Update Article

Diffuse pigmented villonodular synovitis in knee joint: diagnosis and treatment

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ABSTRACT

Pigmented villonodular synovitis is a rare proliferative condition of the synovium. Although the condition can present in any joint, the knee is the most commonly affected site. Despite being a benign condition, pigmented villonodular synovitis is often aggressive, with marked extra-articular extension in some cases. Monoarticular involvement occurs in two forms: localized and diffuse. The latter is more common, with a high recurrence rate. There is no standard method of management of this lesion. Open surgery is a classical and effective method for treatment. Arthroscopic synovectomy, however, has gained popularity, and has several advantages over the open technique particularly in exclusively articular cases. The combined approach is suggested in cases with extra-articular involvement. Synovectomy through any approach may prevent secondary osteoarthritis and subsequent joint arthroplasty. Internal irradiation or external beam radiation as an adjuvant treatment to surgical synovectomy appears to decrease the rate of local recurrence in diffuse cases. The authors observed a great heterogeneity in reporting of functional results, and specific conclusions should not be drawn. Each patient should be managed in accordance with his/her particular condition.

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Palavras-chave:
Sinovite pigmentada vilonodular
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Radioterapia

Sinovite vilonodular pigmentada difusa no joelho: diagnóstico e tratamento

R E S U M O
A sinovite vilonodular pigmentada é uma rara condição proliferativa da membrana sinovial. Apesar de a doença poder estar presente em qualquer articulação, o joelho é o local mais frequentemente afetado. Ainda que doença benigna, geralmente tem comportamento agressivo, pode ter extensão extra-articular em alguns casos. O acometimento monoarticular ocorre em duas formas: localizada ou difusa. A forma difusa é mais comum e tem alta taxa de recorrência. Não há método padronizado para o manejo dessa lesão. O tratamento cirúrgico aberto é o método clássico e efetivo. A sinovectomia artroscópica, entretanto, tem ganho popularidade e tem diversas vantagens sobre a técnica aberta, principalmente em casos exclusivamente articulares. A abordagem combinada é sugerida em casos com envolvimento extra-articular. A sinovectomia pode prevenir a osteoartrite secundária e o subsequente tratamento reconstrutivo. A radioterapia usada como tratamento adjuvante à sinovectomia parece diminuir a taxa de recorrência local na forma difusa da doença. Os autores encontraram grande heterogeneidade na forma como os resultados funcionais foram reportados e não se deve chegar a conclusões específicas. Cada paciente deve ser manejado de acordo com suas particularidades.

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Introduction

Pigmented vilonodular synovitis (PVNS) is a rare proliferative process that affects the synovial joints, tendon sheaths, and bursas. In 1852, Chassaing vat reported the first case of a lesion in the flexor tendon sheath of the second and third fingers; this was subsequently reported in other joints. In 1941, Jaffe et al. coined the term “pigmented vilonodular synovitis”; subsequently, Granowitz et al. expanded the terminology, distinguishing the localized (LPVNS) and diffuse (DPVNS) forms from other synovial lesions. Recently, the World Health Organization has defined PVNS and giant cell tumor to be equivalent terms.

The estimated incidence of PVNS ranges around 1.8 per million. It is usually monoarticular, affecting large joints. The knee is the most affected site (28%–70%), but cases in the hip, ankle, shoulder, and elbow are often observed. The disease presents in two forms, localized or diffuse, and both types have similar appearance: a synovial membrane characterized by inflammation and presence of hemosiderin deposits. Microscopically, it is characterized by the presence of lipid-laden macrophages, multinucleated giant cells, hemosiderin deposits, and proliferation of fibroblasts and stromal cells. LPVNS is characterized by discrete or pedunculated nodular lesions. In turn, DPVNS is the most common presentation, involving intra-articular tissues; it may have extra-articular extension, behaving as a chronic process.

In the last 100 years, little progress has been made regarding treatment. The goal of PVNS treatment is to remove all synovial tissue in order to relieve pain, decrease the risk of joint destruction, and prevent local recurrence. Several treatment options have been proposed for this disease in cases of genicular involvement, ranging from observation and radical local surgery to total knee arthroplasty (Fig. 1).

