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Phosphaturic mesenchymal tumor and related wound problem

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Abstract

Introduction: Phosphaturic mesenchymal tumor mixed connective tissue type (PMT/MCT) is the most common type (up to 90%) of phosphaturic mesenchymal tumor (PMT), a rare clinicopathologic entity. Besides overproduction of fibroblast growth factor 23 (FGF23), there is a big variation of immunohistochemical characteristic across types of PMT, which makes it difficult to obtain an early diagnosis of PMT/MCT. As a benign tumor, PMT/MCT usually happens in subcutaneous tissues and leads to nonhealing of wound. A complete excision of PMT/MCT facilitates wound healing.

Conclusions: Review of the existing evidence indicates that early diagnosis of PMT/MCT is critically important when treating PMT/MCT wound. Hence standardization of early diagnosis for PMT/MCT is mandated.

Abbreviations: FGF23 = fibroblast growth factor 23, PMT = phosphaturic mesenchymal tumor, PMT/MCT = phosphaturic mesenchymal tumor mixed connective tissue type.

Keywords: chronic wound, diagnosis, FGF23, phosphaturic mesenchymal tumor, phosphaturic mesenchymal tumor mixed connective tissue type

1. Introduction

Phosphaturic mesenchymal tumor (PMT) is an extremely rare, distinctive, clinicopathologic entity. Tumor-induced osteomalacia was first described by McCance in 1947.[1] In 1959, Prader et al[2] were the first to recognize that the disease was a tumor that secreted a "rachitogenic" substance. Removal of the tumor received the treatment of the relative symptoms was also noted by Prader et al[2] This entity was reported in the 1970s by Evans and Azzopardi[3] and Olefsky et al[4] In 2004, Folpe et al[5] termed this entity "phosphaturic mesenchymal tumor mixed connective tissue variant" with a large study and detailed literature review and now it is commonly named as PMT. Weidner and Santa Cruz[6] first recognized and named this tumor, suggesting that most of bone-associated tumors can be divided into 4 categories: PMT/MCT, PMT, osteoblastoma-like, PMT, nonossifying fibroma-like, PMT, ossifying fibroma-like.[6–8] PMT/MCT almost occupies 90% of PMT.[9] Meanwhile, over 90% of mesenchymal tumor-induced osteomalacia cases are attributed to PMT/MCTs.[5]

PMT/MCT is histologically benign neoplasms of soft tissue and bone. When it appears in subcutaneous tissue with a nonhealing wound, it often leads to delayed diagnosis, failed diagnosis, or misdiagnosis. It is a situation named "clinical silence" and to large extent explained by small size and slow growth[10] as well as nonspecific symptoms. It is the reason why in average diagnosis of PMT is not established until 5 to 7 years of the disease course.[11–13] A PMT/MCT wound does not have healing potential even under standard wound care, while complete surgical resection of the lesion is the way to cure.[14,15] Thus, it is necessary to summarize the characteristics of PMT/MCT so as to guide early diagnosis and treatment toward healing of a PMT/MCT wound.

2. Epidemiology

It is reported that approximately 53% of PMT/MCT occurs in bone, 45% in soft tissue, and 3% in skin.[16] In most cases, it appears in the extremities,[5] in other words, lesions of the appendicular skeleton are more common than the axial skeleton.[5,17,18] Craniofacial involvement is described in only 5% of literature where paranasal sinuses are the most dangerous predilection sites in this region[5] Involvement of mandibular soft tissue is relatively rare. This tumor dose appear in pelvis while it is rarely found in hip joint.[19] PMT is occasionally found in children with rickets. Around 2/3 of cases are based on the population over 30-year-old.[20] The incidence in men is slightly higher than in women. Clinically, Honda et al[15] discovered patients with PMT were often associated with a history of osteomalacia with exception in certain nonphosphaturic variant cases. Patients exhibit typical characteristics of osteomalacia

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early including generalized fatigue, bone pain, and musculoskeletal weakness and incomplete fractures.

