原文題目(出處)：	Striking Pathology Gold: A Singular Experience with Daily Reverberations: Sinonasal Hemangiopericytoma (Glomangiopericytoma) and Oncogenic Osteomalacia
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內文：

Introduction

Sinonasal hemangiopericytoma-like tumors (SNHPC)鼻竇鼻腔似血管外皮細胞瘤嚐與 球狀血管周邊細胞瘤（glomangiopericytomas）相提並論，被認為跟相對應的軟組織有相似的組織特色，但生理上卻是相異的。
SNHPC是周細胞引起（pericyte-derived）的腫瘤，然而大部分被指認為血管外皮細胞瘤的軟組織腫瘤則是細胞變異成 solitary fibrous tumors 或者是其他像 hemangiopericytoma-like growth的病兆模式。
本篇journal即將介紹一位有SNHPC女子的case，最後導致成瘤軟骨病（oncogenic osteomalacia），並且與近日我們所瞭解的磷酸鹽尿間葉瘤（phosphaturic mesenchymal tumors , PMT）一起討論。

Case Report

(1)一位66歲女性，有無法移動且極度大地彌漫性骨疼痛。
(2)X-ray下，骨骼有 multiple， bilateral osteolytic lesions，肋骨方面沒有被診斷出有骨髓瘤的傾向。
(3)Urine ， serum PTH ， serum calcium，were normal
(4)Alkaline phosphatase數值稍微提高 (222 IU/l, normal range 25 – 140 IU/l)
(5)Serum phosphorus數值偏低 (1.8 mg/dl, normal range 2.5 – 4.5 mg/dl).
(6)病人本來就有nose bleeds, headaches, and nasal obstruction for many years的病史。
(7)首先病人被轉去耳鼻喉科，並在right nasal cavity發現病兆，CT下更發現在right nasal cavity，maxilla，ethmoid sinuses，甚至cribriform plate都有病兆出現。最後腫瘤被切除，術後一切正常，所以開始補充 calcium and vitamin D
(8)病人在25個月的持續追蹤，奇蹟的骨疼痛消失了，並且不再依賴輪椅。

Pathology

(1)由很多short spindle cell組成，使得immediate submucosal region(Schneiderian mucosa）騰出很多空間。