Etiology and pathophysiology

The etiology of PVNS is still unknown. Some authors suggest that the disease occurs as a result of baseline trauma and subsequent bleeding in the affected joint. This theory is supported by the fact that patients with hemophilia present progressive destruction of the cartilage during the natural course of the disease. However, studies that produced PVNS-like histological findings by injecting iron or blood into the joint were unable to replicate the classic lipid-laden histiocytes and giant cells. However, most studies reported a history of trauma in less than one-third of patients. Abnormal metabolic activity has also been indicated as an adjuvant event in the inflammation observed in PVNS, but this is an inconsistent finding. There are also reports in the literature that PVNS may be a neoplastic process. Several authors suggested the presence of chromosome 7 trisomy and clonal rearrangements as a cause. Some reports, albeit rare, indicate the occurrence of malignant transformation and metastases in patients initially diagnosed with PVNS. Despite the case reports of malignant PVNS and aneuploidy, there is evidence against the theory that PVNS is a neoplastic process. In their analysis, Oehler et al. observed a strong evidence of chronic inflammation. Their findings were based on the presence of a cellular marker of inflammation with a heterogeneous population of mononuclear cells. They also postulated that the presence of large amounts of iron in the lesion would stimulate synoviocytes and fibroblasts to develop macrophage-like characteristics.

Histologically, LPVNS and DPVNS are similar. However, they differ in clinical presentation, prognosis, and response to treatment. In the knee, LPVNS is more frequently observed in the anterior compartment. Flandry et al. reported that most lesions begin in the meniscocapsular junction. The most
common site of involvement is the synovium in the anterior horn region of the medial meniscus. Patients with lesions in this location may present signs and symptoms suggestive of meniscal disease. If left untreated, LPVNS may cause pain and discomfort and limit the patient’s activities and functions. No studies have assessed the long-term outcomes in patients with untreated LPVNS, probably due to the low rate of recurrence and the fact that they are easily treated, or even due to the large proportion of asymptomatic patients. Many authors agree that the marginal excision of the lesion results in good or excellent results, especially if treated early.

DPVNS is characterized by the involvement of almost the entire synovial tissue in the knee. Edema and pain are more significant than in LPVNS, and are generally poorly localized. DPVNS tends to be more destructive and consequently have a worse prognosis; it may present extra-articular extension at the time of the primary diagnosis or in cases of recurrence. Extra-articular lesions may also involve neurovascular structures, making surgical resection more challenging and hindering complete excision. Despite treatment, the recurrence rate is high, reaching around 46%.5,7,21

**Clinical presentation**

PVNS is typically a monoarticular process that usually affects large joints. PVNS generally affects patients in the third and fourth decade of life. Historically, it was believed that this condition was more common in males, but recent studies indicated no gender preference.6 Its clinical course is a slow and insidious onset of pain, swelling, and stiffness in the involved joint. Diagnosis is often delayed or confused with initial osteoarthritis, rheumatoid arthritis, and meniscal or ligamentous injury. In both DPVNS and LPVNS, symptoms are usually intermittent.4,12,19,20,30–36

**Diagnosis**

The diagnosis of DPVNS is not always obvious. In the studies by Flandry et al.,19 only 17% of patients were correctly diagnosed before referral.24 Several imaging modalities are needed to rule out other conditions and establish the diagnosis. Synovial fluid can be collected and analyzed by arthrocentesis (Table 1).33–36 Other specific diagnoses should be ruled out. DPVNS demonstrates normal viscosity with varied bleeding

**Table 1 – Classification of the synovial fluid of the knee.**

|                  | Normal | Non-inflammatory | Inflammatory | Infectious | Hemorrhagic |
|------------------|--------|-----------------|--------------|------------|-------------|
| Volume (mL)      | <3.5   | >3.5            | >3.5         | >3.5       | >3.5        |
| Viscosity        | High   | High            | Low          | Variable   | Low         |
| Color            | Light, colorless | Light yellowish | Yellowish    | Variable (opaque) | Red         |
| Leuc (mm³)       | <200   | <2000           | 5000–75,000  | >50,000    | Similar blood level |
| Pol (%)          | <25    | <25             | 50–70        | >70        | Similar blood level |
| Gram             | Negative | Negative       | Negative     | Often +    | Negative    |

Observation: DPVS has characteristics of the hemorrhagic group, however with normal viscosity.
patterns, and radiographs can be useful (Fig. 2), as they may show periarticular erosions with a thin layer of reactive bone. The late radiographic finding of joint space narrowing indicates loss of articular cartilage, which may be difficult to differentiate from primary osteoarthritis. Radiographic findings can be observed in up to 30% of patients.\textsuperscript{4,19,20} More recently, magnetic resonance imaging (MRI) has become the imaging modality of choice for diagnosing DPVNS.\textsuperscript{25} This is a non-invasive examination with high accuracy; furthermore, it assesses the extent of the disease and distinguishes between the diffuse and localized variants. The high hemosiderin content causes the lesion to have an irregular or extensive aspect, with low signal in the T1- and T2-weighted images. Both LPVNS and DPVNS may present with joint effusion. In DPVNS, there is a poorly localized mass or synovial thickening with varying degrees of periarticular erosion. Classically, it

**Fig. 2** – Knee radiograph of a diffuse pigmented villonodular synovitis of the knee in (A) antero-posterior and (B) profile, evidencing areas of bone destruction.

