Pigmented villonodular synovitis: Diagnostic pitfalls and management strategy

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Summary Pigmented villonodular synovitis (PVNS) is a locally aggressive synovial proliferative disorder of unknown aetiology affecting the linings of joints, tendon sheaths and bursae. The prevalence of PVNS is 1.8 patients per million population, equally affecting both genders in the third and fourth decade of life. The most commonly occurring sites are the knee, hand, hip, ankle and shoulder. PVNS represents a part of a disease spectrum that includes a localised form (giant cell tumour of the tendon sheath, GCTTS) and the more diffuse intra-articular form that is referred to as PVNS. A high index of suspicion for PVNS should be observed in cases presenting with a painless or painful swelling in the large joints of chronic duration with or without a history of trauma. Diagnostic dilemma can occur in PVNS, not only at the clinical and radiological level, but also while interpreting the histopathological findings. Complete recovery can be achieved in the majority of cases with localised disease by complete excision. Long-term follow-up is recommended for the diffuse variety because of difficulty in achieving complete excision and a high recurrence rate. External beam radiation therapy and intra-articular instillation of radioactive colloid have been described for local relapsed and residual PVNS after surgical treatment and in the very large diffuse form of PVNS where the primary operative intervention alone may leave some residual disease.

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Introduction

Pigmented villonodular synovitis (PVNS) is a locally aggressive synovial proliferative disorder of unknown aetiology affecting the linings of joints, tendon sheaths and bursae. It was first described by Chassignac1 and later on coined by Jaffe et al.2 The
most commonly occurring sites are the knee, flexor tendon sheaths of the hand and hip joint, followed by the ankle and shoulder.\textsuperscript{2-4}

There are numerous factors causing diagnostic difficulties not only at clinical and radiological levels, but also histologically in the course of PVNS. The management strategy depends on the type, site and aggressiveness of the PVNS lesion. This article is an overview of the aetiopathogenesis, diagnostic pitfalls in the clinical manifestations, radiological evaluation and histopathological interpretation, factors influencing recurrence and appropriate management strategy of patients with PVNS.

**Epidemiology**

**Prevalence**

The prevalence of PVNS is approximately 1.8 patients per million population.\textsuperscript{3}

**Age, sex and side**

PVNS most commonly affects adult patients in the third or fourth decade. There is a slight female preponderance in GCTTS, but equal sex incidence in PVNS. This condition is relatively rare in children. There is no predilection for any laterality.\textsuperscript{3-6}

**Anatomical distribution**

The condition occurs in the form of unilateral monarticular arthritis, although, can rarely be polyarticular. Almost all joints have been reported to be affected. It is most common in the knee joint. The most commonly occurring sites after the knee joint are flexor tendon sheaths of the hand, the hip joint followed by the ankle and shoulder.\textsuperscript{2-4}

**Types of PVNS**

PVNS represents a part of a disease spectrum that includes diffuse and localised forms of GCTTS, to the more diffuse intra-articular form that is referred to as PVNS.\textsuperscript{7} Granowitz and Mankin classified the entity into three categories on the basis of clinical presentation.\textsuperscript{8}

(a) Isolated, discrete lesion occurring within a tendon sheath, most often seen in the hand.
(b) Localised pigmented villonodular synovitis (LPVS), occurring most commonly in the knee and presenting most commonly with mechanical symptoms.
(c) Diffuse pigmented villonodular synovitis (DPVS), presenting with chronic oedema and pain, most commonly in the knee, hip and ankle.