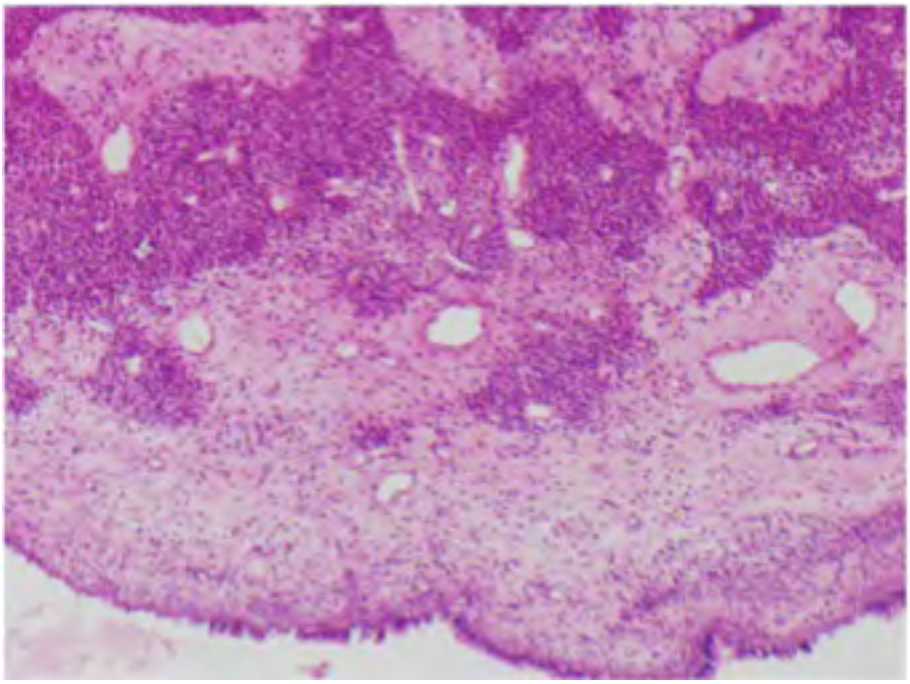


Fig.1低倍率下，SNHPC在immediate submucosa zone被撐出一些空間。

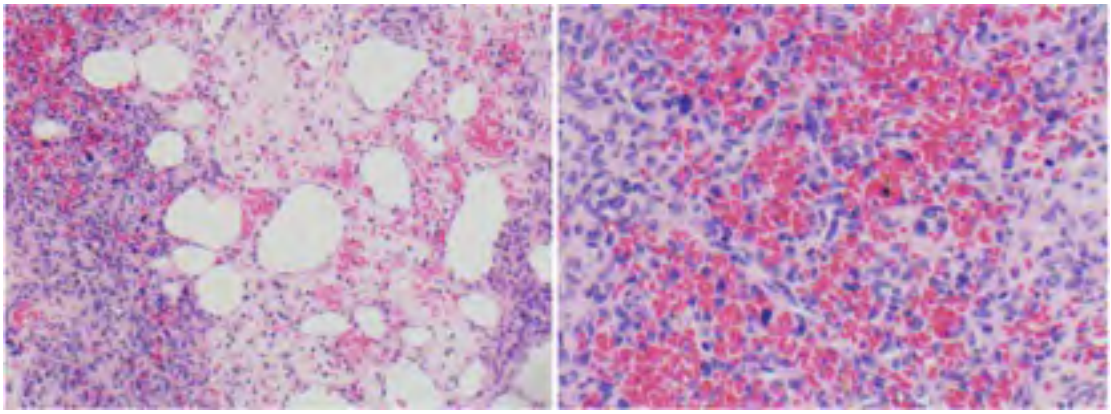


Fig.2（左）中倍率下，變形的靜脈　　（右）溢出的紅血球

(2)在很多變形的靜脈邊緣可以看到溢出的紅血球。另外血管外透明的情形也是可見的。
(3)癌細胞裡，可以發現細長的染色體以及橢圓或spindle狀的細胞核，缺乏細胞質以及不清楚的細胞膜都是其特色，也不見細胞分裂。所有癌細胞大小一致並成細長的結構。
(4)沒有間葉基質，也沒有鈣化物質，類似嗜骨巨細胞。
(5)基於以上所有條件，診斷為SNHPC。

Discussion

(A)Stout and Murray認為hemangiopericytoma源自於 ‘‘Zimmermann’s pericyte’’ （一種血管周邊的平滑肌肉細胞，用於調節微血管的流動）

(B)Compagno and Hyams是首位使用 ‘hemangiopericytoma-like’’ 的字彙來形容從軟組織分化來的鼻竇鼻腔的血管錐狀細胞瘤。

(C)最近WHO鑑於 hemangiopericytoma缺少從周邊細胞分化而來的證據，所以考慮除去這個分類。而普遍來說，軟組織的血管周邊瘤是源自於fibroblast-derived，並且呈現單一纖維瘤的細胞變異。由於，hemangiopericytomas跟球狀瘤比較有關，所以 ‘‘myopericytoma’’ or ‘‘glomangiopericytoma’’ 這兩個分類比較被WHO接受。

(D)Armed Forces Institute of Pathology (AFIP) review of 104 SNHPC (glomangiopericytoma), 好發年齡很廣 (5 – 86 years, mean 62 years) ，most patients complained of nasal obstruction and bleeding. The majority of SNHPC (glomangiopericytomas) involved the nasal cavity, whereas sole involvement of the maxillary or ethmoid sinuses or the nasopharynx was relatively uncommon。

(E)顯微鏡下，SNHPC出現在淺層的stroma和呼吸上皮，呈現皮下單一有邊緣的腫瘤，邊緣是有通透性的。SNHPC由 short, bland spindle cells forming fascicular, storiform, or whorled patterns。

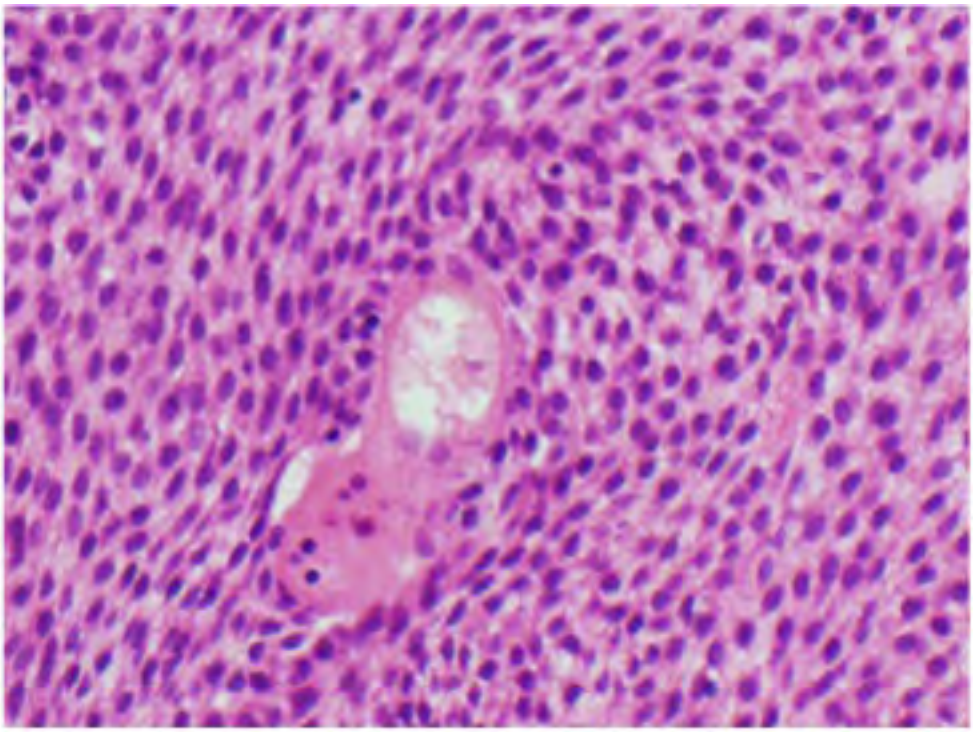


Fig. 3 SNHPC (glomangiopericytoma): high-power view of bland spindle cells forming short fascicles

