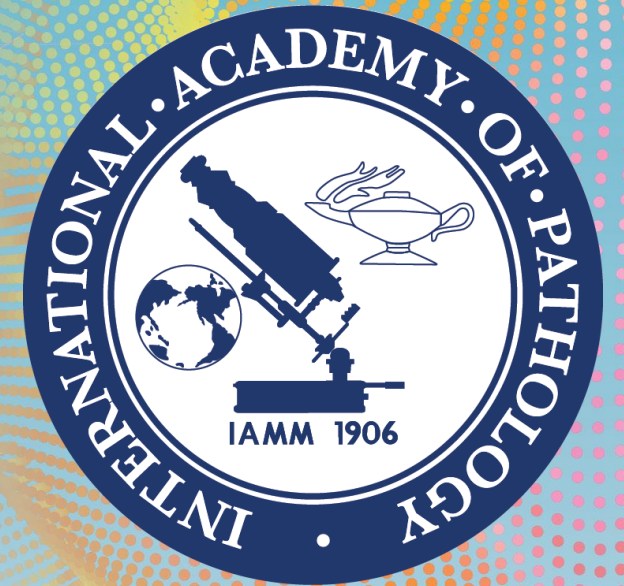


Challenging Cutaneous Spindle Cell Lesions

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The 48th Annual Scientific Meeting *of the*

Australasian Division of the
International Academy of Pathology

Disclosure of Relevant Financial Relationships

Please disclose here any financial relationships that have occurred within the last 24 months with companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

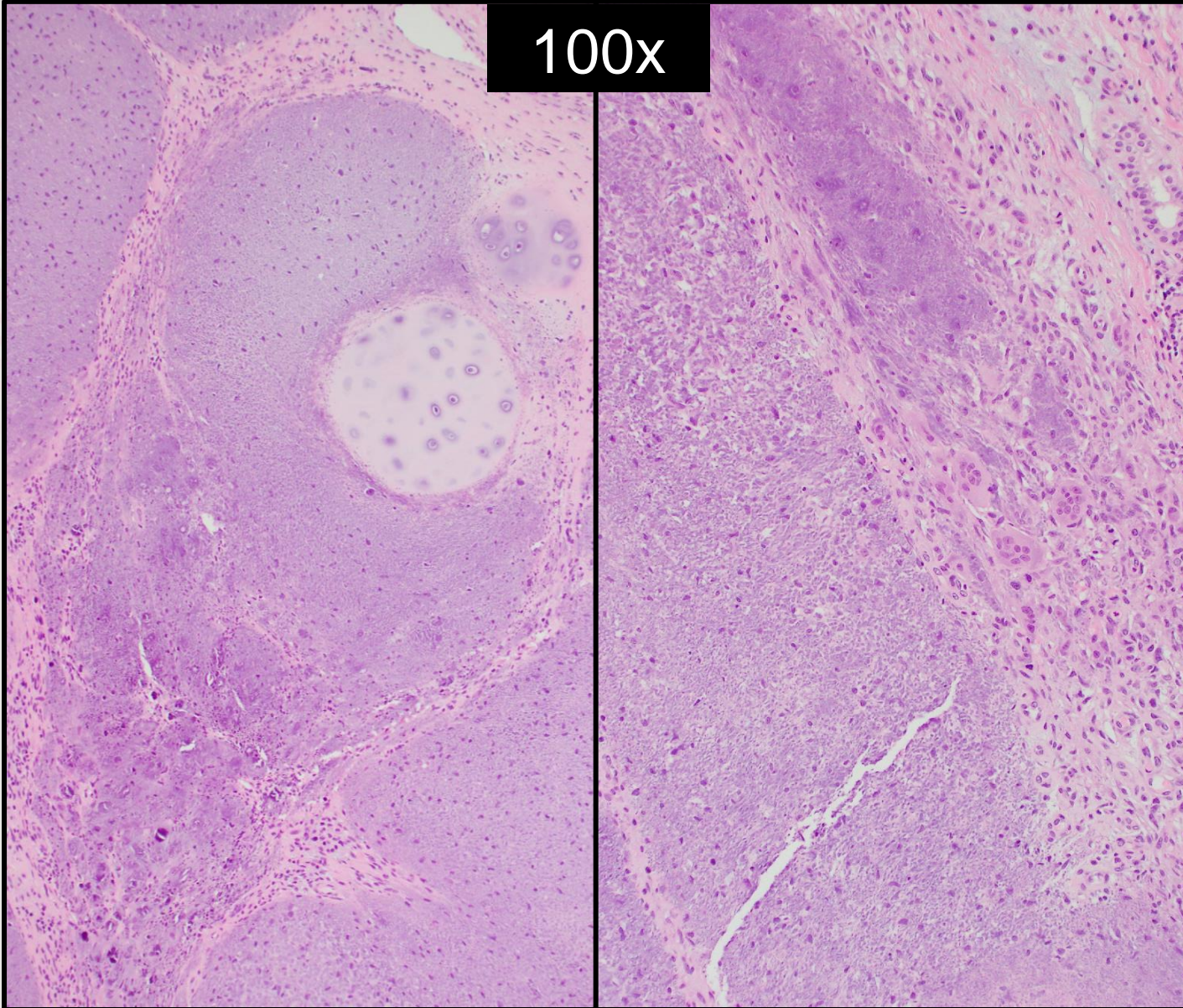
Dr Omar Habeeb has no relevant financial relationships to disclose.