3. Pathogenesis

In PMT, serum phosphorus disorder leads to paraneoplastic syndrome. Although multiple factors may be involved, there is a compelling evidence that FGF23 plays a significant role in this tumor. FGF23 is a hormone produced by osteocytes and osteoblasts. Folpe et al[5] demonstrated that the 17/21 and 2/2 PMT/MCTs in their series showed positive FGF23 expression by immunohistochemistry and RT-PCR, respectively. The expression of FGF23 is identified in more than 80% of PMT/MCT cases[5] and is measured by 2 different assays. The intact FGF23 assay and the C-terminal FGF23 assay which respectively detect intact FGF23 peptide and biologically inactive carboxyl terminal (C-terminal) fragments.[21] FGF23 overexpression inhibits renal phosphate reabsorption in the proximal tubules and acts as a phosphaturic factor.[7,22,23] The main transport protein responsible for phosphate reabsorption in the kidney is Type II sodium-phosphate co-transporter (NPT2a) localized in the proximal tubule. High circulating FGF23 level mediates renal phosphate wasting by downregulation of NPT2a.[9,12,23] Moreover, FGF23 has been shown to restrain 25-hydroxyvitamin D 1-alpha hydroxylase, thereby preventing conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D.[24] Also, FGF23 stimulates 24-hydroxylase and appears to reduce parathyroid hormone secretion, as short-term studies showed.[25] Therefore, patients present osteomalacia and hypophosphatemia with poor response to vitamin D (Fig. 1).

PMT also generates other proteins. Frizzled protein 4 (sFRP4) is a potential phosphatonin to regulate phosphorus homeostasis.[26] Matrix extracellular phosphoglycoprotein (MEPE) associated motif peptide may compromise bone mineralization.[26] FGF7 is an inhibitor of phosphate transport derived from oncogenic osteomalacia-causing tumors,[27] D2–40 is an indicator to assess the relationship between tumor and lymphatic vessel density or lymph node metastasis.[28] CD56 is an adhesion molecule for neural cells.[29] Recently, it was shown that the fibronectin 1 (FN1)-FGFR1 fusion gene is present in 60% of PMT cases.[30]

4. Current diagnosis

Clinically, PMT/MCT appearing as a nonhealing wound of extremities tends to be ignored until it has a remarkable size. Biopsy and pathological examination is able to help confirming the diagnosis. This neoplasm is mainly composed of dense spindle cells arranged in diffused array. The cells are embedded in a distinctive myxoi chondromyxoid matrix that often contains foci of "grungy" or flocculent calcification.[31] PMTs exhibit a particularly developed capillary plexus, when the larger vessels sometimes exhibit a staghorn pattern.[5] There are rich interstitial vessels, with visible clusters of small vessels and dilated sinuses derived from thin-walled vessels. Thick-walled vascular with hyaline degeneration is also noted. Mature adipose tissue and collagenous tissue scatter in tumor interstitial or periphery. PMT/MCT is characterized by slow growth and locally invasive nature with low metastasis. The surrounding boundaries are unclear, while malignancy is not suggested. Other possible features include osteoclast-like giant cells, mature fat, chondroid or osteoid-like matrix, woven bone, and areas of microcystic change.

Biomarker is helpful to the diagnosis (Table 1). Overproduction of fibroblast growth factor 23 (FGF23) always exists based on either blood test or immunohistochemistry test of biopsy samples. If the tumor is incompletely resected, FGF23 level will decline and rise again in a short time. Complete tumor resection will have FGF23 maintained in normal sustainably. Immunohistochemical stains of pancytokeratin, desmin, S-100, CD34,[5] CD31,[32] actin (pan)[33] are predominantly negative in the neoplastic cells. It was reported that PMT has strong and diffused expression of vimentin, but most of the other markers remain negative.[31] Meanwhile, S-100, DES, CD34, and AE1/AE3 bear significant importance in differentiation versus other soft tissue tumors. Somatostatin receptors are found to be present in

