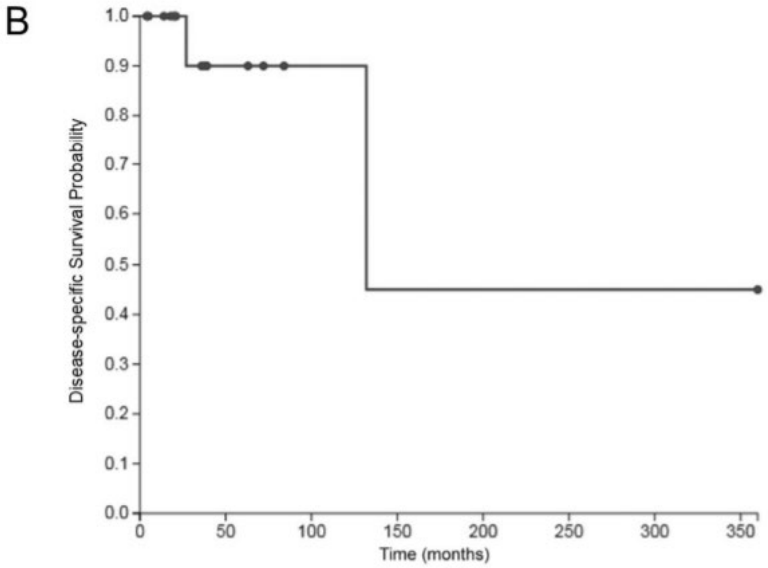


Modern Pathology; https://doi.org/10.1038/s41379-021-00854-2

YAP1-TFE3-fused hemangioendothelioma: a multi-institutional clinicopathologic study of 24 genetically-confirmed cases

Josephine K. Dermawan[1], Elizabeth M. Azzato[1], Steven D. Billings[1], Karen J. Fritchie[1], Sebastien Aubert[2], Armita Bahrami[3], Marta Barisella[4], Daniel Baumhoer[5], Veronika Blum[6], Beata Bode[7], Scott W. Aesif[1], Judith V. M. G. Bovée[8], Brendan C. Dickson[9], Mari van den Hout[10], David R. Lucas[11], Holger Moch[12], Gabriel Oaxaca[1], Alberto Righi[13], Raf Sciot[14], Vaiyapuri Sumathi[15], Akihiko Yoshida[16] and Brian P. Rubin[1]✉