(F)當 ‘‘Schwannoma’’ -like landscape 出現時，細胞的結構程度就很多變異。

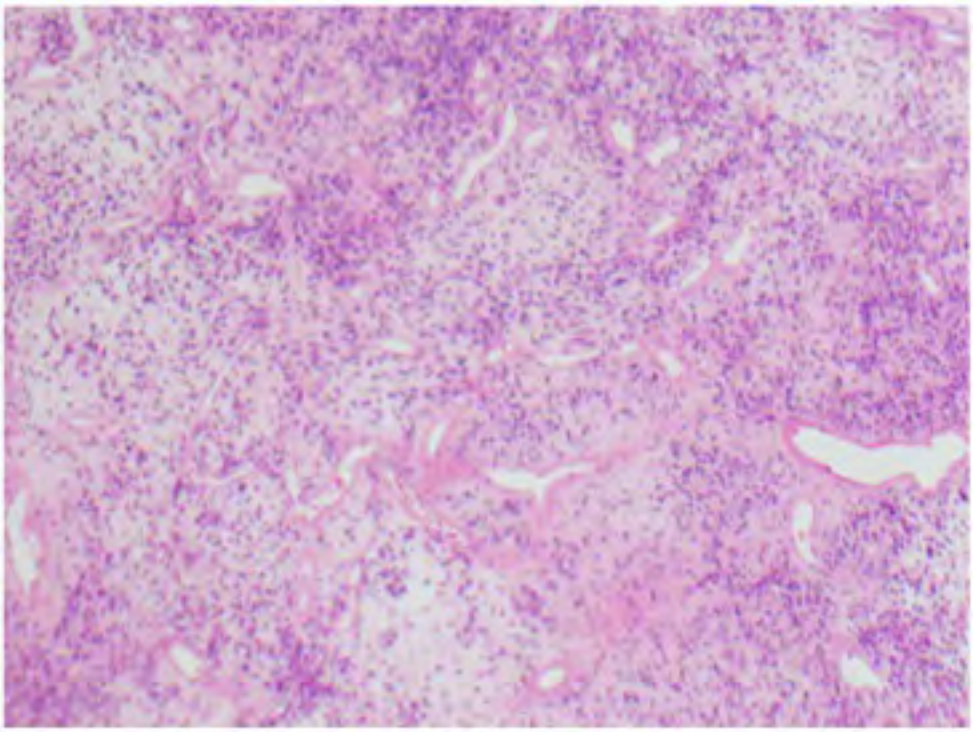


Fig. 4 SNHPC (glomangiopericytoma): low-power view of variable hypercellular and hypocellular regions imparting a ‘‘Schwannoma-like’’ landscape

(G)腫瘤的細胞核：uniform / evenly spaced / moderate amount of eosinophilic cytoplasm / indistinct cell membranes同時有融合的外型。

(H)腫瘤的血管：numerous, thin-walled and branching, (the so-called ‘‘stag- horn’’ vessels) and form clefts and gaping spaces . Perivascular hyalinization is a characteristic feature，腫瘤細胞或許是從這個透明的血管壁延伸而來。

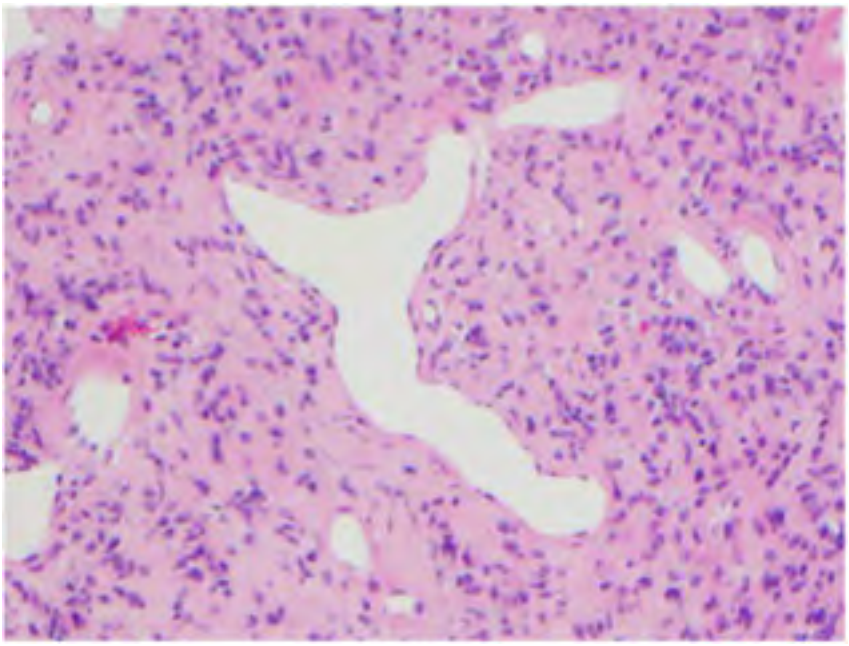


Fig. 5 SNHPC (glomangiopericytoma): Staghorn vessel (center). Note perivascular hyalinization of smaller vessels

(I)大體而言，low mitotic rate / nuclear pleomorphism缺少或很少。不尋常的 keloid-like（疤腫） collagen 出現且lipomatous （脂肪瘤）改變。

(J)以下有各個免疫生化染色的結果：

	Sinonasal hemangiopericytoma	Soft tissue glomangioma/ myopericytoma	Solitary fibrous tumor	Meningeal hemangiopericytoma
Vimentin	Pos	Pos	Pos	Pos
Smooth muscle actin	Pos	Pos	Rare	Neg
Muscle specific actin	Pos	Pos	Rare	Neg
Factor XIIIa	Pos	Pos	Pos	Pos
Desmin	Neg	Neg	Rare	Neg
CD34	Rare	Rare	B	Variable
Bcl-2	Rare	Rare	Pos	Pos
D2-40	A		Neg	Neg
S100 protein	Rare	Rare	Rare	Neg
EMA	Neg	Neg	Neg	Rare variable

A D2-40 stains vascular channels within all SNHPC to a variable degree. By comparison, soft tissue HPC/solitary fibrous tumors reveal no intratumoral D2-40 vascular staining.