**Fig. 3** – Magnetic resonance imaging of a knee with diffuse pigmented villonodular synovitis of the knee. A and B, coronal cut in T1; C, sagittal section in T1; D, T1 axial cut with areas of diffuse synovitis with tibial and femoral bone invasion, resulting in significant joint destruction.
is described as “dark on dark” on T1 and T2 images, but initial lesions with less hemosiderin may have a high signal on T2 sequences (Fig. 3). 

**Treatment of DPVNS**

Historically, non-surgical procedures were the treatment of choice for DPVNS, and led to high rates of recurrence. However, advances in surgical techniques and postoperative care have considerably reduced the frequency of recurrence and complications, making surgical treatment the first choice in most patients.  

**Non-surgical**

The high rates of recurrence and complications associated with DPVNS management led early investigators to advocate observation until total arthroplasty became necessary. Recurrent cases diagnosed on imaging tests, but without progressive synovitis, may not require a new synovectomy. However, such patients should be followed-up more closely.  

Radiotherapy may be indicated in cases where total synovectomy and complete resection of extra-articular lesions cannot be performed, although some studies have discussed the long-term results of this strategy when applied in isolation.

**Surgical treatment**

Many treatment options have been described for DPVNS of the knee. However, total synovectomy is considered the basis of treatment to prevent local recurrence. No specific conclusions should be drawn as to which technique should be used, and each patient should be managed according to their particular case (Fig. 4).

**Arthroscopic approach**

For many years, total synovectomy was performed by open surgery; since 1990, arthroscopy has been the most widely used method. Although arthroscopy has gained considerable support as a technique for treating LPVNS, its role in the management of DPVNS cases remains debatable. In
DPVNS, the anterior compartment is typically involved and requires greater technical care from the surgeon, making complementary portals to the traditional portals made anteriorly, and using 30° and 70° arthroscopes. Patients with large masses in the popliteal fossa or extra-articular involvement generally are not candidates for exclusively arthroscopic approach. Arthroscopic treatment should be reserved for patients with limited, purely intra-articular disease. Disease assessment and choice of best treatment should be made with MRI before the definitive resection. If the arthroscopic approach is selected, a complete synovectomy, including the posterior compartments, should be performed in order to minimize the risk of recurrence.

Two similar-sized groups of patients were identified in the review by Auregan et al.: local recurrences were observed in 28 of 124 patients (23%) in the open surgery group and in twenty of 124 (16%) in the group that underwent arthroscopic surgery, in mean follow-up periods of six and five years, respectively. The lower recurrence rate in the arthroscopic group can be explained by the shorter follow-up period in this group. Nonetheless, a higher rate of postoperative complications was reported in the group that underwent open total synovectomy when compared with the group submitted to arthroscopy. Functional scores appear to be better in the arthroscopic group; however, as discussed earlier, no convincing conclusion can be drawn. This study concluded that posterior open treatment, together with anterior arthroscopic synovectomy, is a viable approach for DPVNS of the knee, with low recurrence rates and few postoperative complications. Based on these results, the arthroscopic approach for arthroscopic synovectomy is recommended whenever technically possible. Colman et al. reported 48 cases of patients treated using the arthroscopic, posterior open with anterior arthroscopic, or anterior open and posterior open synovectomy techniques. Recurrence rates were lower in the open/arthroscopic group when compared with the arthroscopic or with the open/open groups: 9% vs. 62% vs. 64%, respectively. Osteoarthrosis progression was observed in 17% of the total of patients, 8% of whom underwent total knee arthroplasty during the follow-up period.

Although arthroscopy is a less invasive procedure, it is not free of potential complications. In addition to the risk of recurrence, arthroscopic excision presents the theoretical risk of joint tumor dispersion and portal contamination. A failed arthroscopic approach may cause extensive joint involvement and extra-articular dissemination.

Open approach

The open approach followed by complete synovectomy is the standard surgical treatment for DPVNS of the knee. Patients with extensive extra-articular involvement and large masses in the popliteal fossa clearly are not suitable candidates for arthroscopic synovectomy. Moreover, open procedures should be considered for patients with disease in hard-to-reach places, such as the popliteal tendon sheath, between the gastrocnemius heads, and within the semimembranous bursa. Open treatment begins with an anterior approach, arthroscopy, and aggressive anterior synovectomy, followed by an S-shaped posterior approach, protecting the neurovascular structures. Subsequently, joint and extra-articular exploration should be conducted in order to avoid any remaining tumor tissue.