Case #1: 50M

- 5-cm slowly enlarging nodule x 1 year, L medial plantar foot
- XR: Opaque, soft tissue tumor; no direct involvement of bone + no abnormal bone changes
- Excisional biopsy performed



100x



- Unencapsulated, well-defined neoplasm
- Embedded in dermis and extends into subcutis
- Lobulated, granular, basophilic matrix-type material, associated with microcalcifications
- Osteoclast-type giant cells at stroma-tumour interface
- Bland, ovoid nuclei - with rare mitotic activity & scant cytoplasm; no necrosis

Case #1: Pathologic Findings

IHC Positive	IHC Negative
Vimentin SATB2, CD56	CK AE 1/3, EMA, p40, (ERG), CD34, SMA, S-100, SOX-10

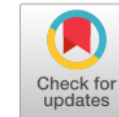
- Neoplasm ulcerates through the skin
- Neoplasm transected at medial radial + deep margin
- CISH: FGF23+, FISH = *FN1::FGFR1*+



ELSEVIER

Case study

Phosphaturic mesenchymal tumor without osteomalacia: additional confirmation of the “nonphosphaturic” variant, with emphasis on the roles of FGF23 chromogenic in situ hybridization and *FN1-FGFR1* fluorescence in situ hybridization[☆]



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Jen-Chieh Lee MD, PhD^b, Andrew L. Folpe MD^c, Omar Habeeb MD^{d,*}

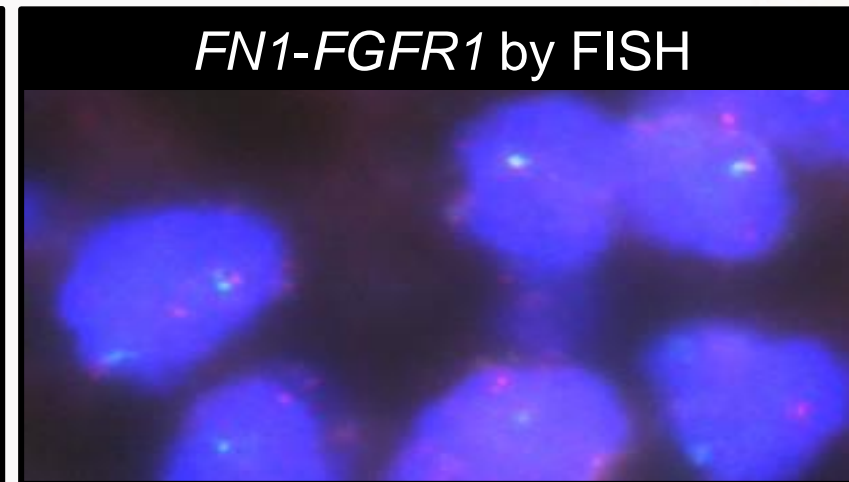
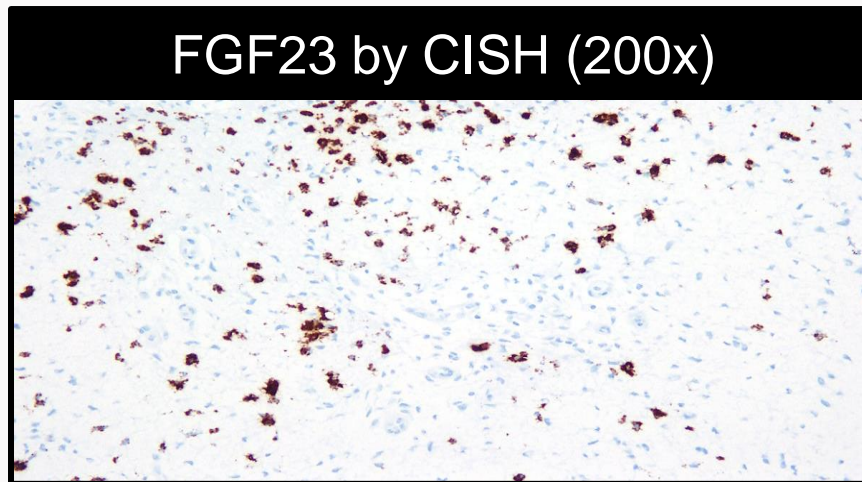
Phosphaturic Mesenchymal Tumor (PMT)

- 1st case series (N=17) described a polymorphous neoplasm associated with osteomalacia that could present in either soft tissue or bone¹
- 2nd case series (N=32) concluded that mesenchymal tumor-associated osteomalacia = PMT & supported link to FGF23, mostly by IHC²
- 3rd case series (N=29) confirmed FGF23 overexpression by RT-PCR (86%), even when PMT was unassociated with paraneoplastic osteomalacia (9/12)³

1) Cancer. 1987 Apr 15; 59(8): 1442-54. 2) Am J Surg Pathol. 2004 Jan; 28(1): 1-30. 3) Am J Surg Pathol. 2009 Sep; 33(9): 1348-54.

PMT - Pathophysiology

- Paraneoplastic FGF23: ↓resorption, ↑excretion of (PO_4^{3-}) by kidney
- Tumor-induced osteomalacia: ↓ $[\text{PO}_4^{3-}]$, ↓ $[1,25-(\text{OH})_2\text{-VitD}] \rightarrow \text{XR } \Delta\text{s}$
- ~40% of PMT's demonstrate *FN1-FGFR1* rearrangement by FISH⁴
(*FN1*: fibronectin → cell adhesion; *FGFR1*: fibroblast growth factor rec. 1)



4) Mod Pathol. 2016 Nov; 29(11): 1335-1346.

