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## CASE REPORT

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# Recurrent Pigmented Villonodular Synovitis with Distant Metastases: Case Report and Review of the Literature on the Efficacy of Targeted Therapies

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### ABSTRACT

*Pigmented villonodular synovitis (PVNS), also known as tenosynovial giant cell tumour, diffuse type, is an uncommon pathological disease of the synovium and tendon sheaths. In most cases the disease is benign but rarely, it presents with aggressive and infiltrative features. We report a case of recurrent PVNS with bone and pleural metastases. Surgical resection remains the mainstay of treatment. For cases that are not amenable to surgery, novel targeted therapeutic agents have demonstrated favourable treatment response in some case reports and early-phase clinical trials. The macrophage colony-stimulating factor receptor inhibition pathway is hypothesised to be responsible for the potential therapeutic effect of targeted therapies. Due to the rarity of the disease, however, the definitive role of targeted therapeutic agents is still not well defined. Further molecular studies and clinical trials are needed to better understand the molecular basis and clinical efficacy of these targeted therapeutic agents.*

*Key Words:* Molecular targeted therapies; Neoplasm metastasis; Synovitis, pigmented villonodular; Therapeutics

## 中文摘要

### 復發性色素沉著絨毛結節性滑膜炎伴遠處轉移： 病例報告和針對標靶治療功效的文獻回顧

李天恩、陳澤林、顏繼昌

色素沉著絨毛結節性滑膜炎亦稱為瀰漫型腱鞘巨細胞瘤，是滑膜和腱鞘的一種罕見病患。此病多為良性，但在罕見情況下可呈現為具入侵性和浸潤性。本文報告一宗復發性色素沉著絨毛結節性滑膜炎伴骨、胸膜轉移的病例。手術切除為色素沉著絨毛結節性滑膜炎的主要治療方法。至於不適合手術的患者，一些病例報告和早期臨床試驗證明新型標靶治療藥物有良好的治療效果。標靶治療有效的原因可能是透過抑制巨噬細胞集落刺激因子受體。然而，由於此病罕見，標靶治療藥物的實際臨床應用仍有待證實。需進一步的分子研究和臨床試驗，以明確地掌握標靶治療的分子基礎和臨床療效。

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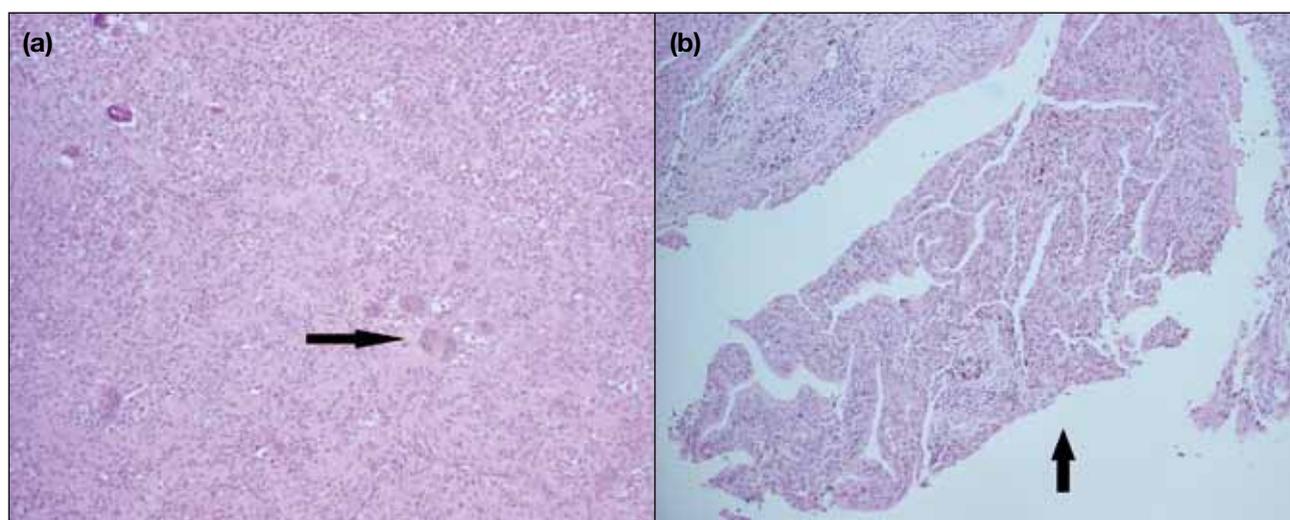
Submitted: 6 Jul 2015; Accepted: 1 Sep 2015.