It has been reported that the diffuse form is four times more common than the localised form in the knee. All three categories display similar histology including villous synovial proliferation with microscopic villi, histiocytes, foam cells and multinucleated giant cells.\textsuperscript{8} However, in the localised form, the synovial tissue does not display a reactive hyperplasia as seen in the diffuse variant.\textsuperscript{3,4}

**Aetiopathogenesis**

The aetiopathogenesis still remains uncertain. Inflammatory synovial hyperplasia, benign neoplasia of unknown aetiology, abnormality of local lipid metabolism, repetitive trauma and haemorrhage are the various hypotheses put forward to explain the possible aetiology of PVNS. The main aetiology of PVNS has been proposed to be precipitated by trauma. In 1941, Jaffe et al. originally described the lesion histologically and showed that PVNS lacked neoplastic cells. He proposed a hypervascular cellular phase subsequent to trauma produced hyalinisation and fibrosis.\textsuperscript{2} More recently, cytogenetic abnormality in the form of monoclonality and chromosomal abnormality has been described.\textsuperscript{9}

The mechanism of bone involvement in PVNS is controversial. Increased joint pressure attributable to synovial overgrowth, external compression by the tumour, erosion by lysosomal enzymes released from synovial histiocytic cells or invasion of granulation tissue through the vascular foramina are some of the proposed hypotheses put forward to explain the bony invasion in PVNS (Figs. 1–3).\textsuperscript{10,11}

**Clinical presentation**

It is insidious in onset. The patient usually presents with local discomfort and swelling of chronic duration. Patients may have mechanical symptoms in the form of locking, catching, stiffness or instability. The atypical clinical course consists of areas of erythema, stiffness and a palpable big mass. A previous history of trauma to the affected region can be found in less than 50% of patients.\textsuperscript{3,11}
GCTTS and LPVS usually present with a slow growing nodular soft tissue mass related to a tendon sheath or joint capsule. Lesions in the hand are usually painless, while lesions in the foot and ankle may be painful due to pressure effects of footwear. The factors causing diagnostic dilemma in PVNS are summarised in Table 1.

Radiological findings

Plain X-rays

Plain radiographs are usually normal in early PVNS. Additionally, the patients with radiographic changes are those with more extensive disease involving bone and at a late stage of the disease. Plain X-rays typically show a soft tissue mass or joint effusion in the early stage, whereas erosions with a sclerotic rim and subchondral lucencies in the advanced cases. Well-defined erosions with relative preservation of the joint space are noted early in the disease.12 With disease progression, joint space loss may become severe and concentric, particularly when involving joints with a limited volume capacity such as the hip.13 In the localised form of PVNS (GCT of tendon sheath) 15–25% of the patients can have erosive bony lesions, while in the diffuse PVNS, bone erosions are present in as many as 33–56% of cases.14–17

Bone scan

Isotope 99m Technetium polyphosphate scan is sensitive but non-specific. It is very difficult to distinguish between the increased uptake seen in the PVNS and other generic causes like infection, trauma and tumours. Recently, Mackie18 confirmed that increased Thallium-201 uptake was found in all cases of PVNS on early and delayed phases.

CT scan

CT scanning seems to be less accurate than MRI to observe soft tissue extension and to assess the recurrence of the lesion after excision. A soft tissue mass of high density in relation to surrounding muscle is usually seen on CT due to a high
haemosiderin content. Underlying bone erosions or cysts can be well appreciated in the CT scan.

**MRI scan**

MRI is a useful non-invasive means of diagnosis and the current investigation of choice. The MR imaging appearance of PVNS consists of multiple synovial lesions with low or intermediate signal intensity on T1-weighted and low signal intensity on T2-weighted and gradient-echo images.4,7,14 Findings on MRI are mainly attributable to the haemosiderin deposition in the affected tissues due to its magnetic susceptibility properties. In addition to the deposits of haemosiderin, the signal characteristics also reflect the histological composition of the tissue, particularly lipids and inflammatory fibrosis (Figs. 4–6).

The utility of MRI in determining the distribution of abnormal tissue is crucial in the subsequent surgical planning and decision making process.7,14,19–22 Magnetic resonance imaging is also useful for postoperative surveillance of the patients. Although very sensitive in diagnosing these lesions, the MRI appearance is non-specific, and is often confused with rheumatoid pannus or soft tissue sarcoma. The uncommon diffuse variant of GCTTS has an ill-defined appearance that may be indistinguishable from soft tissue sarcomas or the rare malignant GCTTS. Recurrent GCTTS can also
mimic soft tissue sarcoma clinically and on imaging studies.