B CD34 is positive in SFT- fibrous variant, but expression is less frequent in SFT-cellular variant

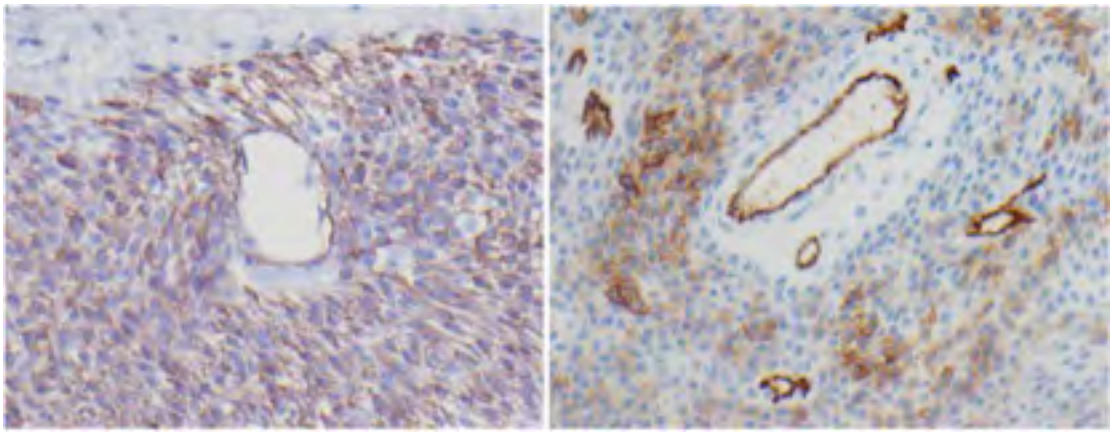


Fig. 6(左)對smooth muscle actin彌漫性顯現，而(右)對CD34呈現negative時，染色呈局限性。

Phosphaturic Mesenchymal Tumors (PMT) and Oncogenic Osteomalacia (OO)

(A)Oncogenic osteomalacia (OO) (tumor-induced rickets, ossifying mesenchymal tumor associated with vitamin-D resistant rickets) 是極少出現的疾病，通常造成renal phosphate wasting, hypophosphatemia, normo- or hypocalcemia, and lytic bony lesions有關，以上都是腫瘤的附屬症狀，但當腫瘤被移除之後，磷酸離子的過度浪費就會得到緩解。

(B)（The concept of OO was first codified by Weidner under the nosology of ‘‘Phosphaturic Mesenchymal Tumor’’ (PMT) . A recent review estimates that over 300 cases of PMT have been reported in the English literature ）

(C)常見症狀：

bone pain, loss of height, and profound muscle weakness lytic bony lesions

normal parathyroid hormone levels

normo- or hypocalcemia, hypophosphatemia, hyperphosphaturia

normal 25-hydroxyvitamin-D3

low 1, 25-dihydroxyvitamin D3 levels

(D)This biochemical profile is identical to that seen in (1)體顯性autosomal dominant hypophosphatemic rickets, (2)體隱性autosomal recessive hypophosphatemic rickets, and (3)x-linked hypophosphatemia, the latter being the most common form of inherited rickets。

(E)Clinical location: 通常很小，不易發現，且unusual locations (e.g. great toe)

(F)Radiographically localized by FDG PET/CT; scans should specifically include hands, feet, and the head

(G)Targeted : venous sampling for fibroblast growth factor-23 , has a high affinity for somatostatin receptors, which are present in many PMT.

The Diverse Histologies of Phosphaturic Mesenchymal Tumors

大部分的PMT都是良性的，只有少數在生理上是惡性表現， Weidner將PMT分成四大類：

PMT--mixed connective tissue variant

PMT—ossifying fibroma-type

PMT—non-ossifying fibroma-type

PMT—osteoblastoma type

以第一分類最多，剩下三個臨床案例實在是太少了，所以只大致上用二分法，分為PMT-mixed connective tissue variant (PMTMCT)或PMT-Other。

Phosphaturic Mesenchymal Tumors: Mixed Connective Tissue Variant (PMTMCT)

(A)Occur : soft tissues or bone , cranio- facial bones and sinonasal tract。大致上來說，PMTMCT像是well-circumscribed，但實際顯微鏡下，整個腫瘤是浸潤在周邊的結締組織裡。

(B)包括了 small, primitive, round to spindled mesenchymal cells，細胞核鮮少有多形性。

(C)製造很多mesenchymal matrices, 尤其是myxoid或myxochon- droid matrices with hyalinization, basophilic ‘‘smudginess’’ , 還有net-like, flocculent, or ‘‘grungy’’ calcification。（見下圖）