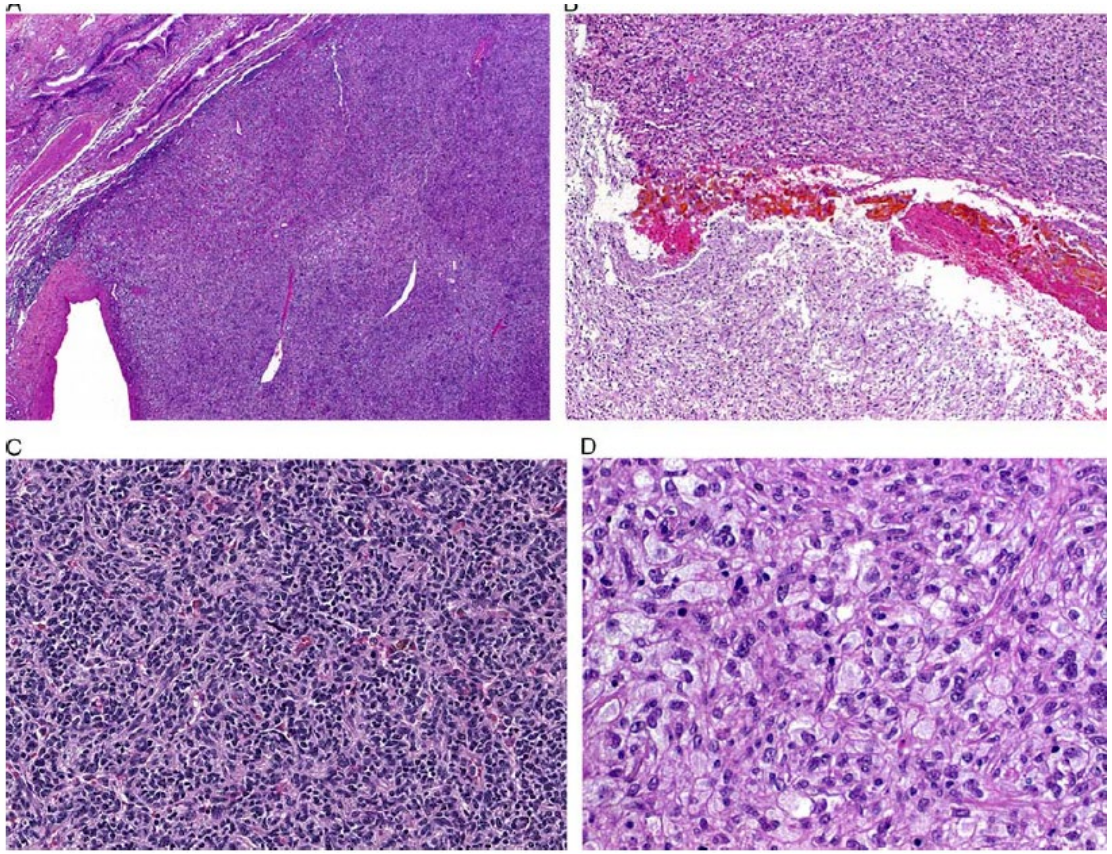




Recurrent *YAP1-TFE3* Gene Fusions in Clear Cell Stromal Tumor of the Lung

Abbas Agaimy, MD, Robert Stoehr, PhD,* Michael Michal, MD,†‡ Petros Christopoulos, MD,§‖ Hauke Winter, MD,‖¶ Lei Zhang, MD,# Albrecht Stenzinger, MD,** Michal Michal, MD,†‡ Gunhild Mechtersheimer, MD,** and Cristina R. Antonescu, MD#*

Am J Surg Pathol 2021;00:000–000



Epithelioid hemangioendotheliomas with *TFE3* gene translocations are compossible with *CAMTA1* gene rearrangements

Seok Joo Lee[1], Woo Ick Yang[1], Woo-Suk Chung[2] and Sang Kyum Kim[1]