## INTRODUCTION

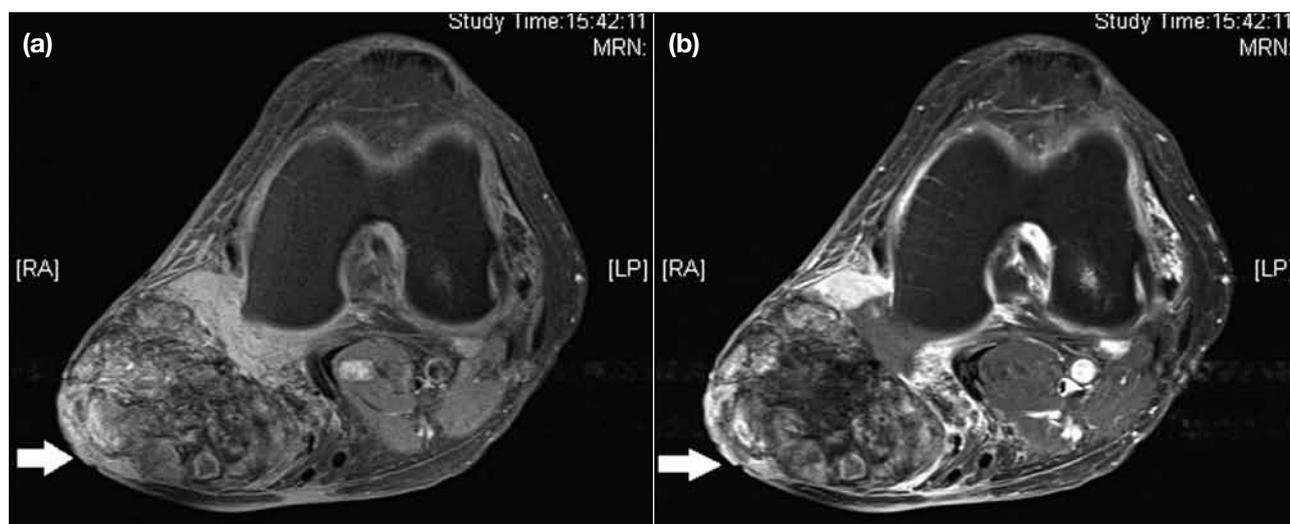
Pigmented villonodular synovitis (PVNS), also known as tenosynovial giant cell tumour, diffuse type, is an uncommon pathological entity of the synovium and tendon sheaths. It is in most cases a benign and localised disease, although aggressive and infiltrative behaviour has also been reported in the English literature.<sup>1</sup> We report a case of recurrent PVNS with bone and pleural metastases, and review the existing literature on the use of novel targeted therapeutic agents in such a setting.

## CASE REPORT

A 71-year-old woman presented with left knee swelling in mid-2008. Magnetic resonance imaging (MRI) showed an intra-articular mass in the popliteal region along the joint line of the left knee. Radiological features were compatible with PVNS. Surgical excision and arthroscopic synovectomy for the left knee tumour was performed in September 2008. Pathology confirmed PVNS with the external surfaces focally touched by the lesion (Figure 1). Subsequent MRI in September 2009 showed radiological residual PVNS in the left knee. She



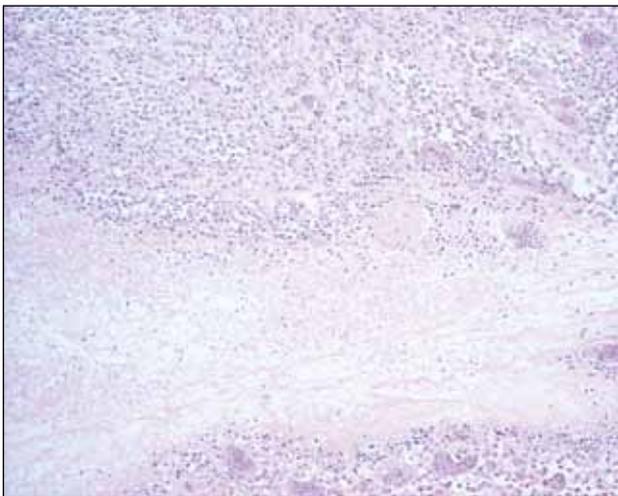
**Figure 1.** (a) The tumour resected in 2008 consists of a mixture of mononuclear cells intermixed with osteoclast-like giant cells (arrow) [H&E; original magnification, x 100]. (b) Villous structures with haemosiderin deposition and mononuclear cells in the core are focally present (arrow) [H&E; original magnification, x 100].