PMT – Clinical Behavior

- Benign
 - Recurrence +/- persistent osteomalacia if incompletely excised
- Rare malignant/metastatic cases do occur^{2,6}
 - Key: hypercellularity, cytological atypia, mitotic activity >5/10 HPF
- Unusual: normal $[PO_4^{3-}]$, $[Ca^{2+}]$, $[PTH]$; no osteomalacia on bone scan
 - ?FGF23 production not high enough, ?Patient compensation

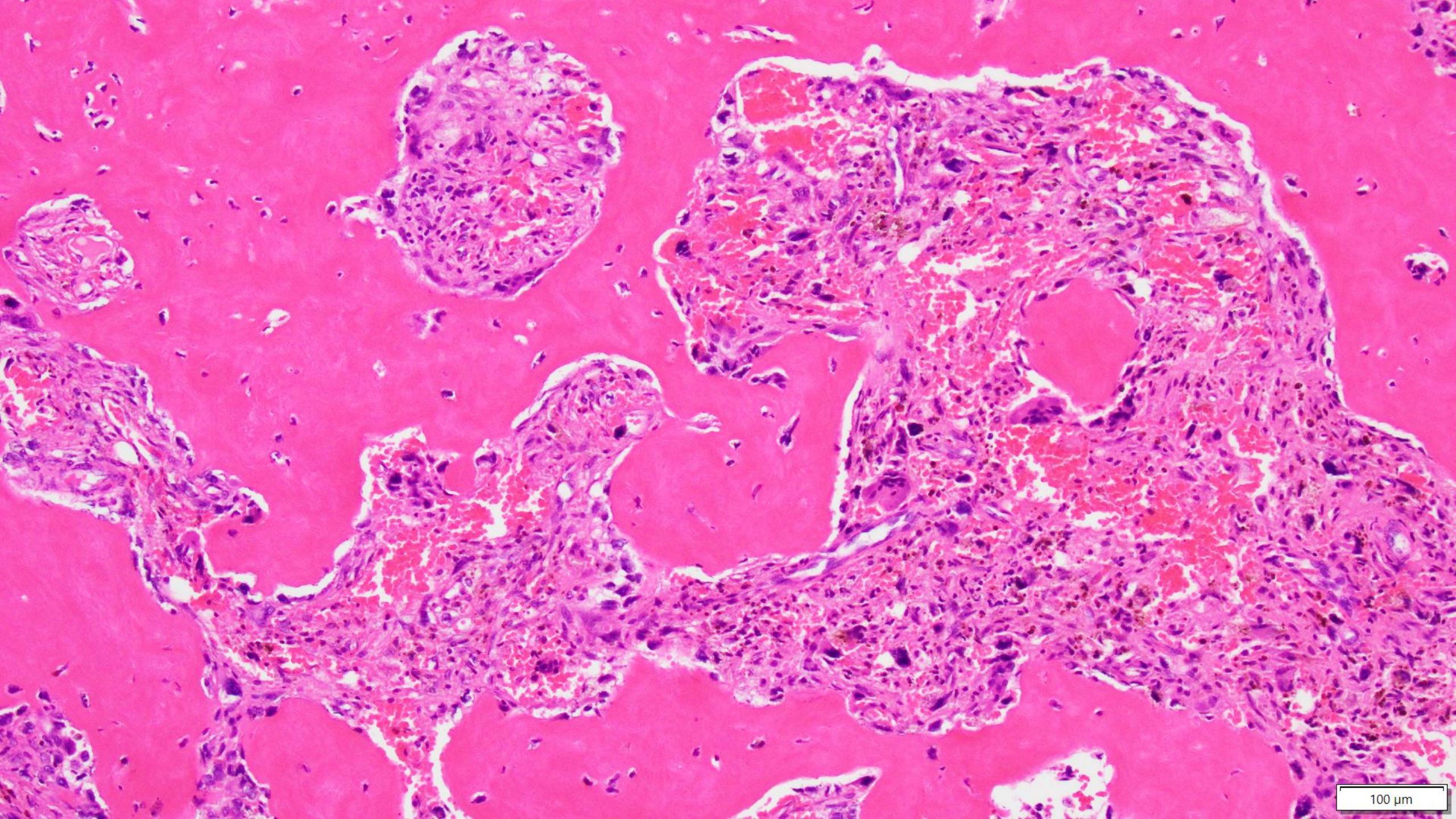
2) Am J Surg Pathol. 2004 Jan; 28(1): 1-30. 6) Am J Surg Pathol. 2017 Oct; 41(10): 1371-1380.

Case #1: PMT – Clinical Follow-Up

- Alive, 5+ years after excisional biopsy
- 4 months after excisional biopsy: Scar on WLE
- Excision site repaired by FTSG by Plastic Surgery
- No recurrence - patient discharged back to GP

Case #2: 54M

- 1.8-cm mass, R posterior shoulder
- 7-month h/o subcutaneous lesion, fluctuating in size
- Clinically: ?Sebaceous cyst. No pre-operative imaging.
- Excision attempted by GP, then curetted in ER
- Post-curette MRI: no underlying IM/osseous lesion



100 μ m

Case #2: Pathologic Findings

IHC Positive	IHC Negative
SATB2	CK AE 1/3, CD34, SMA, desmin, S-100, Melan-A, MDM2

- Highly atypical spindle cells with 6 mitoses/10 HPF
- No geographic necrosis
- Referred for wide local excision

ANATOMICAL PATHOLOGY

Primary cutaneous extraskeletal osteosarcoma: a series of 16 cases



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Extraskkeletal osteosarcoma (EOS)

- WHO: A malignant tumor characterized by the production of osteoid or bone matrix by its neoplastic cells, but without a connection to the skeletal system¹
- 1-2% of soft tissue sarcomas, 3-4% of osteosarcomas²
- Typically found in the deep soft tissue of lower extremities,³ but can also arise in visceral organs⁴
- Patients typically 30-50 years-old at presentation¹
- High local recurrence (up to 25%) & distant metastasis (40%)^{5,6}
- 5-year survival: 50-60%^{6,7}