**Histological findings**

Aspiration can be attempted in large joints with effusion. Joint aspiration usually reveals 75% blood and 25% yellow fluid. Arthroscopic or CT guided biopsy may be undertaken to obtain preoperative diagnosis and is likely to yield positive histology. Grossly, PVNS may be nodular or globular yellowish villous growths associated with synovial membranes. Microscopic findings include haemosiderin deposits both intracellular and intracellular, foamy histiocytes, giant cells and large synovial cells. Osteoids and few mitotic figures can be seen. Malignant transformation, fortunately rare, has also been described in the literature.

**Differential diagnosis**

The main differential diagnosis is rheumatoid arthritis. Unlike PVNS, rheumatoid arthritis tends to affect multiple joints. Contrary to PVNS, ganglion cyst, sebaceous/inclusion cyst, lipoma, post-traumatic loose body in the large joints, haemangioma, nerve sheath tumour, foreign body granuloma and the majority of synovial sarcomas typically display high intensity signals on MRI. Some soft tissue sarcomas like malignant fibrous histiocytoma, fibromatosis, xanthoma, Morton’s neuroma, “burnt out” rheumatoid pannus, amyloidosis, tophaceous gout and synovial osteochondromatosis can have similar low/intermediate intensity signals on MRI as seen in PVNS. Appropriate histological assessment is crucial in differentiating these lesions from PVNS. Haemophilia, haemochromatosis, haemosiderosis and haemorrhagic synovitis also demonstrate haemosiderin deposits on histological sections; however, the pigment is largely confined to the synovial cells and macrophages in all of these conditions, whereas the distribution in PVNS is more diffuse (both intra- and extra-cellular). Giant cells and histiocytes seen in PVNS are not classically seen in the other three conditions.

**Treatment**

A combination of clinical, radiographic and histological correlation is necessary to make the diagnosis with certainty. Clinical correlation in these cases is utilised to differentiate between
these different pathologic disease processes. Aggressive forms of the disease should be closely observed, and managed by appropriate investigations and treatment planning to obtain optimal outcome. Total synovectomy (open or arthroscopic) is required for the diffuse form (recurrence common), local excision for the nodular form (recurrence rare) and radiotherapy has been used in the management of recurrent and residual lesions with varying success.

**Surgery**

Surgical excision is the treatment of choice for localised GCTTS and diffuse PVNS. In localised disease, wide excision usually minimises the chances of local recurrence but recurrence is common if excision is inadequate. In diffuse disease, total synovectomy has a much lower recurrence rate than partial synovectomy and is the preferred treatment of choice.24 To ensure complete excision of the abnormal mass and the affected surrounding tissues, an open procedure on both sides of the joint should be performed. Aggressive control of the disease should be contemplated as early as possible. Complete excision may sometimes be limited by the proximity of the neurovascular bundle.

Arthroscopy is an effective tool for both diagnosis and treatment of PVNS. Arthroscopy is the treatment of choice for localised forms. Arthroscopic synovectomy may be indicated for the inactive form of diffuse disease. Open complete synovectomy is the preferred treatment for diffuse forms of PVNS. Incomplete removal most likely results in recurrence of the lesion.11

Subsequent consideration for arthrodesis or arthroplasty of the affected joint for secondary osteoarthritis should be well explained to the patients during the consenting process. The bone destruction caused by PVNS may be extensive and this can necessitate joint reconstruction (particularly when the hip or the knee is involved). If PVNS is seen as an incidental finding, it should not affect the decision to proceed with a preplanned reconstructive procedure.