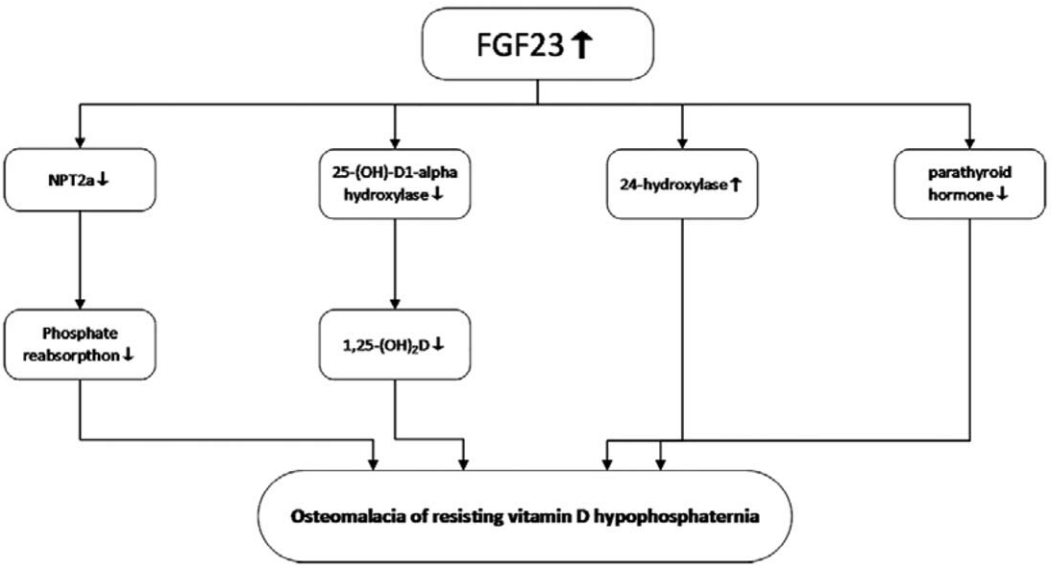

Figure 1. The mechanism of osteomalacia caused by FGF23 (arrows in square brackets denote abnormality seen occasionally, which means upward indication of an increase and downward indication of a decrease); NPT2a type II sodium-phosphate cotransporter.

Table 1

Typical laboratory examinations with phosphaturic mesenchymal tumor.

Laboratory data	Characteristic findings
Phosphate	↓ or ↑ or ↔
FGF23	↑
1,25-Dihydroxyvitamin D(1,25-(OH)2D)	↔ or ↓
25-Hydroxyvitamin D(25-(OH)-D)	↔
Tumor markers	↔
Alkaline phosphatase	↑
Antinuclear antibody	↔
Phosphate clearance (24-h urine sample)	↑
Fractional excretion of phosphate	↑
RF, PTH, TSH, LH, FSH, PRL	↔

FSH = follicle-stimulating hormone, LH = luteinizing hormone, PRL = prolactin, PTH = parathyroid hormone, RF = rheumatoid factor, TSH = thyroid stimulating hormone, (arrows in table denote abnormality seen occasionally, which means upward indication of an increase and downward indication of a decrease).

PMT.[34–37] Houang et al[37] concluded that positive staining for FGF23 and SSTR2A were highly sensitive but not specific, while negative staining was of good value in ruling out the diagnosis. Interestingly, it was documented by Williams et al[38] that lymphatic vessels presented in PMTs also expressed characteristic markers such as LYVE1 and podoplanin. These findings can distinguish PMT from other vascular tumors. Moreover, D2–40 is suggested to be a useful diagnostic marker of PMT and the implication is that PMT might have a lymphatic endothelial immunophenotype. CD56 may be a more useful immunohistochemical marker than somatostatin receptor 2A for the diagnosis.

Radiological examination is valuable to detect localization of tumor and other tissue lesions. Whole body high-resolution magnetic resonance imaging (MRI) is proposed for confirming the location of the tumor. Since PMT expresses somatostatin receptors,[39] octreotide scintigraphy or octreotide SPECT/CT is useful to locate the position. 18 F-FDG PET/CT is a nonspecific but very sensitive method that can be used to detect tumors.[12,40,41] In addition, anatomical imaging is used to confirm the location of the neoplasm, while selective venous sampling can significantly improve the success of tumor localization as identified multiple suspicious lesions.[42] Recently, 99Tc-HYNIC-TOC SPECT/CT and 68Ga-DOTATATE PET/CT are considered to be ideal in locating PMT. Jadhav et al[43] showed that the above 2 methods were superior to 18 F-FDG PET/CT.[44,45] From another aspect, electron microscopy is a helpful complementary diagnostic tool in cases of inconclusive histopathology, but limited by its availability.[46]

Multiple diagnostic modalities should be used for diagnosis and in particular, differential diagnosis. It is necessary to rule out analogous tumors of the histological spectrum as well as other conditions presenting hypophosphatemia, such as hereditary hypophosphatemic osteomalacia represented by X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, and autosomal recessive hypophosphatemic rickets.[21]

Based on the diagnostic tools available currently, a flowchart is created to facilitate diagnosis (Fig. 2). First, it is necessary to collect medical history and perform physical examination carefully followed by laboratory investigation. Then, all hypophosphatemia cases should be further evaluated to determine whether the low circulating levels of phosphate are due to excessive elimination of phosphate from kidneys, this could be determined by calculating the value of TMP/GFR (tubular maximum reabsorption of phosphate to glomerular filtration rate).[21] Immunohistochemistry plays a definitive role in the diagnosis. FGF23 is the most important biomarker. Bcl-2, CD99, SMA, and other immunohistochemical markers are helpful but nonspecific in the diagnosis. Ultimately, early diagnosis is of great significance to treat PMT patients.