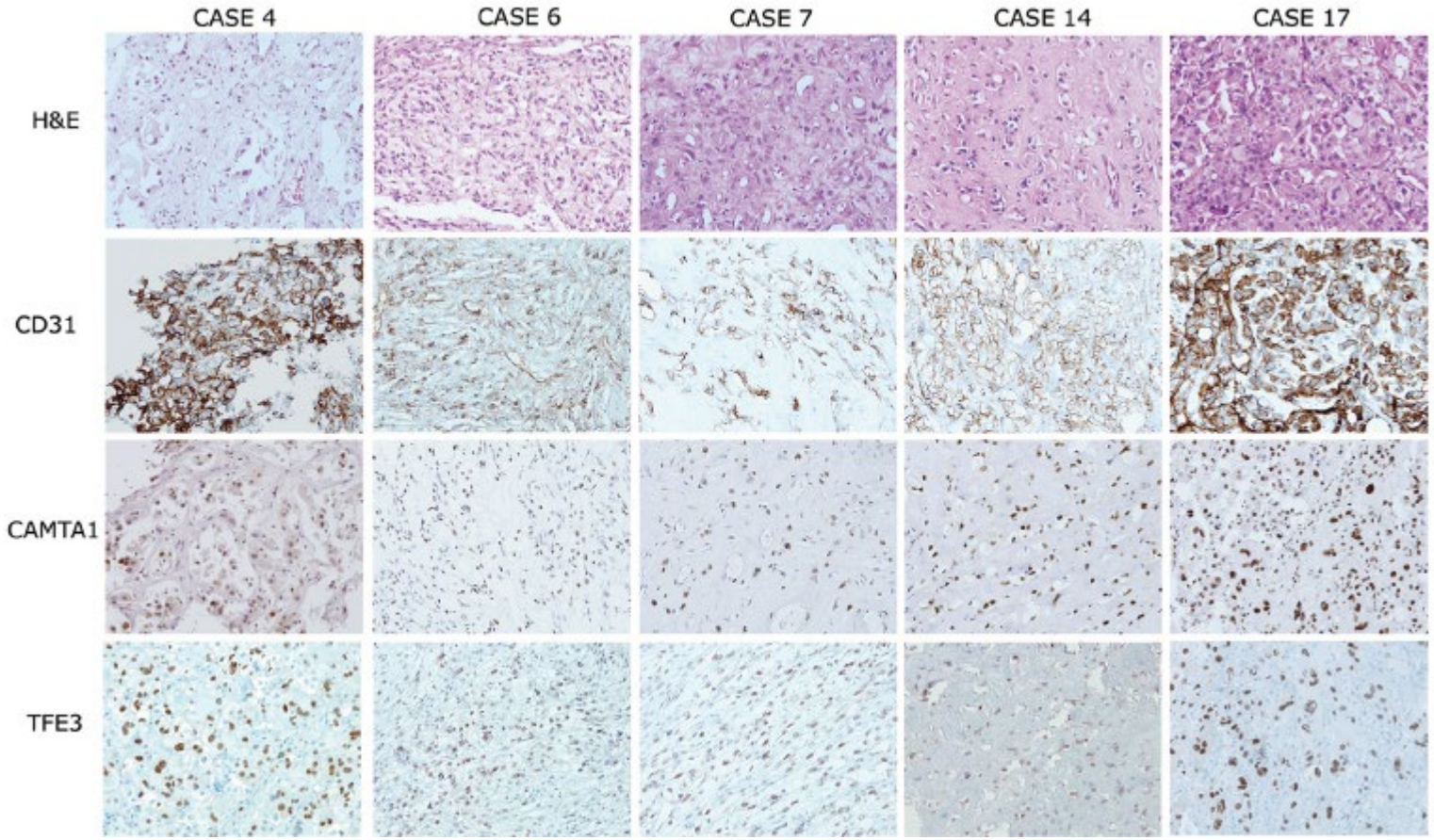
[1] Department of Pathology, Yonsei University Medical Center, Seoul, South Korea

[2] Department of Diagnostic Radiology, Konyang University Hospital, Daejeon, South Korea

