*LETTER TO THE EDITOR*

# LOCALIZED PIGMENTED VILLONODULAR SYNOVITIS OF THE ANTERIOR CRUCIATE LIGAMENT OF THE KNEE: AN EXCEPTIONAL PRESENTATION OF A RARE DISEASE WITH NEOPLASTIC AND INFLAMMATORY FEATURES

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**Pigmented villonodular synovitis (PVNS) is a rare condition, most commonly involving the knee joint. PVNS is locally aggressive and can invade and destroy surrounding soft tissue and bone, leading to anatomical and functional deterioration of the affected joint. Localized PVNS is an unusual presentation of the disease, generally consisting of a nodular lesion protruding into the articular cavity. Localized PVNS of the knee can mimic other joint disorders which may pose a challenge for a correct diagnosis. Given the locally aggressive behavior of PVNS, prompt identification and excision of the lesion are instrumental to avoid complications. Here, we report a rare case of localized cystic PVNS involving the anterior cruciate ligament of the knee in a 32-year-old woman with persistent knee pain, in whom magnetic resonance imaging was inconclusive. The diagnosis was achieved via arthroscopy and histology. We also present a concise review of the literature on this pathological entity as well as a discussion on the differential diagnosis between localized PVNS and other intra-articular cystic lesions.**

Intra-articular cystic lesions associated with the anterior cruciate ligament (ACL) of the knee are uncommon (1). These lesions are often asymptomatic or oligosymptomatic and usually represent incidental findings (1). The common tendency is to consider these cysts as "ganglia" and to treat them only if symptomatic. However, are all intra-articular knee cysts associated with the ACL ganglia? And also, is magnetic resonance imaging (MRI) always adequate for a correct characterization of such lesions? Here, we report a unique case of localized, cystic pigmented villonodular synovitis (PVNS) arising from the ACL in a 32-year-old woman with persistent knee pain. MRI findings were elusive, and arthroscopy was performed to excise the lesion. Macroscopically, the mass exhibited the typical appearance of PVNS. Histological examination of the surgical specimen confirmed the diagnosis of PNVS.

After the case description, a concise review of the literature on the nature of PVNS is presented along with a brief discussion about the differential diagnosis between this pathological entity and other intra-articular cystic masses.

*Case presentation*

A 32-year-old woman presented at the outpatient clinic of our Department of Orthopaedics and Traumatology with persistent right knee pain in the absence of past relevant traumatic events. Symptoms had begun one year before and were exacerbated by activities such as stair climbing or driving a car. Physical examination revealed no

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swelling of the knee and a normal range of motion (ROM) of the joint, with pain evoked by flexion over 90°. The knee was stable at conventional clinical tests, including the Lachman test, pivot shift, anterior and posterior drawer and varus and valgus stress tests. The McMurray and Apley tests were also negative, excluding the presence of meniscal lesions. Standard radiographic examination of the knee was unremarkable, whilst the MRI revealed the presence of a cystic lesion associated with the ACL (Fig. 1, a-d). The lesion was 32 x 15 mm in size and presented high signal intensity on T2-weighted images and low signal intensity on T1-weighted images. The mass occupied the posterior aspect of the intercondylar notch. Arthroscopy was performed using an anterolateral portal for the arthroscope and an anteromedial portal for the surgical instruments. After inserting the arthroscope through the intercondylar notch, it was possible to visualize a synovial lesion lying posteromedially to the ACL (Fig. 2a). Following the removal of the thin layer of synovial membrane covering the ACL, the lesion appeared as a solid mass (Fig. 2b). The macroscopic appearance of the mass suggested the presence of a localized form of PVNS, which was confirmed by the biopsy. Complete excision of the lesion was performed by means of a motorized blade (shaver) (Fig. 2c). No further intra-articular lesions were detected.