**Figure 2.** Magnetic resonance imaging scans of the left knee in April 2014 show a heterogeneous lesion in the posteromedial aspect of the left knee with communication to the knee joint (arrows): (a) T1-weighted, axial cut; and (b) T2-weighted, axial cut.

was managed conservatively with regular follow-up. She later complained of progressive left knee swelling and reassessment MRI in October 2013 confirmed that the residual nodular mass had increased in size in the posteromedial knee. Surgical excision was offered, however, the patient opted for further observation.

Further clinical disease progression was noted in early 2014 and confirmed by an interval MRI scan in April 2014 (Figure 2). Subsequent excision of the recurrent tumour with sural flap and partial thickness skin graft was performed in the same month. Pathology showed a 9-cm PVNS with circumferential margin focally



**Figure 3.** Necrosis is focally seen in the tumour resected in 2014 (H&E; original magnification, x 100).

involved. Mitotic count was 7 per 10 high-power fields (HPFs; adjusted to 1 HPF = 0.159 mm<sup>2</sup>), and atypical mitotic figures were not found. Some of the tumour cells exhibited an atypical appearance with larger nuclei, prominent nucleoli, and more abundant eosinophilic cytoplasm, and necrosis was evident (Figure 3). Sarcomatous component was not found despite the presence of these atypical histologic features.

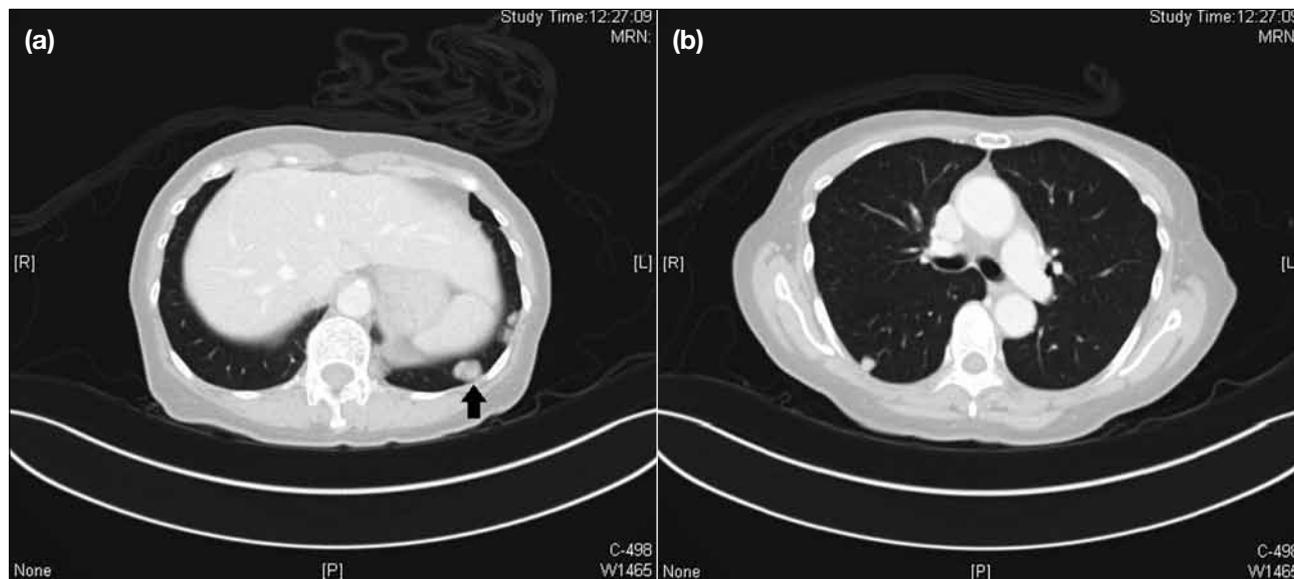
The patient developed progressive left mid-shin pain 6 months later in December 2014 with X-ray showing an osteolytic lesion over her left tibia with cortical erosion (Figure 4). Myeloma workup was negative. Bone scan showed increased tracer uptake with corresponding increased perfusion and blood pooling at the left mid-tibial osteolytic lesion, features worrisome of a primary malignant bone tumour. MRI in December 2014 showed a large destructive intramedullary tumour in the left mid-tibia with soft tissue extension into the soleus muscle, suggestive of an aggressive lesion (Figure 4).

