The role of medical therapy in refractory pigmented villonodular synovitis

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Dear Editor,

Pigmented villonodular synovitis (PVNS) is a rare benign condition characterized by synovial proliferation in a joint that affects mostly young adults and is usually monoarticular, with the knee being the most frequently involved joint[1].

The etiology is unclear but a specific translocation involving the colony stimulating factor 1 (CSF-1) and the collagen 6A3 genes has been identified in PVNS cells[2]. The most common symptoms are pain, joint effusion and swelling, with thickening of the synovium being a frequent feature in the histologic examination as well as the presence of lymphocytes, multinucleated giant cells and xanthoma cells. The synovium usually appears brownish due to hemosiderin deposition[3].

Magnetic resonance imaging (MRI) is the gold standard imaging technique with characteristic findings: on T1- and T2-weighted images the synovial mass displays low signal intensity and on gradient-echo sequences, a magnetic susceptibility artifact (blooming artifact) is pathognomonic of PVNS[4]. Complete synovectomy remains the standard treatment[5], however, recurrence rates are common (30%-50%)[4].

We present the case of a 38-year-old male patient referred from Orthopedics to Rheumatology due to refractory diffuse PVNS of the right knee. The diagnosis was made fifteen years earlier and since then, three arthroscopic synovectomies and one open synovectomy have been performed, always with subsequent and significant disease recurrence.

In 2019, in the first clinical appointment in our Rheumatology outpatient clinic, the patient complained of mechanical pain and fluctuant swelling in the right knee, being regularly submitted to intra-articular injections of glucocorticoids (up to 2 times a year) in the last three years, with minimal improvement. On physical examination crepitus, effusion, limited and tender passive flexion (115º) of the right knee were observed. MRI was later performed for further characterization showing extensive and diffuse proliferative changes of the synovial membrane (Figure 1).

Given the severe involvement of the joint and the disease`s refractoriness to multiple surgical interventions, the case was discussed in a multidisciplinary team meeting and it was decided to start off-label treatment with oral imatinib (400mg/day). After six months of treatment, the patient did not present new episodes of right knee swelling requiring arthrocentesis, only complaining of occasional mechanical pain responsive to etoricoxib. Physical examination showed improvement in the maximum passive flexion (125º) of the right knee, with no tenderness.

Indeed, after twelve months of treatment, not only the patient referred continuous improvement of the clinical symptoms, but also the MRI showed no progression of synovial proliferation, with slightly decreased in hemosiderin deposition (Figure 1). No intolerance or adverse events were observed and the patient is still on imatinib.

Recent evidence has shown that a t(1;2) translocation implicating the collagen 6A3 gene and CSF1 gene is present in PVNS cells. This fusion gene is thought to encode a fusion protein that attracts non-neoplastic cells expressing macrophage colony stimulating factor receptor (M-CSFR)[6]. Imatinib, a tyrosine kinase inhibitor, has been claimed to block M-CSFR activation, supporting its use as a new therapeutic agent for PNVS[7]. In fact, several case reports and small studies have demonstrated a positive response with imatinib[6,8,9], suggesting it might be a potential therapeutic agent for patients with refractory PVNS.

Recently, pexidartinib also a tyrosine kinase inhibitor that selectively inhibits CSF1R, was approved by the Food and Drug Administration for the treatment of PVNS, based on ENLIVEN study, becoming the first drug approved for PVNS[10]. This drug is not yet ap-

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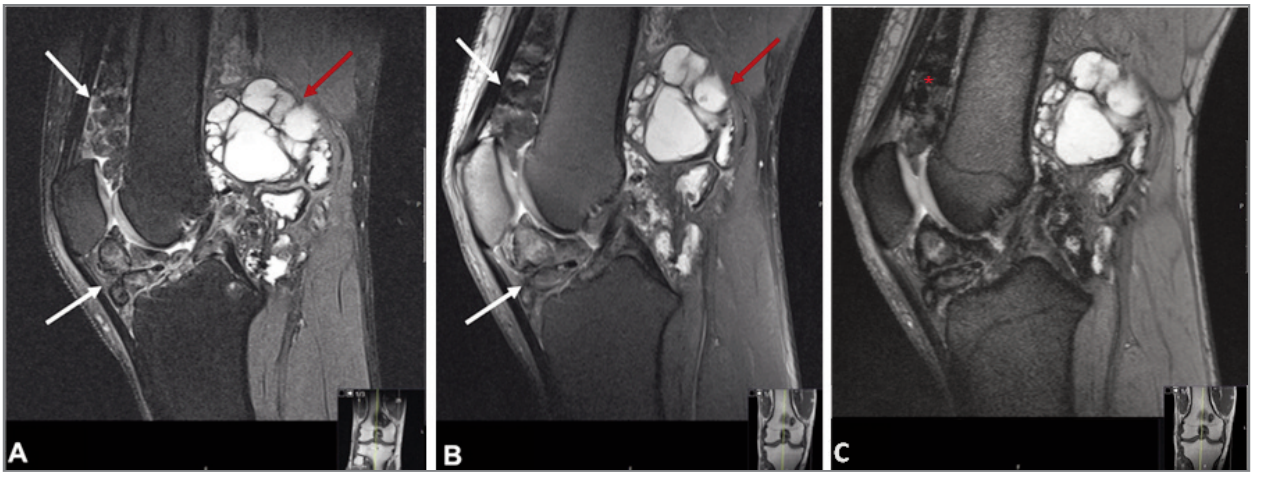

FIGURE 1. Sagittal T2 weighted turbo spin-echo images (A and B) show multiple frondlike foci of low signal intensity that represent hemosiderin-laden synovial tissue (white arrows). The multilocular popliteal cyst (red arrow) might be a way of articular decompression.
Image 1A was acquired in 2019 before treatment with imatinib and image 1B was acquired in 2021 after one year of treatment was completed. Imaging findings in 2021 (image 1B) show a slightly decreased in hemosiderin deposition with no significant synovial progression.
Sagittal T2* weighted gradient echo image (C) shows the blooming artifact*, pathognomonic of PVNS.

proved by European Medicines Agency.

This case emphasizes the positive results of imatinib use in clinical improvement and imaging stability of PVNS, suggesting it may be an option in patients with disease recurrence or in whom surgery is not viable and would result in significant functional impairment.

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