Correspondence to: Sang Kyum Kim, email: nicekyumi@yuhs.ac

***Keywords**: epithelioid hemangioendothelioma, TFE3, YAP1, CAMTA1, WWTR1, Pathology Section*

***Received**: September 02, 2015* ***Accepted**: January 21, 2016* ***Published**: January 28, 2016*

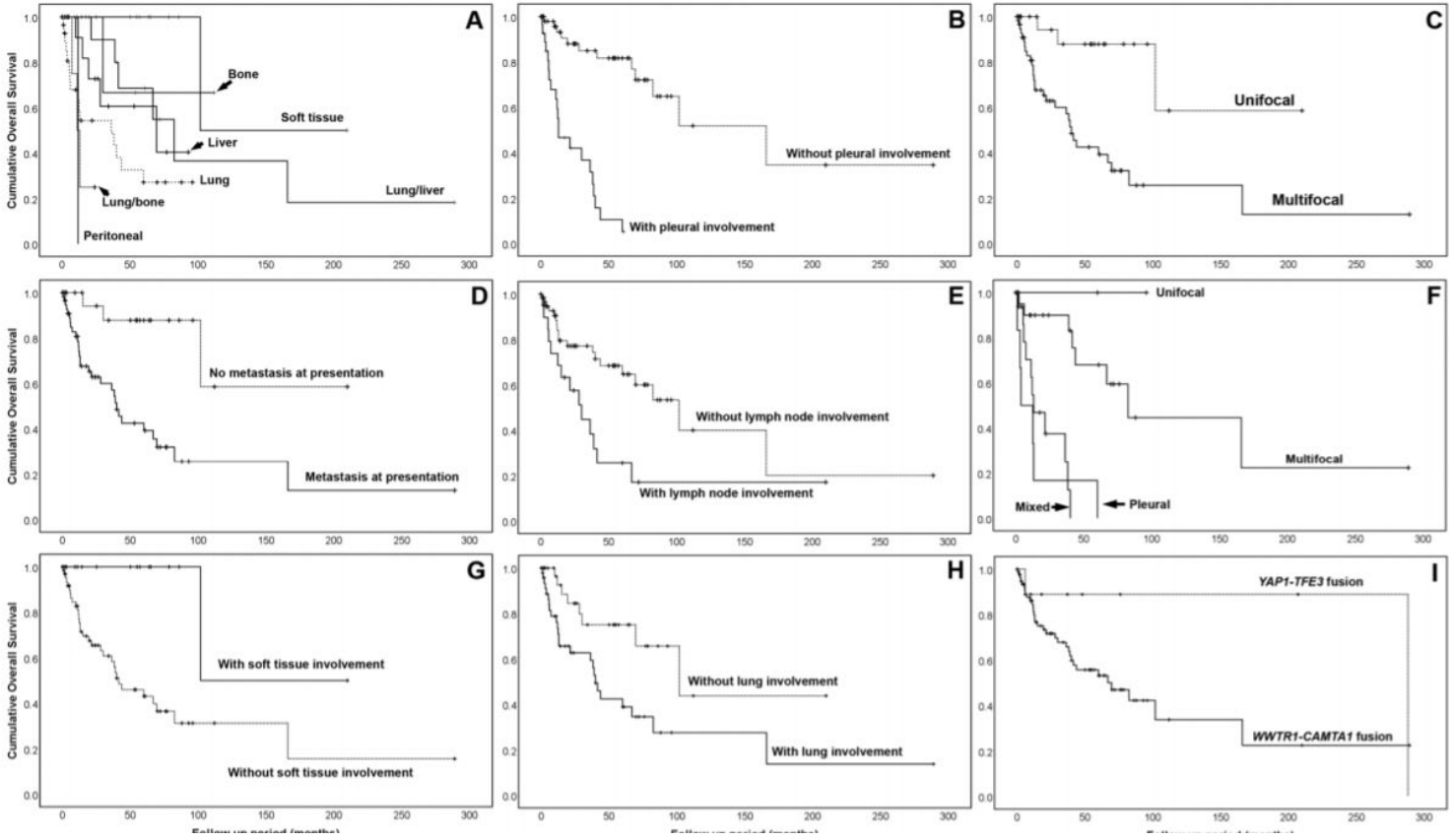


Modern Pathology (2020) 33:591–602
https://doi.org/10.1038/s41379-019-0368-8

ARTICLE

Prognostic stratification of clinical and molecular epithelioid hemangioendothelioma subsets

Evan Rosenbaum[1] · Bhumika Jadeja[2] · Bin Xu[3] · Lei Zhang[3] · Narasimhan P. Agaram[3] · William Travis[3] · Samuel Singer[2] · William D. Tap[1,4] · Cristina R. Antonescu[3]