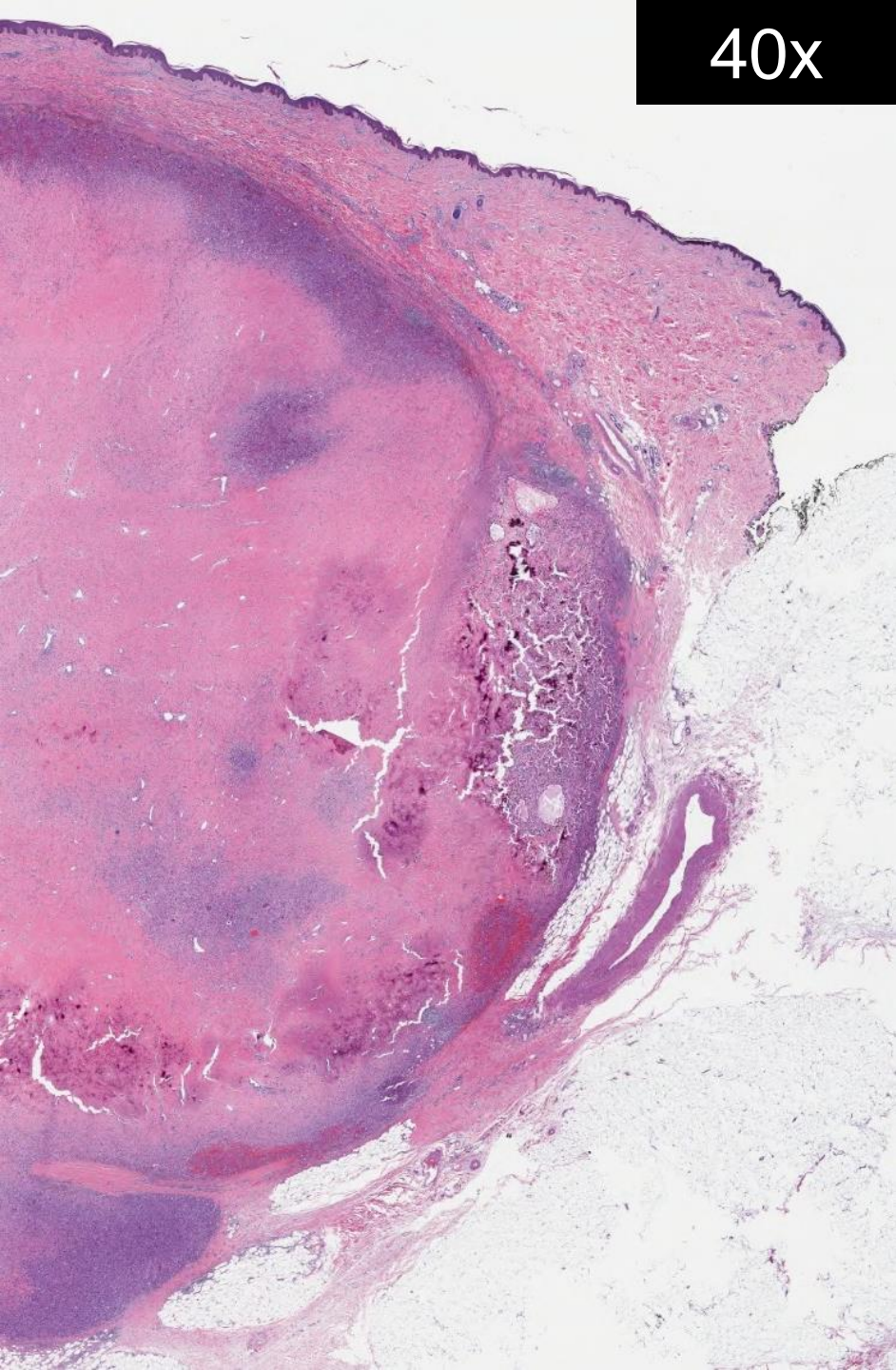
1) WHO Classification of Tumors Editorial Board. Soft Tissue and Bone Tumors (5th ed., 2020). 2) Int J Surg Case Rep. 2020; 75:403-407. 3) J Cutan Pathol. Feb 2008;35(2):231-5. 4) Mol Clin Oncol. Sep 2018;9(3):287-292. 5) J Bone Joint Surg Am. Jan 1 2014; 96(1): e2. 6) Eur J Cancer. Mar 2017;74:9-16. 7) Sarcoma. 2014;2014:902620.

Primary Cutaneous Extraskeletal Osteosarcoma (PC-EOS)