Staging computed tomography of the thorax, abdomen, and pelvis was performed in January 2015, and revealed multiple pleural-based metastatic nodules and suspicious bone metastases in multiple thoracic vertebrae and the right iliac bone (Figure 5).

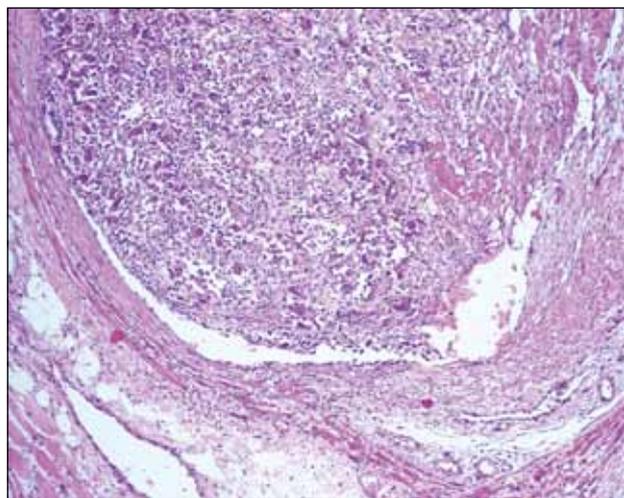
An above-knee amputation was performed in January 2015. Pathology confirmed PVNS with atypical histologic features similar to the previous specimen. There was no sarcomatous component, but vascular invasion was observed (Figure 6).



**Figure 4.** Magnetic resonance imaging scans and X-ray of the left knee in December 2014 show a large destructive intramedullary tumour of the mid-tibia with soft tissue extension into the soleus muscle (arrows). The overall feature is suggestive of an aggressive lesion: (a) T1-weighted, sagittal cut; (b) T2-weighted, sagittal cut; and (c) X-ray.



**Figure 5.** Staging computed tomographic thorax, abdomen, and pelvis scans in January 2015 show multiple pleural based nodules in the posterolateral aspect of the (a) left lower lobe (arrow), and (b) apical region of the right upper and right lower lobe; the largest was approximately 1.9 cm in the left lower lobe diaphragmatic surface.



**Figure 6.** Invasion into a blood vessel is observed in the tumour resected from the left tibia (H&E; original magnification, x 100).

Postoperative recovery was uneventful. In view of her advanced age and asymptomatic distant metastases, the patient opted for conservative management. No further palliative systemic or local therapy has been offered.

## DISCUSSION

Tenosynovial giant cell tumour is usually a benign neoplastic condition affecting the synovium and tendon sheaths. It can be classified as localised type (also

called nodular tenosynovitis or giant cell tumour of tendon sheath, usually is extra-articular and affects the small joints) or diffuse type (also called PVNS, which commonly affects the large joints and is intra-articular and infiltrative).<sup>1,2</sup>

PVNS occurs more often in young adults, predominantly affecting the knee joints. The most common presentations are joint pain, joint swelling, and effusion with haemarthrosis.<sup>3</sup> Surgery is the mainstay of treatment, while adjuvant external beam radiotherapy is also effective in improving the local control of PVNS.<sup>4</sup> The use of adjuvant isotopic synoviorthesis using Yttrium 90 or Rhenium 186 has also been reported with potential improvement in local disease control.<sup>3,5</sup>

Although tenosynovial giant cell tumour is often considered a benign condition, the diffuse subtype (PVNS) is often more aggressive with a tendency for local infiltration. There have been case reports and case series with malignant features and distant metastases, including pulmonary, intra-abdominal, and inguinal lymph node metastases.<sup>6,7</sup> The diagnostic criteria for malignant PVNS vary among different series, and we share the view that atypical histologic features (such as increased mitotic activity >20 mitoses per 10 HPFs, necrosis, spindling of the mononuclear cells, and cytologic atypia) are not indicative of malignancy when present individually, and cases with one or more

of these features in the absence of frank sarcomatous change should not be termed 'malignant'.<sup>7</sup>

In the era of targeted therapy, molecular oncology and novel targeted therapeutic agents are being studied for this neoplastic entity. Over-expression of colony-stimulating factor 1 (CSF1; also known as macrophage colony-stimulating factor, M-CSF) is commonly found in PVNS. The aberrant CSF1 expression in the neoplastic cells leads to an abnormal accumulation of non-neoplastic inflammatory cells forming a tumorous mass through the paracrine or 'tumour-landscaping' effect.<sup>8</sup> Inhibition of CSF1-driven chemotaxis can potentially target the underlying cause of the disease.