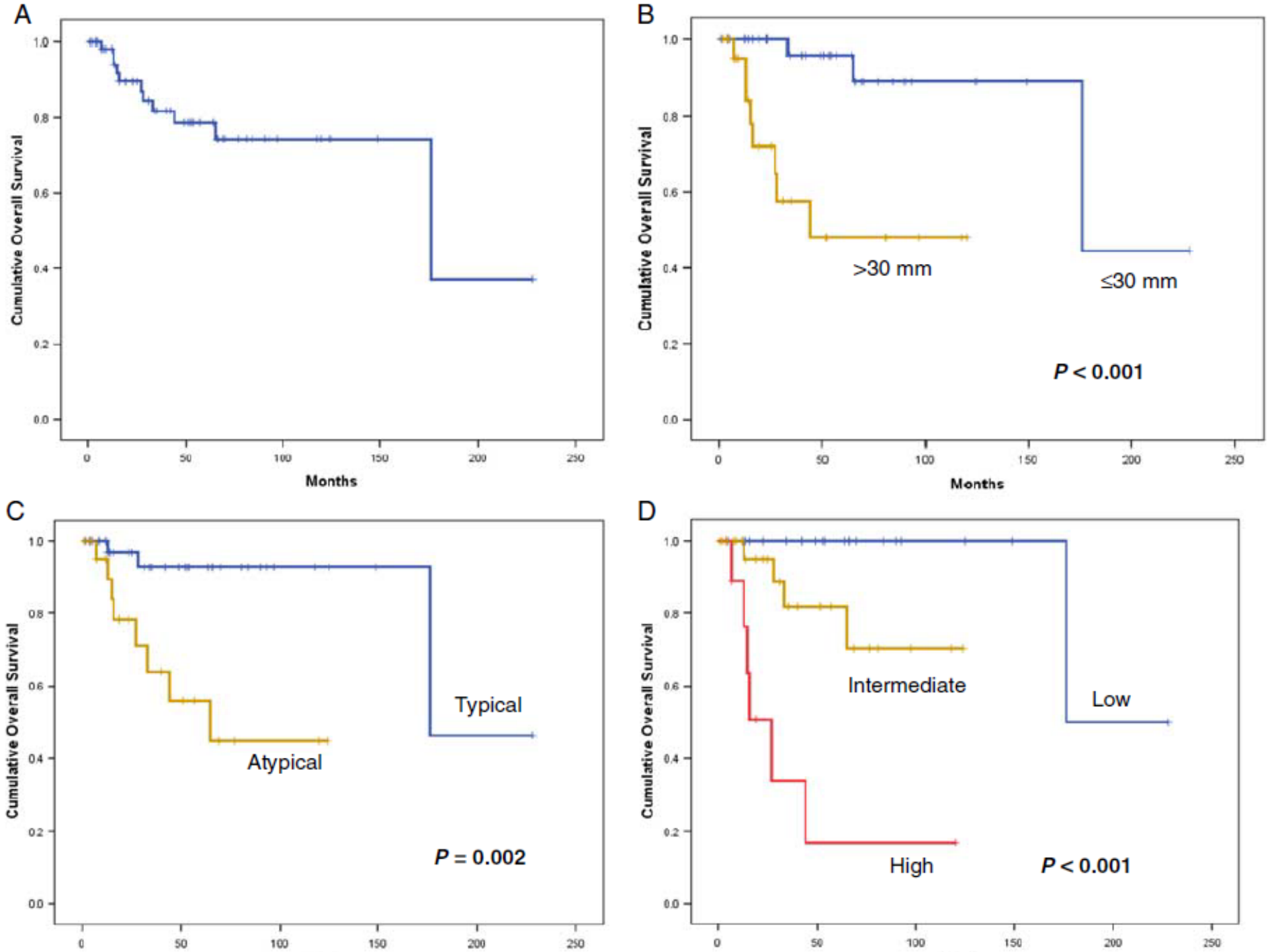


Am J Surg Pathol 2021;45:616–626

Clinicopathologic Characterization of Epithelioid Hemangioendothelioma in a Series of 62 Cases