5. Therapy and prognosis

In terms of wound treatment, it is estimated that 90% of PMT patients with complete resection and clear margin achieve clinical cure.[47,48] Biomarkers will return to normal level within hours to days after successful PMT resection,[5,7,47] while improvements in clinical symptoms, such as fatigue, bone pain, musculoskeletal weakness, and pseudofractures may take months. Radical radiotherapy is the primary option for treatment in unresectable tumors as well as residue of incomplete resection.[36,49] Recently, postoperative radiotherapy for neoplasms with high risk of recurrence is still controversial, as most patients do not have acute or chronic recurrence.[50,51–53] Caudell et al[49] observed that patients with combination therapy had better control of tumors than radiotherapy alone. In addition, as the tumor expresses somatostatin receptors due to the regulation of phosphate metabolism, beneficial effect octreotide treatment is observed. New treatment options include intensity modulated radiation therapy (IMRT), image guide radiation therapy (IGRT) or segmented stereotactic radiotherapy, with limited dose and radiation toxicities to surrounding tissues.[54]

Recurrence and metastasis are rare. According to reports, it only happened in approximately $< 5\%$ of patients.[5,12,55,56] Recommendation is to give adjuvant radiotherapy after the surgery with 40 to 50 Gy. Small parts of the initially benign tumor will be transferred, for example, it can metastasizes to the lungs through hematogenous metastasis.[15,50,56] Morimoto et al[56] reported that it was necessary to follow-up postoperative patients due to the potential risk of metastasis of PMT. Serum phosphate level is recommended as a method to detect recurrence. Regular serum FGF23 test is used to evaluate if PMT was removed completely.[57]

6. Discussion

It is known that PMT/MCT may present as skin ulceration. Once the diagnosis is established, surgery, if feasible, will achieve cure. The lesson learned is that early diagnosis is so important, yet challenging, to spare a disease course of 5 to 7 years before the tumor is self-evident. There are 2 reasons why PMT/MCT is very difficult to be diagnosed in the early stage. The first is the rareness of the disease and low awareness among doctors. The second is the lack of tumor-sensitive markers. Fortunately, FGF23 is shown to have a positive correlation with PMT and has the potential to be a sensitive indicator for early diagnosis. Tumor-induced skin ulcer is categorized into benign or malignant tumor origin. Malignant tumor, like squamous cell carcinoma, is easy to induce nonhealing wound. Most benign tumors usually do not lead to skin ulceration, while PMT/MCT is exceptional. Logically, the reasons why a benign tumor in subcutaneous tissue induces skin ulceration might be explained by skin tension and tumor invasiveness. In fact, benign tumor may present invasiveness in some way. As an example, PMT/MCT usually do not have clear boundary with surrounding normal tissues. In the reported literatures, it was found that PMT-related wounds may be associated with expression of immunohistochemical-related proteins such as CD31,[32] CD56,[30] and D2–40.[29]