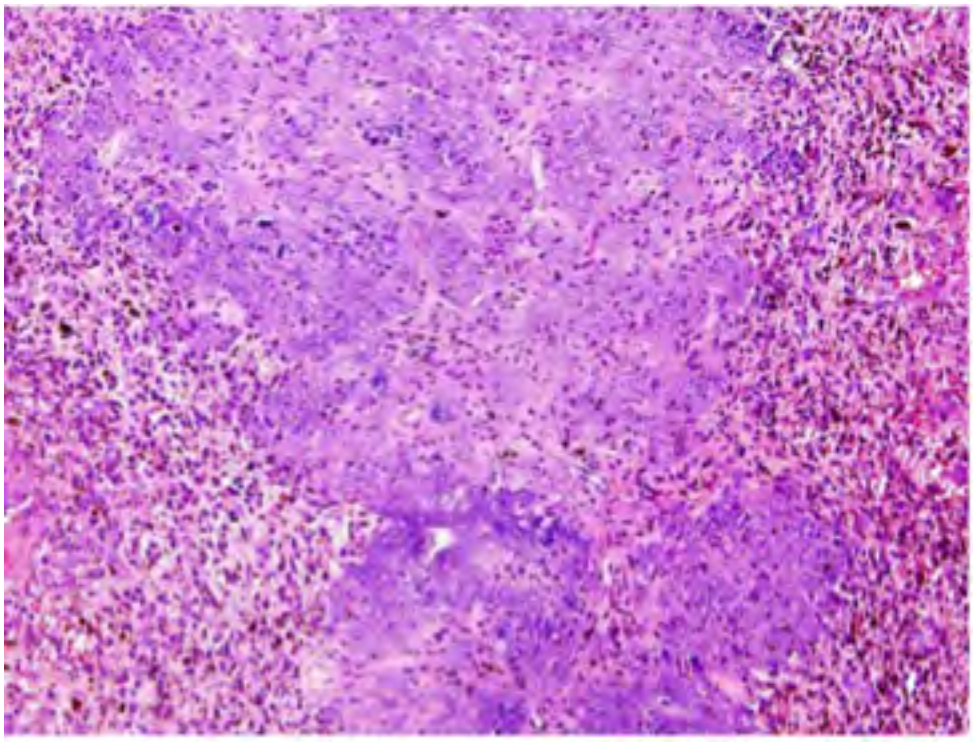


Fig. 7 Phosphaturic mesenchymal tumor: Chondromyxoid matrix with ‘‘grungy’’ calcifications. Courtesy of Dr. Michal Michal, Prague, Czech Republic

(D)Chondroid or osteoid-like matrix can be seen in either soft tissue or osseous PMTMCT.osteoid-like類骨質由腫瘤細胞製造，而軟骨類區域則包含了營養不良的鈣化物質。

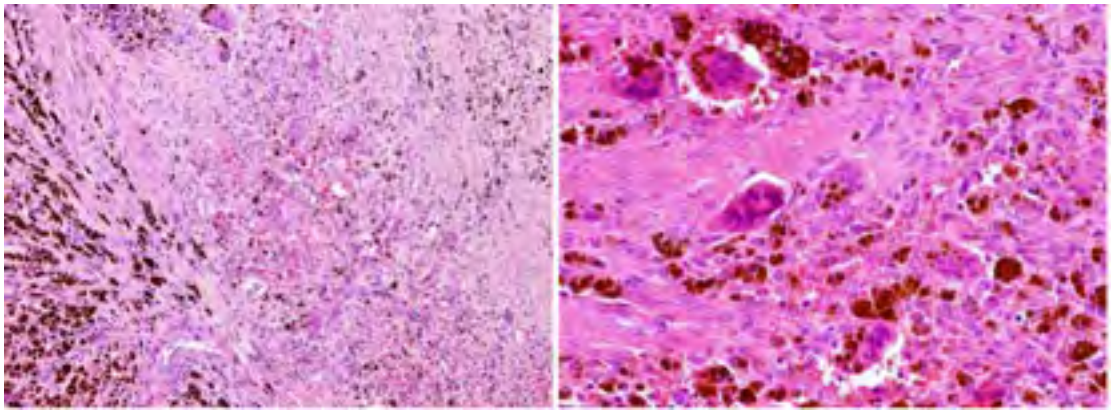


Fig. 8 Phosphaturic mesenchymal tumor: (Left) The bland spindle cell stroma reveals 血鐵質hemosiderin deposition and osteoclastic giant cells. (Right) High-power view of bland tumor spindle cells, osteoclastic giant cells, and hemosiderin. Courtesy of Dr. Michal Michal

(E)By definition, hemangiopericytoma-like tumors associated with OO and containing intratumoral woven bone, osteoblasts, and grungy calcification are best classified as PMTMCT.

Phosphaturic Mesenchymal Tumors: Others

(A)Other specific osseous entities can also be associated with OO including osteosarcoma,內生性軟骨瘤 enchondroma, nonossifying fibroma, and hemangioma。

(B)文獻指出PMT-Other缺少以下：bland mesenchymal cells, mesenchymal matrix, and grungy calcifications。另外，由軟組織血管周邊瘤所造成的軟骨瘤也可被分作PMT-Other.