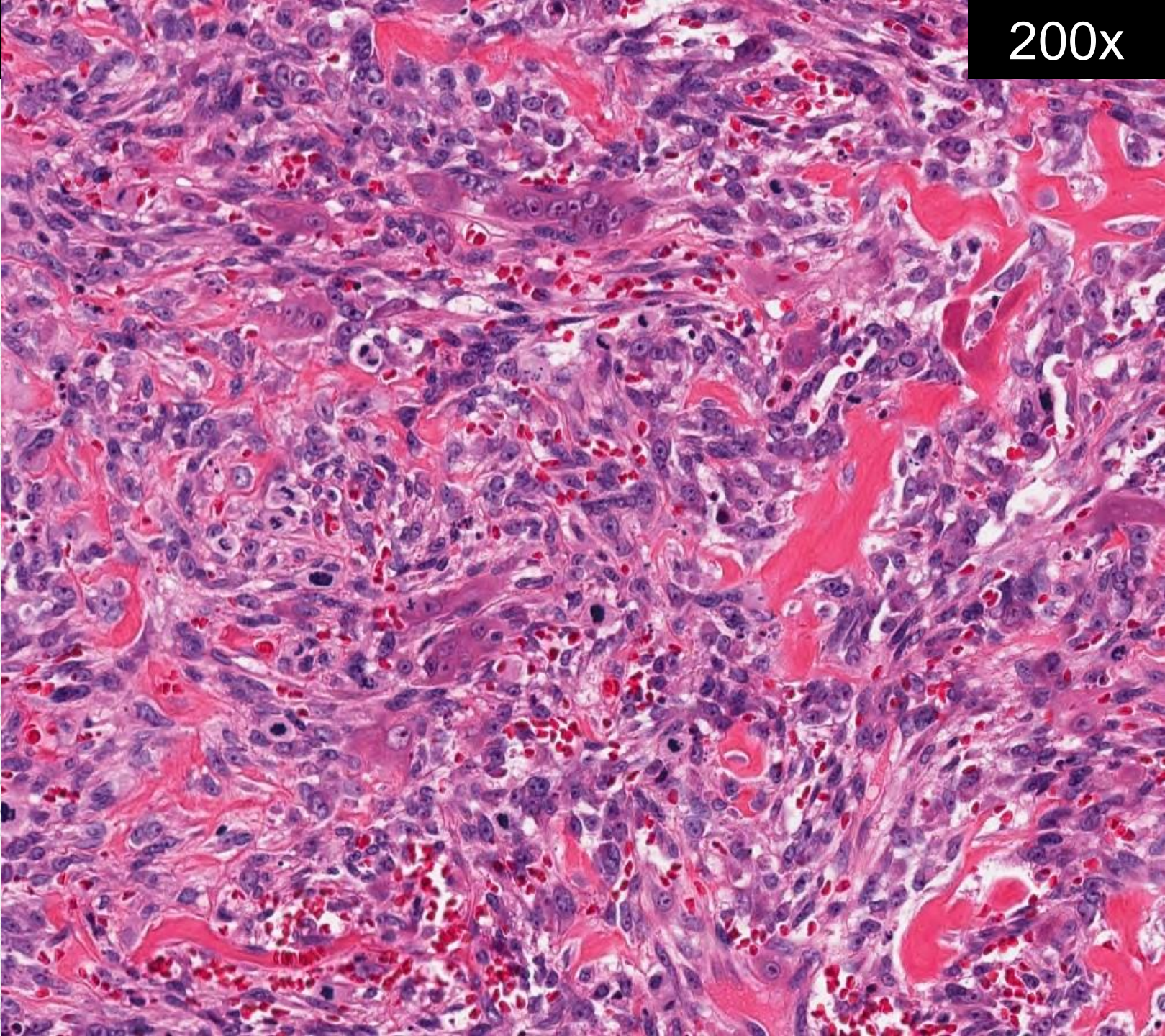
- Dermal/subcutaneous involvement only (i.e., no deep soft tissue or visceral origin; exclude metastasis)
- Rarely reported in the literature (mostly as case reports)
- Prior literature suggests a relatively low rate of recurrence (6%) and metastasis (11%) & relatively high 5-year survival (80%)⁸

8) Mol Clin Oncol. Sep 2018;9(3):287-292.