**Radiotherapy**

Two types of radiotherapy in the form of external beam radiation therapy and intra-articular instillation of radioactive colloids have been described in the literature. The radiation therapy is indicated for local relapsed and residual PVNS after surgical treatment and in the very large diffuse form of PVNS where the primary operative intervention alone may leave some residual disease. Synoviorthesis with Yttrium-90 seems to be a good adjuvant for the treatment of recurrent PVNS.25 The risk of periarticular fibrosis and more sinister complication in the form of radiation-induced sarcoma after radiotherapy has been reported in the literature.9 In addition, growth arrest may occur in skeletally immature patients. Blanco et al. presented the results of combined partial arthroscopic synovectomy and low-dose radiation therapy in the treatment of diffuse PVNS of the knee.26 The authors conducted a prospective study of the treatment of 22 patients with clinical, ultrasonic and histologically confirmed findings of diffuse PVNS of the knee. They found that combination therapy was effective in reducing symptoms of pain and oedema, and in improving overall function of patients. Three had clinically and ultrasonically confirmed recurrence of disease and were treated with repeat arthroscopic synovectomy without harmful effects from radiotherapy.26

**Recurrence**

Recurrent tumours are more tissue destructive and more invasive. Recurrence is documented as high as 30% in the previously published literature.4,27 Recurrence is more common in diffuse variants treated with intralesional primary treatment with incomplete synovectomy.

Delay in diagnosis, delay in instituting treatment, intralesional primary treatment and intraoperative hesitation in thoroughly debriding the lytic lesions from the articular surface can lead to recurrence. Recurrences may be re-excised or may be treated with radiotherapy alone or combined radiotherapy and surgery. Amputation has been suggested for widespread recurrent 'hard to control' disease.28 Joint arthrodesis may be considered when there are associated degenerative bone changes.29 At follow-up, clinical examination with plain X-rays should suffice, although MRI scan is helpful and recommended in symptomatic postoperative patients. Table 2 summarises the factors influencing recurrence of PVNS.

**Conclusion**

In conclusion, a high index of suspicion for PVNS is required for cases presenting with a painless or painful mass in the large joints of chronic duration. Complete recovery can be achieved in the majority
of cases with localised disease by complete excision of the lesion. Delay in diagnosis, delay in instituting treatment, intralesional primary treatment and intraoperative hesitation in thoroughly debriding the lytic lesions from the articular surface can lead to residual disease and possibly recurrence later on. Diffuse intra-articular disease in young people remains a difficult problem.

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Practice points

- Monarticular synovial swelling, most common site is the knee, but other joints affected include hip, ankle and shoulder
- Most commonly in the third and fourth decades with no sex predilection
- Intra-articular PVNS tends to be of the diffuse form, while tendon sheath PVNS is the nodular form
- MRI is the current imaging technique of choice
- Aspiration of the joint will characteristically reveal a blood tinged/haemorrhagic, dark brown aspirate. Synovial biopsy should be performed if there is any doubt
- Microscopic findings include haemosiderin deposits, foamy histiocytes, giant cells and large synovial cells
- A combination of clinical, radiological and histological correlation is necessary to make the diagnosis with certainty
- Early diagnosis and aggressive surgical treatment is recommended

Table 2 Summary of the factors influencing recurrence of the pigmented villonodular synovitis.

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<th>Factor</th>
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<td>Delay in diagnosis</td>
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<td>Intralesional primary treatment</td>
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<td>Intraoperative hesitation in thoroughly debriding the lytic lesions from the articular surface.</td>
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<td>Arthroscopic treatment for diffuse form of PVNS affecting large joints.</td>
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Research directions

- A prospective determination of the factors responsible for recurrence in the diffuse variety of PVNS
- Further research is needed to determine the aetiopathogenesis of aggressive forms of PVNS
- More research efforts are needed for primary prevention of the disease

References

14. Harris O, Ritchie DA, Maginnis R, Lamb GR, Hellwell T, Jane M, Davies AM. MRI of giant cell tumour of tendon sheath and