(C)約略有9例 sinonasal and skull base hemangiopericytomas (glomangiopericytomas) associated with OO用英文來呈現，1例 meningeal hemangiopericytoma causing OO被發表。

The Discovery of Fibroblastic Growth Factor-23 (FGF23)

(A)phosphaturic substance最近被証實為 fibroblastic growth factor-23 (FGF23)。一般來說， FGF23由骨頭裡的 osteocytes, osteoprogenitor cells ,osteoblasts製造，並在腎臟還有副甲狀腺作用。

(B)FGF23-specific receptor被 Klotho這種衰老相關分子和 FGFR1(IIIc)所控制。

(C)PTH和FGF23同時都可以減少磷酸在腎造近曲小管的再吸收，但又以PTH對於血磷酸過低所造成的影響最鉅，如果病人體內增加FGF23但PTH濃度很低甚至偵測不到的狀況下，血磷酸過低的狀況並不會出現。但

FGF23卻可以調節 25-hydroxyvitamin D3 1-a9-hydroxylase這個因子，使25(OH)2 vitamin D 轉化成活性的 1,25(OH)2 vitamin D。且在實驗中，FGF23也會直接影響PTH，但臨床上病人的PTH通常表現正常或是suppressed in patients with OO。

(D)Serum FGF23 is abnormally elevated in patients with OO, autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, and x-linked hypophosphatemia.

(E)在老鼠實驗中，老鼠被注入穩定的細胞，使FGF23持續過度顯現，結果跟有OO的病人有一模一樣的情形。

(F)PMT也有過度呈現 mineralization-related genes，像是 matrix extracellular phosphoglycoprotein (MEPE), frizzled-related protein, DMP, and FGF7。以上這些蛋白被假設跟PMTMCT的鈣化基質有關，使得osteoblasts被吸收，導致 fibrohistiocytic and aneurysmal bone cyst-like reactions。相反的，很少有腫瘤在生理上跟PMTMCT一樣，這些腫瘤可能分泌非活性或不足的FGF23，有或者這些病人可能可以藉由提高FGF23來補償。

Treatment of Phosphaturic Mesenchymal Tumors

(A)Tumor resection

(B)Accompanied by a rapid decrease in serum FGF23 ，Serum phosphate returns to normal levels within days of definitive surgery.

(C)Oral replacement of phosphorus and high-dose 1, 25 (OH)2 vitamin D is usually indicated.

(D)Long-term follow-up (bony lesions should resolve within months to 1 year)

(E)大部分的PMT都是良性且在手術切除後可以治癒，但有很少的例子是持續低血磷酸尿，那就有可能是腫瘤切除不完全。

(F)至於那些惡性的PMT或者是很難定位或很難切除的PMT，有另外一種方式來治療，那就是就前面提到，PTH才是主要造成低血磷酸鹽的主要因子，所以我們可以用 CinacalcetÒ，一種 calcium-sensing受體拮抗劑，可以直接降低PTH，這些病人就必須搭配 thiazide diuretics的使用，來降低預防尿鈣和腎結石，

Differential Diagnoses: Glomus Tumors

Glomus Tumors：

(A)Location:Subcutaneous neoplasia of the hands, feet, or forearm, which are typically painful.

(B)中耳的副神經節瘤也稱為glomus tumors ，這種瘤源自於有收縮性的血管周邊細胞，因此跟SNHPC有關。

(C)顯微鏡下，glomus tumors 有uniform, 多邊的polyhedral, epithelioid cells, with more cytoplasm , prominent cell membranes