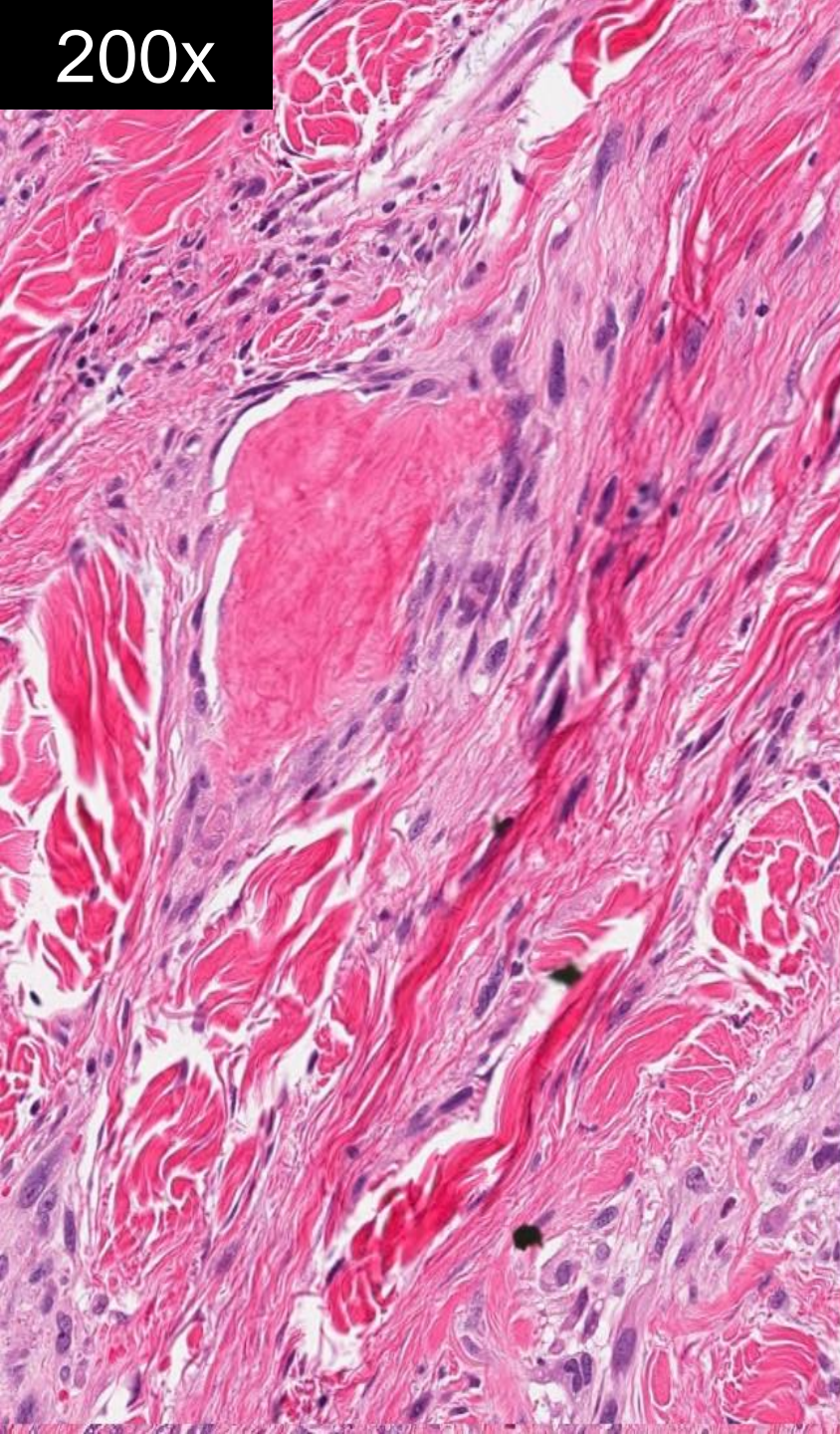
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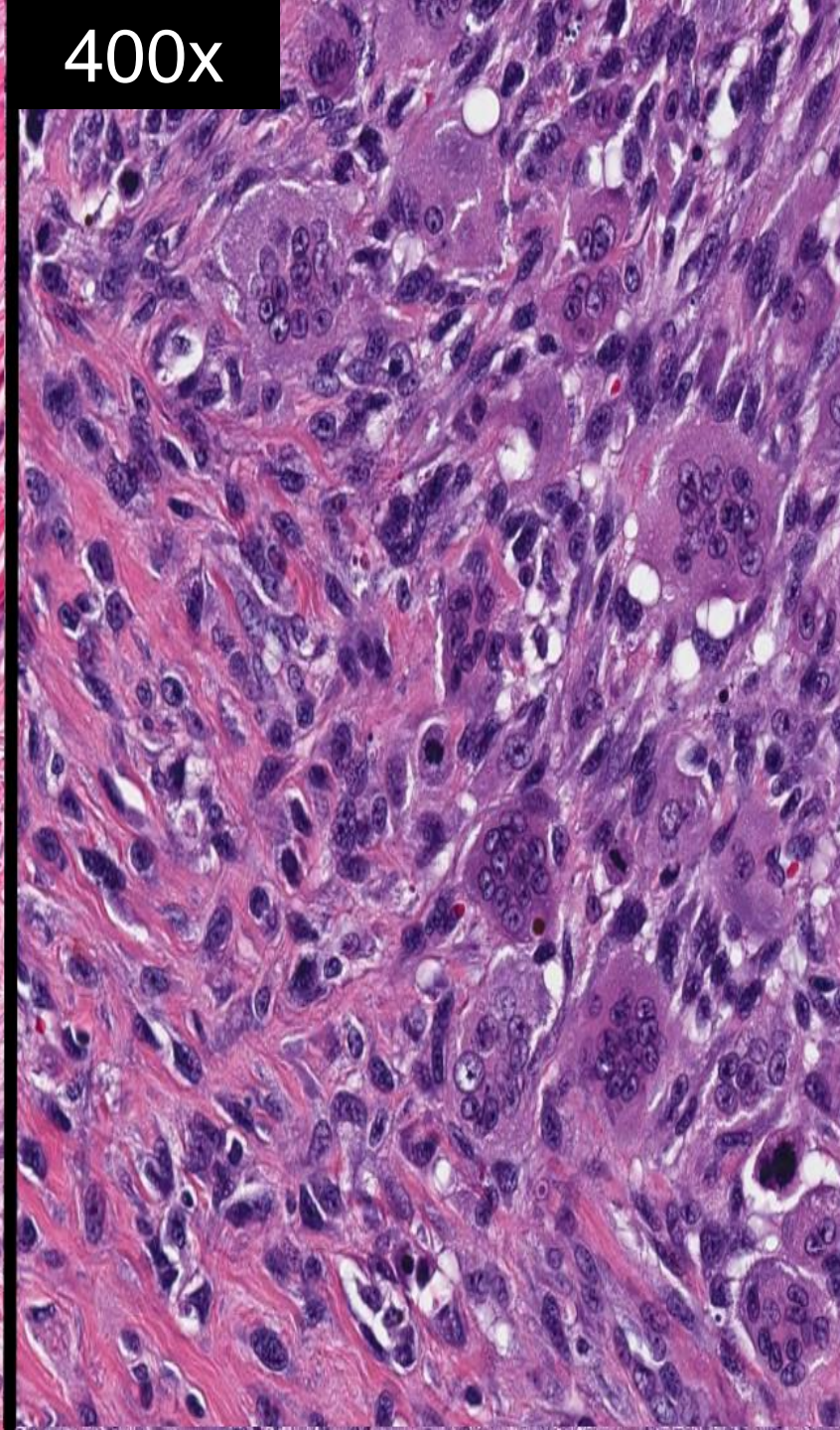