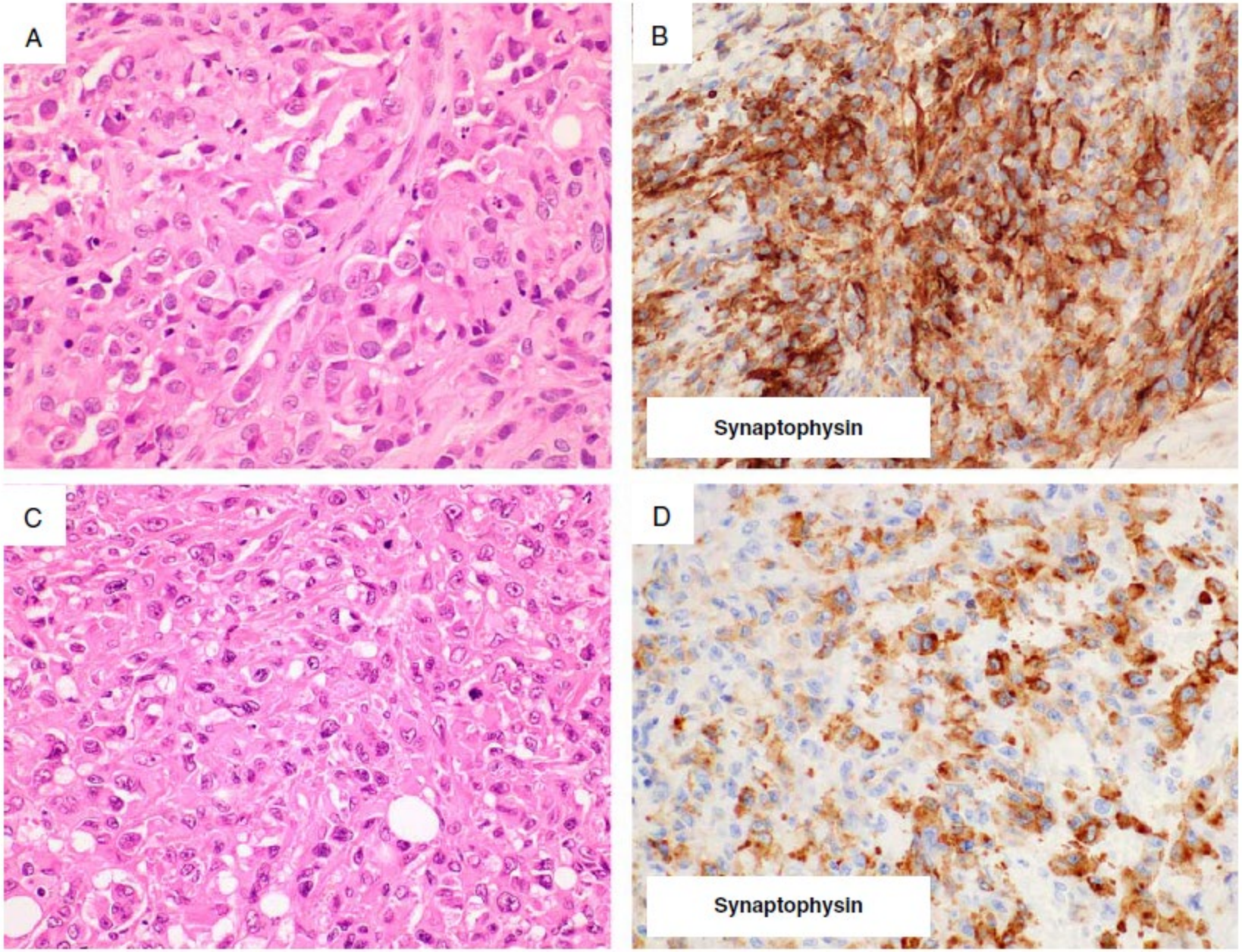
A Proposal of Risk Stratification and Identification of a Synaptophysin-positive Aggressive Subset

Takahiro Shibayama, MD, Naohiro Makise, MD, PhD,† Toru Motoi, MD, PhD,‡ Taisuke Mori, DMD, PhD,* Nobuyoshi Hiraoka, MD, PhD,* Kan Yonemori, MD, PhD,§‖ Shun-ichi Watanabe, MD, PhD,¶ Minoru Esaki, MD, PhD,# Chigusa Morizane, MD, PhD,‖** Tomotake Okuma, MD, PhD,†† Akira Kawai, MD, PhD,‖‡‡ Tetsuo Ushiku, MD, PhD,† Yasushi Yatabe, MD, PhD,* and Akihiko Yoshida, MD, PhD*‖*


A
Cumulative Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
Months
B
Cumulative Overall Survival
>30 mm
≤30 mm
P < 0.001
Months
C
Cumulative Overall Survival
Typical
Atypical
P = 0.002
D
Cumulative Overall Survival
Intermediate
Low
High
P < 0.001

Risk Factors	Score
Tumor size (mm)	
≤ 30	0
> 30	1
Histology	
Typical	0
Atypical*	1
Risk category	Total score
Low	0
Intermediate	1
High	2

*Atypical histology is defined as having at least 2 of the following 3 findings: mitosis > 1/2 mm^2, high nuclear grade, and coagulative tumor necrosis. Any tumor histology that does not meet these criteria is considered typical.


A
B
Synaptophysin
C
D
Synaptophysin

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN | CANCER HORIZONS

REVIEW

Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts

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