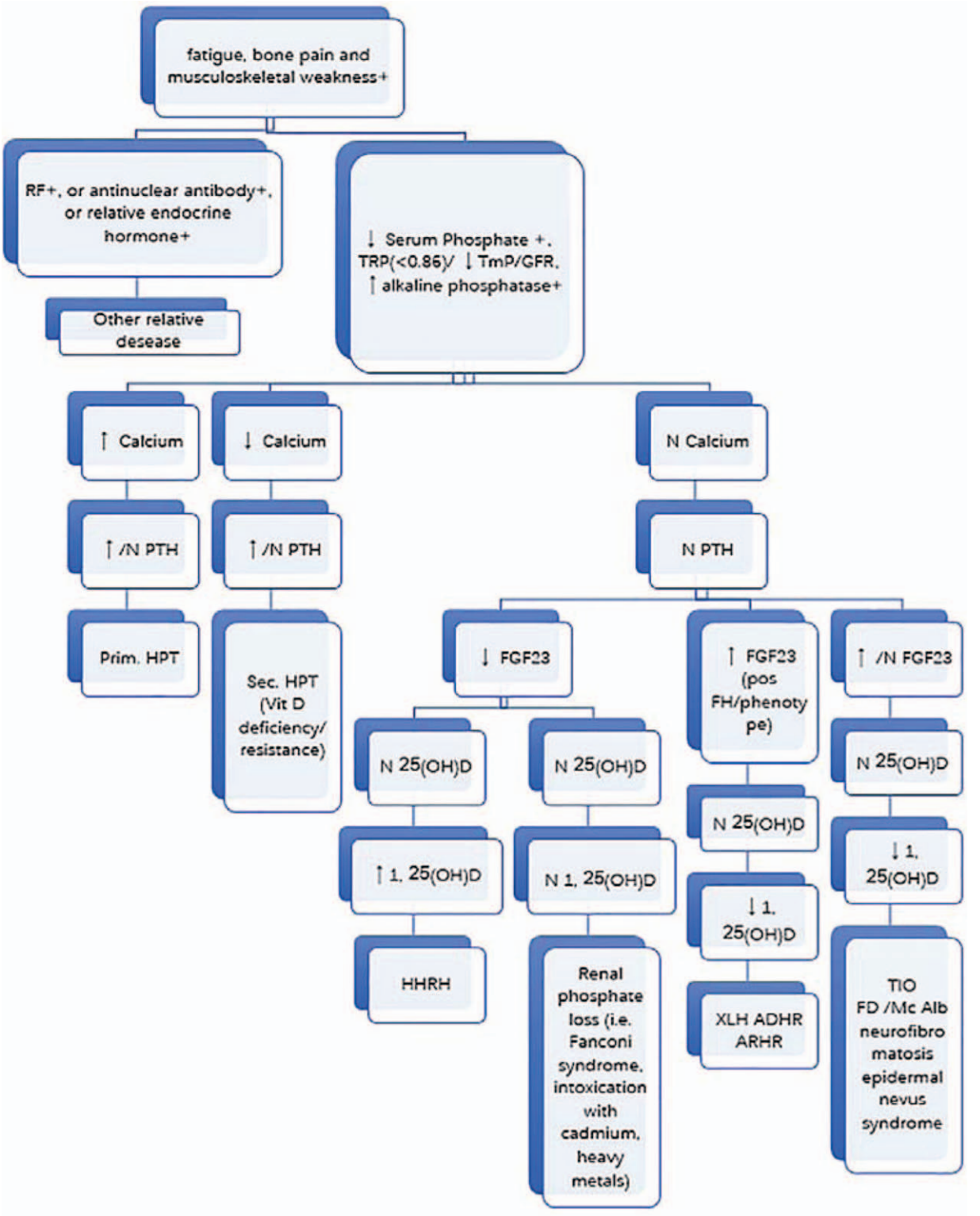

Figure 2. Flowchart of the differential diagnosis and characteristics of hypophosphaturic osteomalacia (N normal; arrows in square brackets denote abnormality seen occasionally, which means upward indication of an increase and downward indication of a decrease); ADHR = autosomal dominant hypophosphatemic rickets, ARHR = autosomal recessive hypophosphatemic rickets, FH = family history, FGF23 = fibroblast growth factor 23, FD = fibrous dysplasia, HHRH = hereditary hypophosphatemic rickets with hypercalciuria, Mc Alb = McCune Albright syndrome, PTH = parathyroid hormone, Prim. HPT = primary hyperparathyroidism, RF = rheumatoid factor, Sec. HPT = secondary hyperparathyroidism, TRP = fractional tubular reabsorption of phosphate, TMP/GFR = tubular maximum reabsorption of phosphate to glomerular filtration rate, TIO = tumor-induced osteomalacia, XLH = X-linked hypophosphatemic rickets.

CD31 is a regulatory factor for angiogenesis,[32] and is shown to be closely related to endothelial cell motility and angiogenesis. The expression of CD31 in PMT is usually negative. Thus, it is a reasonable expectation that the insufficiency of vascular endothelial cell proliferation might inhibit angiogenesis, and accordingly affect wound healing.

CD56 is a neural cell adhesion molecule that can affect interaction between cells and the interaction between the extracellular matrix and cells. It plays an important role in cells recognition and migration, cell aggregation, and invasion of malignant tumor. The positive expression of CD56 in PMT may explain the invasive behavior of the tumor, and destruction of skin tissue matrix structure.

The expression of D2–40 has been used to assess the relationship between tumor and lymphatic vessel density or lymph node metastasis.[58] D2–40-expressed malignant tumors indicate a high risk of invasiveness and potential metastasis. One of the possible mechanisms of metastasis by D2–40-promoted tumor involves increasing activity of matrix metalloproteinases. Through this mechanism, it enhances the activity of tumor cells penetrating the matrix layer and thus destroys the normal structure of the skin tissue. It is shown that most cases of PMTs had D2–40 immunoreaction and contained D2–40-positive lymphatic vessels.

In conclusion, PMT is a mesenchymal tumor with wound-inducing potential when occurring in skin and soft tissue. PMT tends to be missed out from diagnosis in this early stage due to rareness. FGF23 is a candidate biomarker from diagnosis to postoperative evaluation and follow up. Radiology is very helpful. Pathological sections may demonstrate the characteristic morphology of the tumor. For understanding the mechanism of skin wounding in terms of PMT, so far it has not clear that how PMT induce skin wound, on which it might be something with invasiveness of the tumor.

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Writing – original draft: Xian Xiao.
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