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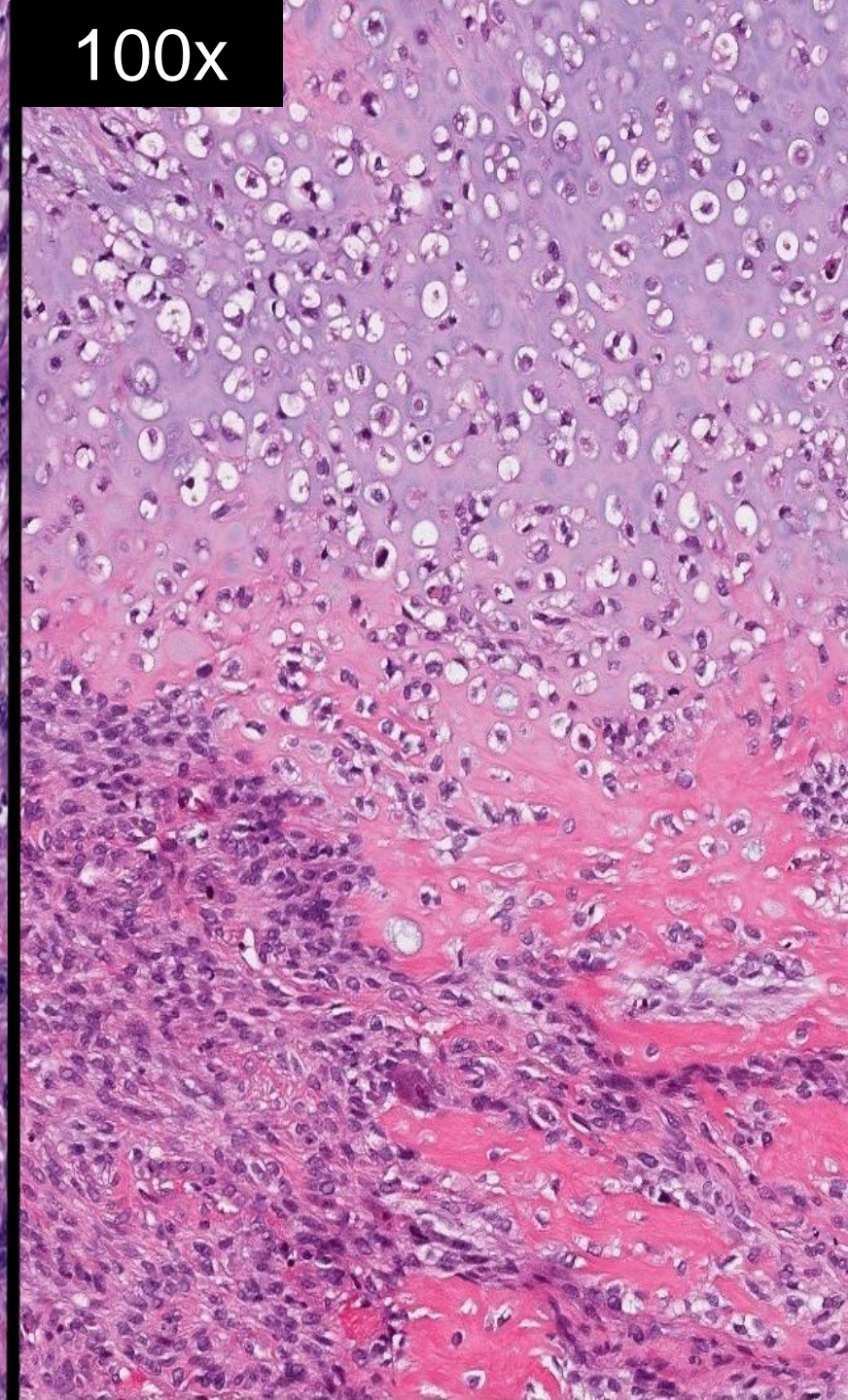
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100x