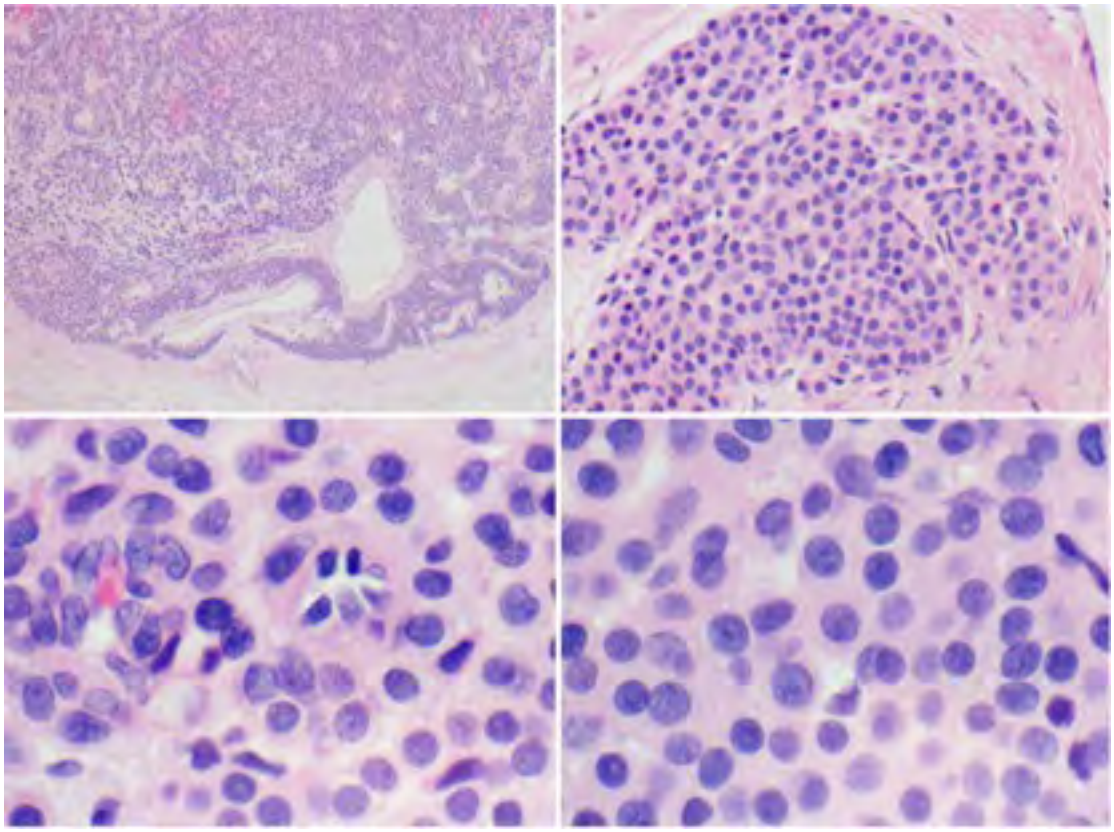


Fig.9(左上)低倍下的 glomus tumors(右上)Epithelioid cells forming a paragan-gioma-like ‘‘zell-ballen’’ pattern (下二圖)bland nuclei, abundant cytoplasm/discernable cell membranes

(D)但相同點是對於生化染色上有一樣的偏好，都對SMA和MSA是有反應的，對desmin和CD34皆為negative。

Differential Diagnoses: Solitary Fibrous Tumor (SFT)

(A)很多 soft tissue ‘‘hemangiopericytomas’’ 被分到 solitary fibrous tumor-cellular variant

(B)顯微鏡下，SFT-fibrous variant lesions有明顯的fibrous, with regions of 無定型amorphous keloid-like collagen deposition, 錯亂的haphazardly arranged cells, and alternating hypercellular and hypocellular regions. Tumor cells can form fascicular and storiform patterns 。

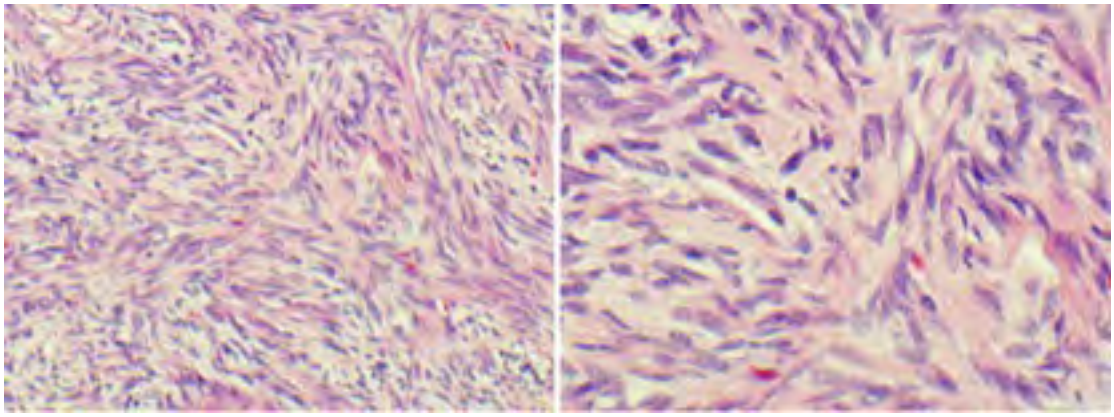
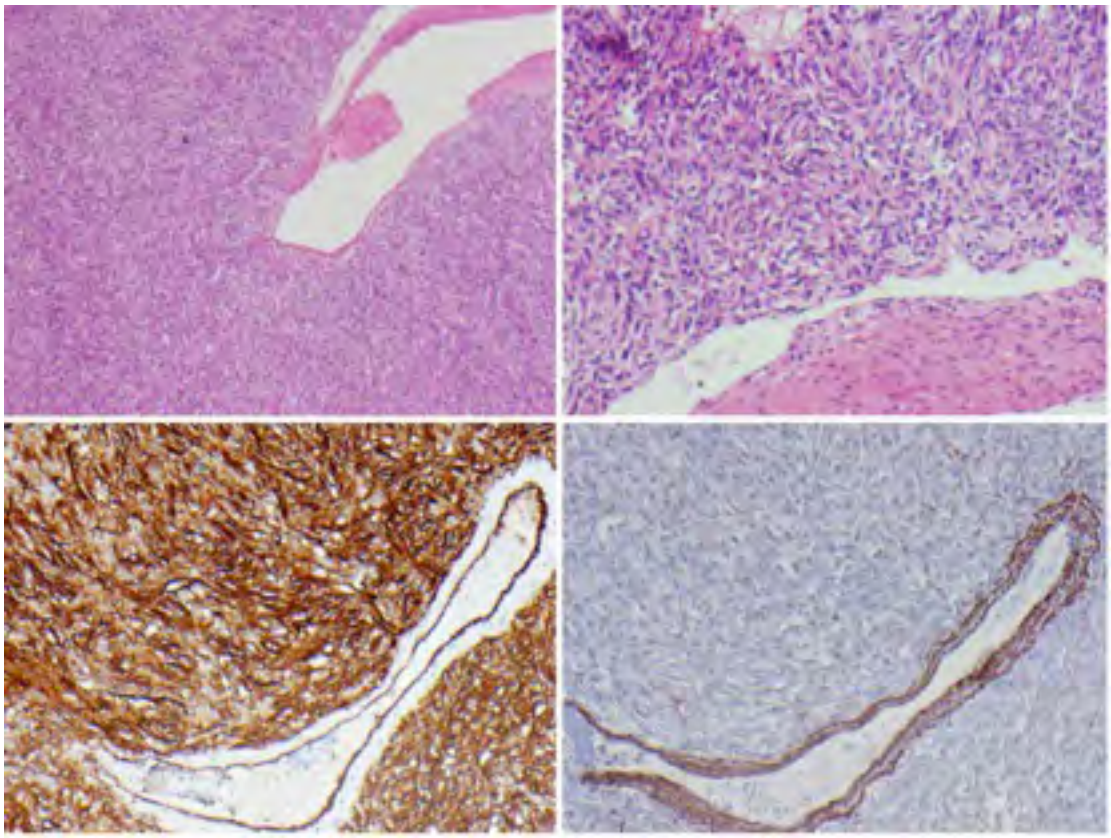