Histological examination of the lesion documented a localized form of PNVS, characterized by a fibrous stroma, with presence of histiocytic and spindle cells, irregularly-shaped multinucleated giant cells, and hemosiderin deposition (Fig. 3). The postoperative period was uncomplicated and the patient was able to resume her usual daily activities

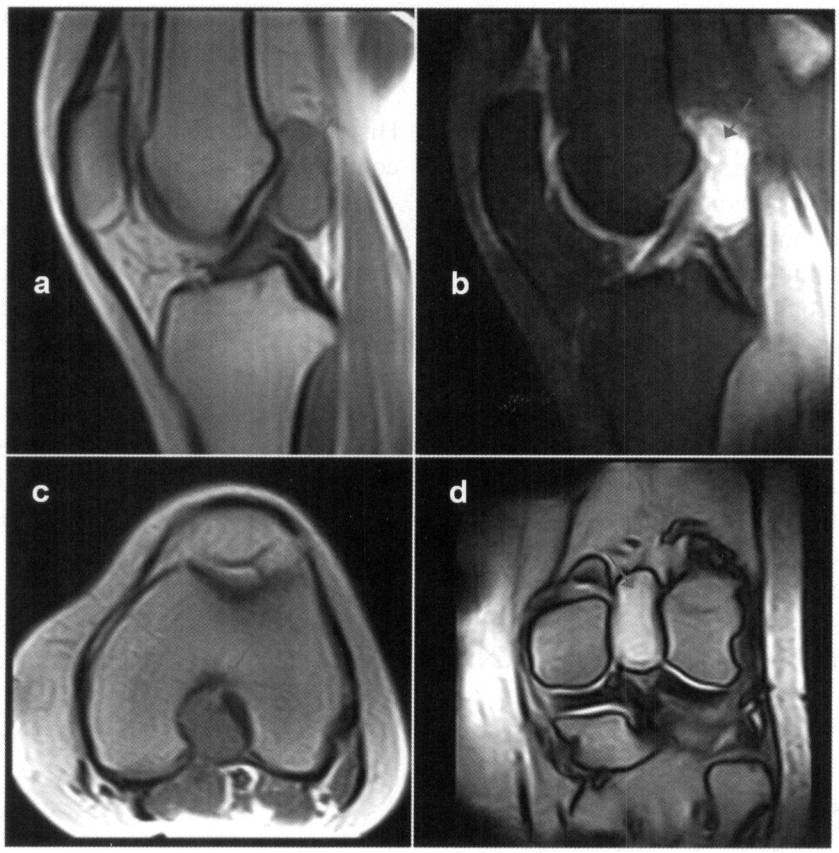


**Fig. 1.** ***a)*** *Sagittal T1- and T2-weighted MRI* ***(b)*** *showing a defined mass, with cystic appearance, localized in the posterior aspect of the ACL.* ***c)*** *Transverse and coronal views* ***(d)*** *showing a mass occupying the intercondylar notch with posterior extension. No other lesions are evident.*

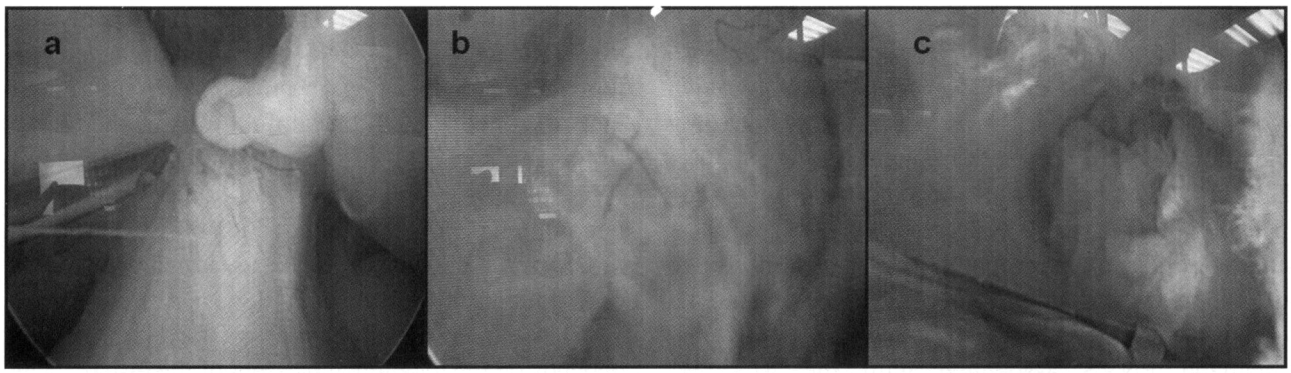


**Fig. 2.** ***a)*** *Arthroscopic view of the intercondylar notch showing a mass adjacent to the posterior aspect of the ACL.* ***b)*** *Detailed arthroscopic view of the mass prior to the biopsy suggestive of PVNS.* ***c)*** *The bioptic excision confirmed the solid nature of the lesion with the typical macroscopic resemblance of PVNS.*