Old studies assessing open treatment reported excessively high rates of recurrence. Nonetheless, in these studies recurrence probably indicated incomplete excisions of the lesions and likely referred to inadequate surgical exposure. Flandry et al. reported a series of 25 knees with biopsy and proven DPVNS that were treated by double open approach. The authors reported a recurrence rate of 8% in a follow-up of 58 months.

Open treatment, however, is not free of risks and complications. Compared with the arthroscopic procedure, open synovectomy is associated with longer hospital stay and longer rehabilitation period. One of the main criticisms of the open procedure is postoperative stiffness, which often requires manipulation under anesthesia. In the study by Flandry et al., the rate of postoperative stiffness was 24%. Therefore, many experts advocate the use of less invasive and less aggressive procedures.

Combined open and arthroscopic approach

The combination of open and arthroscopic approach has not been well described in the literature. Patients with posterior involvement associated with minimal anterior involvement may benefit from anterior arthroscopic synovectomy combined with posterior open synovectomy. Another suitable scenario for the combined approach is in cases in which total synovectomy by arthroscopic approach alone is impossible. In this scenario, several authors suggest a combination of anterior arthroscopic synovectomy and open posterior synovectomy. Moreover, arthroscopy may play an important role in the pre- and postoperative diagnosis, as well as in the treatment of residual disease after open surgery. De Carvalho et al. reported that patients diagnosed with DPVNS treated with partial arthroscopic synovectomy combined with anterior open synovectomy presented a recurrence rate of 12.5% in a mean follow-up of 8.6 years; no major complications were observed during follow-up.

Adjuvant radiotherapy

Radiotherapy has been used for many years as an alternative to surgical synovectomy in patients with nonspecific synovitis. Radiation-induced synovectomy in the treatment of DPVNS has been increasingly discussed, but with conflicting results. From 1950 onwards, good results have been reported with the use of adjuvant external radiation in the management of recurrent DPVNS. Potential complications are associated with external radiation, including skin reactions, poor wound healing, joint stiffness, and neoplastic transformation.

De Carvalho et al. assessed patients diagnosed with DPVNS treated with partial arthroscopic synovectomy combined with anterior open synovectomy followed by adjuvant radiotherapy (2000 cGy). No cases of major postoperative complications or radiotherapy-related side effects were observed. No progression to arthritis was detected. Recurrence was observed in only one patient (12.5%), in a mean follow-up
period of 8.6 years.\textsuperscript{14} Blanco et al.\textsuperscript{29} described 22 patients with knee DPVNS treated with arthroscopic synovectomy combined with postoperative external radiotherapy (total dose of 2600 cGy). The recurrence rate was 13.62%; these patients underwent a second surgical procedure. Ustinova et al.\textsuperscript{31} described their experience with 24 patients with DPVNS. Radiation (in two doses, one of 1.2–1.5 cGy in five fractions and a focal dose of 16–20 cGy) was applied, since the affected synovial tissue had not been completely removed during surgery. No recurrences were observed in the follow-up period, which ranged from six months to six years, and occupational rehabilitation was achieved in 87.5% of the patients.\textsuperscript{31} O’Sullivan et al.\textsuperscript{22} also reported the cases of 14 patients with intra- and extra-articular lesions who received adjuvant radiation. Those authors concluded that after DPVNS removal, the use of moderate external radiation was very effective in preventing recurrence, avoiding amputation in advanced cases and preserving limb function.

Local radiotherapy can also be applied with intra-articular radioisotope injection. Chin et al.\textsuperscript{31} assessed a large number of patients (n = 40) with DPVNS, each subjected to either open or arthroscopic surgery, but who presented recurrence. The number of residual lesions in the groups treated with radiotherapy was lower than in the untreated group. Shabat et al., in a mean follow-up of six years, assessed ten patients with DPVNS who underwent one or more partial synovectomies and received intra-articular injection of yttrium isotope (90Y; 15–25 mCi) between six and eight weeks after the last surgery. In nine patients, no evidence of recurrence was observed during follow-up, whereas in one patient the disease stabilized.\textsuperscript{32}

Final considerations

DPVNS of the knee is a rare condition in which treatment may be associated with a significant risk of local recurrence, postoperative complications, and functional limitations. Regarding local recurrence, there was no difference in the literature between open or arthroscopic total synovectomy for the treatment of DPVNS. However, a lower rate of complications was reported after arthroscopic synovectomy. Incomplete synovectomy for the treatment of DPVNS should not be performed in isolation, due to the high risk of recurrence. Internal or external radiation as an adjuvant treatment method to surgical synovectomy appears to decrease the rate of local recurrence in cases of DPVNS. Cases of DPVNS with extra-articular involvement should be treated with total synovectomy, open excision of extra-articular lesions, and adjuvant radiotherapy treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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