PC-EOS: IHC + DDX

- Immunohistochemistry (IHC) essentially unhelpful
- SATB2 could be used to raise the possibility of osteoblastic differentiation,⁹ but not specific enough to be conclusive
- Differential diagnosis (DDX) would include heterologous osteosarcomatous differentiation arising within another tumor (e.g., melanoma, MPNST, sarcomatoid carcinoma)
- Myositis ossificans is a benign pitfall

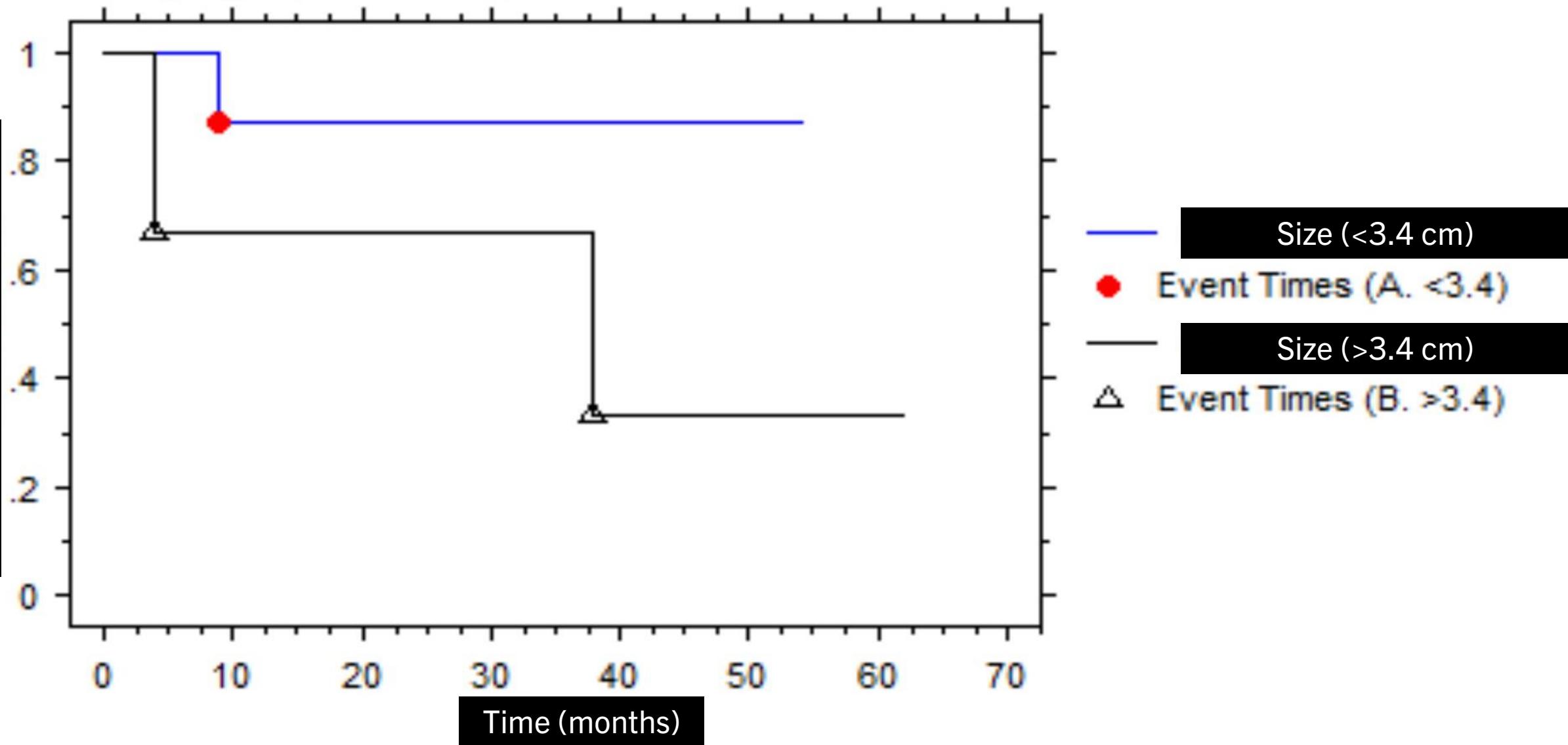
9) Histopathology. 2013 Jul;63(1):36-49

Table 1 Demographics and clinical characteristics of patients with PC-EOS

Patient	Age, years	Gender	Site	Size, cm	Subtype	Initial treatment	Local recurrence (treatment)	Mets (treatment)	Outcome (follow-up time, months)
1	44	M	Thigh	3	FB	WLE	None	None	ANED (24)
2	89	F	Thigh	2	OB	Punch biopsy	None	None	Lost to follow-up
3	71	M	Forehead	1	OB	Mohs	None	None	ANED (48)
4	66	F	Thigh	5	FB	WLE	None	None	ANED (62)
5	77	M	Thigh	4.2	OB	Excision + Radiation	None	Lung, 2 mo (none)	DOD (4)
6	96	M	Shoulder	3.3	OB	WLE	None	Neck, 9 mo (none)	ANED (9)
7	65	F	Leg	10	OB	WLE	8 mo (chemo)	Lung, 8 mo (chemo)	DOD (38)
8	77	F	Thigh	3	OB	WLE + Radiation	None	None	ANED (48)
9	67	F	Inframammary	2.4	OB	WLE	None	None	ANED (54)
10	79	M	Scalp	~	FB	~	~	~	~
11	31	F	Scalp	~	OB	~	~	~	~
12	68	M	Lip	~	OB	~	~	~	~
13	75	M	Scalp	1.5	CB	WLE	None	None	ANED (14)
14	61	F	Thigh	3.3	OB	WLE + Radiation	None	None	ANED (27)
15	54	M	Shoulder	1.8	OB	WLE + Chemo	None	None	ANED (15)
16	69	F	Scalp	1	OB	WLE	None	None	AWD (2)

ANED, alive with no evidence of disease; AWD, alive with disease; CB, chondroblastic; DOC, died of other cause; DOD, died of disease; F, female; FB, fibroblastic; M, male; OB, osteoblastic; WLE, wide local excision.

Proportion without metastasis



KM $p=0.13$ (N=12); Univariate Cox Model (Size vs. DOD): HR = 1.37, $p=0.14$

Table 3 Combined data of all well characterised patients with PC-EOS

	Present series	Past cases	Total reported
N	16	31	47
Male	8	20	28
Female	8	11	19
Age range, years (mean)	31–96 (65.7)	15–96y (64.5)	15–96 (65.7)
Tumour size range, cm (mean)	1–10 (3.2)	0.5–11 (4.2)	0.5–11 (3.9)
Anatomical location			
Head	6	11	17
Lower extremity	7	9	16
Upper extremity	2	5	7
Trunk	1	6	7
Outcome (mean follow-up time, months)			
ANED	8 (38.3)	15 (21.1)	23 (27.2)
DOD	2 (21)	5 (22)	7 (21.7)
AWD	2 (5.5)	4 (17.25)	6 (13.3)
DOC	0	4 (25)	4 (25)
Unknown	4	3	7
Local recurrence rate (mean time to occurrence, months)	8% (8)	11% (10.3)	10% (9.4)
Metastasis rate (mean time to occurrence, months)	25% (5.7)	25% (13.6)	25% (11.3)

ANED, alive with no evidence of disease; AWD, alive with disease; DOC, died of other cause; DOD, died of disease.

PC-EOS: Treatment

- Most of the published data focuses on EOS
- WLE with 2-cm margins appears to be treatment of choice
- (Neo)adjuvant chemotherapy may be of some benefit, but inconclusive due to conflicting data
- Most recent/largest retrospective review (N=370, 45 y follow-up) found no association between chemotherapy & improved survival for EOS¹⁰
- No significant effect of radiation therapy on survival¹⁰

10) Eur J Cancer. Jan 2020;125:130-141

PC-EOS: Summary

- Largest series of PC-EOS to date (N=16)
- PC-EOS may be more aggressive than first suspected
 - ❑ Recurrence: 10%
 - ❑ Metastasis: 25%
- Evolving trend between tumor size & risk of metastasis/DOD
- Radiation/chemotherapy show limited/controversial benefit
- Clinical outcome of case presented:
 - Residual PC-EOS (up to 5 mm) on WLE, well clear of surgical margins
 - Treated with adjuvant chemotherapy. ANED (now 29 months).

Summary

Two, selected cases of challenging cutaneous spindle cell lesions

1) Phosphaturic mesenchymal tumour, non-phosphaturic variant

- Lobulated, basophilic, matrix-type material + bland, ovoid nuclei
- IHC: (SATB2, ERG, CD56)
- Molecular: *FN1::FGFR1*

2) Primary cutaneous extraskeletal osteosarcoma

- Malignant (sub)cutaneous tumor that produces osteoid or bone matrix
- IHC: (SATB2)
- Molecular: None

THANK YOU!

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