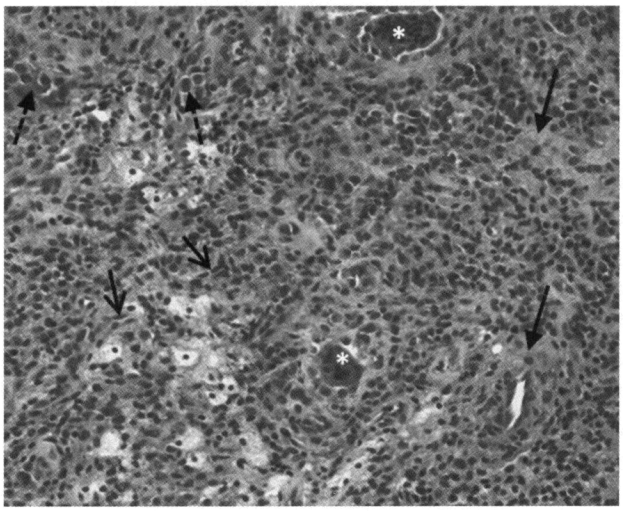

**Fig. 3.** *Histology confirmed the diagnosis of PVNS. Hematoxylin and eosin stain shows a fibrous stroma (arrows), with presence of histiocytes (dashed arrows), spindle cells (open arrows), and irregularly shaped multinucleated giant cells (asterisk).*

within the following 3 weeks. At 5-month follow-up, the patient was asymptomatic with no signs of recurrence (Fig. 4, a-b).

## DISCUSSION

PNVS is an uncommon disease, with an annual incidence of 1.8 cases per million persons (2). The lesion can affect the entire synovium (diffuse PVNS)

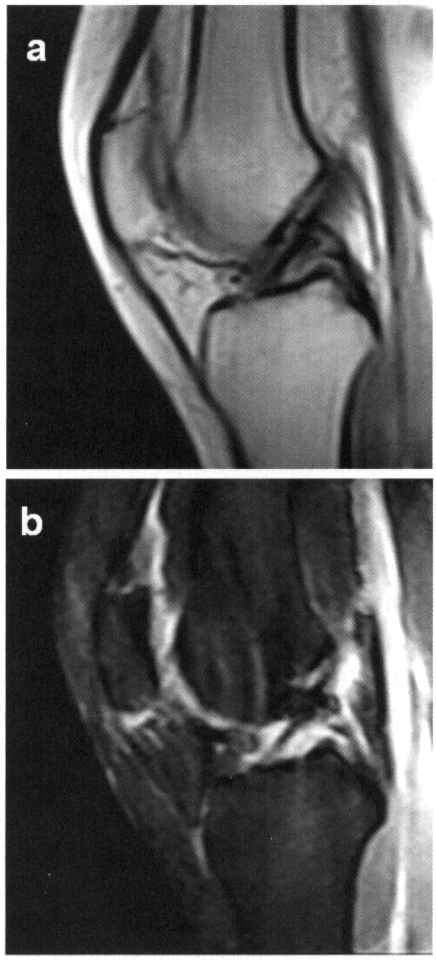


**Fig. 4.** ***a)*** *T1- and T2-weighted sagittal MRI* ***(b)*** *showing the complete excision of the lesion with no signs of recurrence at 5-month follow-up.*

or present as a discrete mass (localized PVNS). Both forms con arise from intra-articular or extra-articular synovial tissues (3). PVNS may involve any synovial joint; however, large joints (i.e., knee, hip and shoulder) are the most frequently affected (4). The axial skeleton is only exceptionally involved (5). Localized knee PVNS generally consists of a single nodular mass, often pedunculated, protruding into the joint cavity (6). Bilateral knee involvement, although extremely rare, has been described (7). Localized PNVS associated with the ACL is exceptional, and to our knowledge, only one other case has been previously reported (8).