Imatinib is a tyrosine-kinase inhibitor with activity against the BCR-ABL fusion protein, the c-KIT (CD117), the platelet-derived growth factor receptors, the fms-like tyrosine-protein kinase 3 (FLT3), the RET, and the CSF1 receptor. Therefore imatinib has been hypothesised as a treatment for patients with PVNS through its inhibition of CSF1 / CSF1R-driven chemotaxis.<sup>9</sup>

The initial use of imatinib was first presented in 2008 in a case report by Blay et al<sup>10</sup> who reported complete response to imatinib (at a daily dose of 400 mg) in a patient with relapsing PVNS.

Subsequently a multi-institutional retrospective study was conducted to assess the effectiveness of imatinib in 27 patients with locally advanced or metastatic PVNS.<sup>2</sup> According to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, imatinib achieved an overall response rate of 19% (one complete response and four partial responses) and stable disease in three-quarters of patients. The common toxicities associated with imatinib include fluid retention, nausea, fatigue, and dermatitis. Nonetheless, it is notable that the two patients with metastatic disease had rapid disease progression despite starting imatinib. This may suggest that additional molecular changes may occur and render the disease resistant to CSF1R inhibition.<sup>2</sup>

Nilotinib also has inhibitory properties on the CSF1R pathway. It has been studied recently by an open-label international multicentre phase II study for treating progressive PVNS not amenable to surgery.<sup>11</sup> The preliminary result shows that nilotinib induces disease stabilisation in a large proportion of patients with PVNS.<sup>11</sup> In the event of disease progression, a

case report indicated that imatinib showed anti-tumour activity in two patients with nilotinib-resistant PVNS.<sup>12</sup>

Recent breakthrough in molecularly targeted therapies was made possible through the use of X-ray co-crystallography. A more potent, specific CSF1R inhibitor, PLX3397, has been evaluated in a multicentre phase I trial (with dose-escalation study and extension study).<sup>13</sup> A total of 23 patients with advanced PVNS (one had metastatic disease) were included in the extension study. At the chosen phase II dose of 1000 mg daily, PLX3397 achieved an overall response rate of 52% (12 out of 23), which was much higher than the overall response rate of 19% reported with imatinib.<sup>2,13</sup> Three patients who had received prior treatment with imatinib or nilotinib also showed tumour volume reductions of 40% to 55%. Nevertheless, further randomised trials are recommended to validate this extrapolation of phase I data. It is worth noting that the only patient who had disease progression during treatment was the one with metastatic disease.<sup>13</sup> This may suggest that possible resistance to CSF1R inhibition or additional molecular alterations may occur.

Another recent phase I clinical trial showed promising results with emactuzumab (RG7155), a recombinant, humanised anti-human CSF1R monoclonal antibody that selectively inhibits CSF1 receptor dimerization. An objective response was achieved in 24 (86%) of 28 patients, of whom two (7%) patients achieved a complete objective response.<sup>14,15</sup>

In view of the low incidence of PVNS and limited number of trials, the definitive role of targeted therapeutic agents remains uncertain. Targeted therapy may represent a valuable treatment option for patients with symptomatic PVNS not amenable to surgery or with disseminated disease as observed in our patient.

Following the recent advancement in drug-discovery research, there is an ongoing phase III trial that aims to evaluate the effectiveness of a study drug PLX3397 in treating patients with PVNS (NCT02371369). Indeed, further molecular studies and clinical trials are needed to better understand the molecular basis of the disease and the clinical efficacy of these targeted therapeutic agents.

## CONCLUSION

PVNS is an uncommon disease that affects the synovium and tendon sheaths. In rare cases that

demonstrate aggressive and infiltrative behaviour and those not amenable to surgery, novel targeted therapeutic agents have demonstrated favourable treatment response in some case reports and early-phase clinical trials. The early clinical results of pilot study agents targeting the CSF1/CSF1R pathway are particularly promising. In view of the rarity of the disease, however, the definitive role of targeted therapeutic agents is still not well defined. The results of ongoing clinical trials are eagerly anticipated.

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