Fig. 10 Solitary fibrous tumor: low (left) and higher (right) power revealing fasicular arrangement of relatively bland spindle cells that are longer than those of the typical SNHPC (glomangiopericytoma)比SNHPC來的較長的spindle cell。

(C)SFT-fibrous variant和SFT-cellular variant在形態上有點不一，後者有中等大小的分支，且CD34在前者較為顯著。



(左上)缺乏perivascular hyalinization(右上)短的spindle cell(左下)CD34染色明顯(右下)癌細胞對SMA呈negative，但血管卻是可染色的。

(D)大部分的SFT為細胞良性，但有些SFT卻是惡性的，主要端看其不典型的細胞核，增加的細胞活性，有絲分裂。CD34在惡性的SFT反應更不明顯。

Differential Diagnoses: Meningeal Hemangiopericytoma

(A)早先被分類為 angioblastic meningioma，現今被分類為 soft tissue-type hemangiopericytoma

(B)顯微鏡下，特色為： irregularly-shaped, randomly-oriented spindle cells which do not form any fascicles / rich, branching vascularity / scant, ill-defined cytoplasm / tumor nuclei are crowded and overlapping

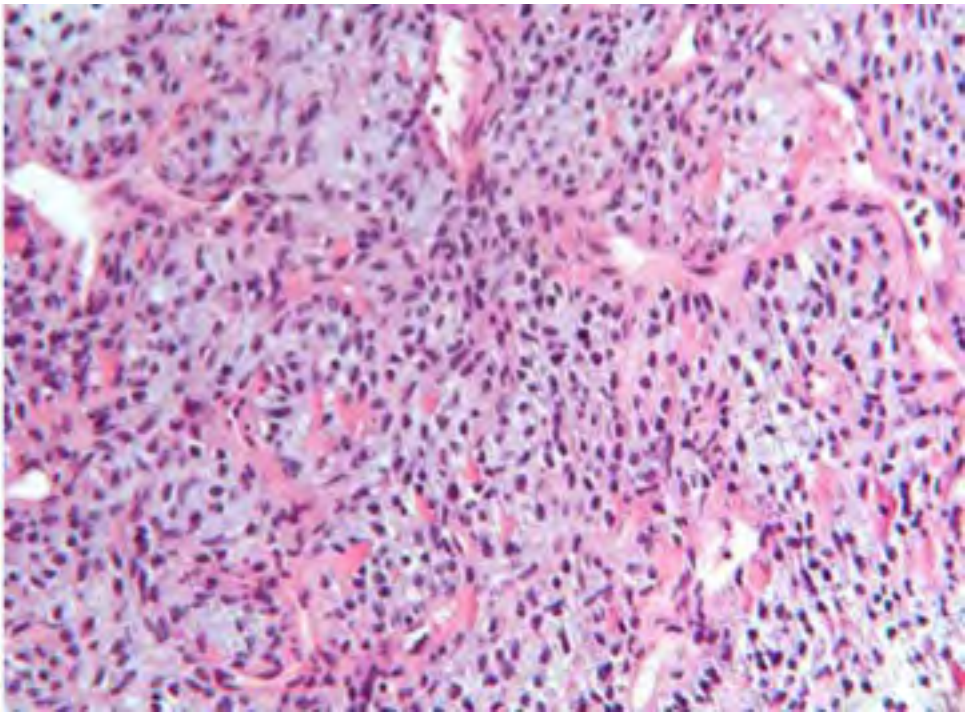


Fig.12 MeningealHPC:irregularly-shaped,randomly-orientedspin- dle cells embedded in a rich, branching vascularity

(C)生化染色上， HPS 對SMA,MSA,desmin皆為negative，對EMA和CD34則是變異的。

題號	題目
1	哪種染色在Meningeal Hemangiopericytoma和 Sinonasal hemangiopericytoma-like tumors (SNHPC)中結果是不一樣的？ (A) desmin (B) SMA (C) CD34 (D) S-100
答案(B)	出處： Striking Pathology Gold: A Singular Experience with Daily Reverberations: Sinonasal Hemangiopericytoma (Glomangiopericytoma) and Oncogenic Osteomalacia
題號	題目
2	FGF23由以下分子製造，除了？
	(A) osteocytes

	(B) osteoprogenitor cells (C) osteoblasts (D) PTH
答案(D)	出處： Striking Pathology Gold: A Singular Experience with Daily Reverberations: Sinonasal Hemangiopericytoma (Glomangiopericytoma) and Oncogenic Osteomalacia