The etiology of PVNS is unclear. Chronic inflammation, traumatisms, hemarthrosis, and chromosomal disorders have been invoked as possible causes (9). At present, there is no consensus as to whether PVNS should be considered an inflammatory or neoplastic disease. Indeed, both hypotheses may be correct. Synovial cells positive for either macrophage (CD68/CD163) or fibroblast markers (h4Ph/CD55) as well as double-labeled cells have been detected in both rheumatoid arthritis (RA) and PVNS patients (10). In addition, West et al. (11) found that cell proliferation in PVNS was maintained by a tumor landscaping effect triggered by the clonal expansion of cells expressing the macrophage colony-stimulating factor (M-CSF or CSF1). Such aberrant expression usually results from a balanced translocation involving the collagen 6A3 gene on chromosome 2q35 and the CSF1 gene on chromosome 1p13 (11). The translocation is absent in about one-third of patients with PVNS (12). CSF1 overexpression in translocation-negative cases suggests that other mechanisms can lead to aberrant CSF1 up-regulation. In PVNS, CSF1 is expressed by a small percentage of intralesional cells (2-16%), whereas the majority expresses the CSF1 receptor (11). This implies that most cells are reactive and proliferate as a consequence of CSF1 production by neoplastic cells (12). It is worth noting that CSF1 is also implicated in the formation of osteoclast-like giant cells and bone resorption in RA (13). Indeed, CSF1 overproduction has been detected in the synovium of RA patients as well as in cases of chronic reactive synovitides of various nature (12). However, in such cases, CSF1 expression is limited to synovial lining cells, whereas in PVNS CSF1 is expressed throughout the lesion (12). Notably, an association between PVNS of the hip and systemic lupus erythematosus has been reported, suggesting that the two conditions might share the same triggers of synovial overgrowth (14). Recurrence of PVNS after surgical excision, although reported, is uncommon (6, 15). Imatinib, which blocks the action of CSF1, has shown some efficacy in relapsing cases or in patients with diffuse PVNS (16, 17).

The clinical presentation of localized PVNS depends on the location and extent of the disease. The onset is typically insidious and the progression slow. Swelling and mechanical symptoms such as locking, giving way and catching, dominate the scene (4). Mild to moderate joint pain can also be present, as was observed in our case. Metastatic dissemination has never been reported, supporting the benign nature of the disease. However, PVNS can be locally aggressive, due to the invasive and destructive proliferation of synovial tissue. Complete joint destruction may occur in severe cases of diffuse PVNS (4).

Because the clinical presentation of PVNS is nonspecific, the diagnosis may be considerably delayed. The differential diagnosis includes ganglion cysts, loculated effusion and other synovial proliferative disorders such as chondromatosis, hemangiomas and sarcomas (18). These conditions, albeit uncommon, present easily recognizable MRI patterns. The main challenge in the differential diagnosis of PNVS associated with the ACL is to distinguish it from a ganglion cyst. The latter is a benign, rare condition, characterized by a cystic mass with mixoid matrix that occurs within muscles, tendon and menisci, and occasionally affects the cruciate ligaments of the knee (19). The MRI incidence of ganglion cysts of the knee ranges between 0.29 and 0.49% (20, 21), and equals 0.54% in a review of 6,500 arthroscopic examinations (22). Similar to localized articular PVNS, ganglia cause mechanical symptoms, such as locking or limited ROM, depending on their anatomical location, and mild localized pain, which is usually intermittent and worsens with weight-bearing (1, 23, 24). MRI is considered to be the most sensitive and specific method for indentifying localized PVNS and ganglion cystic masses and defining their size and location (1, 23-25). Ganglion cysts usually display a homogeneous low signal intensity on T1- and a

high signal intensity on T2-weighted images (1). Likewise, MRI features of localized PVNS are relatively specific, with decreased signal intensity on T1- and T2-weigthed images, and low T1 and T2 signal areas within the lesion, corresponding to hemosiderin deposits (26). Noteworthy, both in our case and in that reported by Otsuka et al. (8), the MRI appearance was different from the typical pattern of PVNS (26), resembling more a ganglion cyst. Hence, in cases of localized PVNS associated with the ACL, a correct differential diagnosis may not be achievable via MRI, and arthroscopic excision is necessary in case of persistent pain or radiographic signs of bone changes typical of PNVS, including cyst formation or cortical erosions (27). Similarly, in all cases of suspected PVNS, patients should be directed to arthroscopy, since underestimation of such lesions could lead to a delay in diagnosis and definitive treatment. Treatment of intra-articular PNVS should always be surgical. Due to its minimally invasive nature, arthroscopic excision is the treatment of choice, at least initially (28).

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