Case 1 – Response to imatinib re-challenge in recurrent pigmented villonodular synovitis (PVNS)

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Abstract
Pigmented villonodular synovitis (PVNS) is a rare, locally-aggressive tumor arising from synovial membrane and characterized by a specific t(1;2) translocation resulting in CSF1 overexpression. This case report describes the unusual case of a young woman, with obesity as the only relevant comorbidity, with a relapsed PVNS of the left knee successfully treated with imatinib.

Key words: bariatric surgery, imatinib, pigmented villonodular synovitis

Introduction

Pigmented villonodular synovitis (PVNS), also known as diffuse-type tenosynovial giant cell tumor (TGCT) [1], is a rare locally-aggressive tumor that arises in the synovial membrane and usually affects larger joints in young adults. In general, PVNS is characterized by a specific t(1;2) (p11;q35-36) translocation that involves colony stimulating factor-1 (CSF-1) and the collagen 6A3 gene leading to CSF-1 overexpression [2].

This genomic alteration results in a paracrine recruitment of inflammatory cells (mainly macrophages) to the tumor site. Although primary surgical resection is the mainstay of PVNS treatment, these tumors have a tendency to relapse, mainly locally [3]. In order to avoid re-excisions and the associated functional consequences, along with psychological distress, new treatment strategies for relapsed PVNS have been investigated. In 2008, Blay and colleagues reported a complete response in a patient affected by PVNS/TGCT treated with imatinib mesylate, a multi-tyrosine kinase inhibitor that blocks the colony stimulating factor-1 receptor (CSF-1R), among other targets [4]. A subsequent retrospective multi-institutional study of 29 patients confirmed the activity of imatinib, strengthening its role as an option for the treatment of this rare disease [5]. Furthermore, Stacchiotti and colleagues described response to imatinib in two cases of PVNS resistant to nilotinib [6]. We present the case of young woman with relapsed PVNS of the left knee who was successfully treated with imatinib.

Case report

A 25 year-old woman, who had grade 1 obesity as the only relevant comorbidity (body mass index [BMI] 33.6 kg/m^2), presented to her General Practitioner with a 5-month history of pain and swelling of the left knee. The patient denied any trauma. Due to increasing pain during activities, the patient underwent ultrasound scan (US) of the affected region in February 2010. This showed the presence of an heterogeneously hypoechoic mass associated with thickness of the synovium. The patient's orthopedic specialist suggested arthroscopic partial synoviectomy and the final histological report was consistent with PVNS.

In November 2010, after a new episode of local pain accompanied by knee swelling, the patient underwent a magnetic resonance imaging (MRI) that confirmed local recurrence of PVNS, showing a heterogeneous lesion characterized by T1-hypointensity and T2-hyperintensity. Subsequently, local resection of the lesion was performed, which confirmed the diagnosis of PVNS.

New-onset local symptoms developed in May 2011 and the

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patient was referred to our center. During the initial examination she complained of worsening of pain with articular swelling and impaired articular function. A repeat MRI showed a solid mass (maximum diameter 60 mm) with irregular margins located in the lateral and medial compartments of the left knee. The lesion was characterized by irregular hypointense signal in T1-weighted images, hyperintense signal in STIR-images, sharp contrast enhancement and articular effusion with a hemorrhagic component.

The case was discussed by the multidisciplinary board at the treating center. Given the relevant knee functional impairment associated with previous surgery and the patient's high BMI, imatinib therapy was proposed. Therefore, the patient started imatinib 400 mg daily in May 2011. A good clinical response was achieve, with improvement of both pain and joint functional status after a few weeks of therapy. After 3 months on imatinib, MRI showed a reduction in tumor size along with a decrease of signal intensity in STIR-images and in contrast enhancement, in particular in the lateral part of the lesion (Figure 1). These findings were consistent with a partial response to the treatment according to RECIST 1.1 criteria [7] and therefore imatinib was continued. Therapy was well tolerated; the only toxicities reported (CTCAE v4.03 [8]) were grade 1 edema, cramps and fatigue. BMI remained stable during imatinib treatment.

The PVNS tumor remained stable from October 2011 to November 2013 when patient expressed a willingness to undergo bariatric surgery. After a thorough discussion with the patient regarding the risk/benefit ratio of such a decision, and in the absence of a clear-cut scientific evidence, the patient decided to stop imatinib therapy. In January 2014 the patient underwent uncomplicated bariatric surgery (adjustable gastric banding). Despite initial weight loss of 8 kg, there was no significant improvement in the patient's BMI.

The patient reported worsening of her left knee arthralgia in April 2014, after 5 months off imatinib therapy. An MRI conducted at that time revealed multiple hyperintense nodules on STIR-sequences with high contrast enhancement located behind the rotula, consistent with PVNS relapse. It was suggested that imatinib be restarted, based on the good response to this therapy during previous treatment. To optimize therapy and to evaluate the impact of bariatric surgery on imatinib absorption, plasma concentrations of imatinib were evaluated. Imatinib levels were within the reported active range (>1100 ng/mL) [9], suggesting that drug intake was unaffected by bariatric surgery. After 2 months of therapy, the patient reported a dramatic improvement in pain control and was able to stop the use of analgesics. Clinical improvements were mirrored by the new MRI findings, which confirmed a partial response of the tumor (Figure 2). The patient continues to receive imatinib treatment with maintained disease response. On the basis of in-depth discussions of the clinical picture and perspective with the patient and our multidisciplinary board, a new resection is planned to enable the patient to pursue her desire to have children.

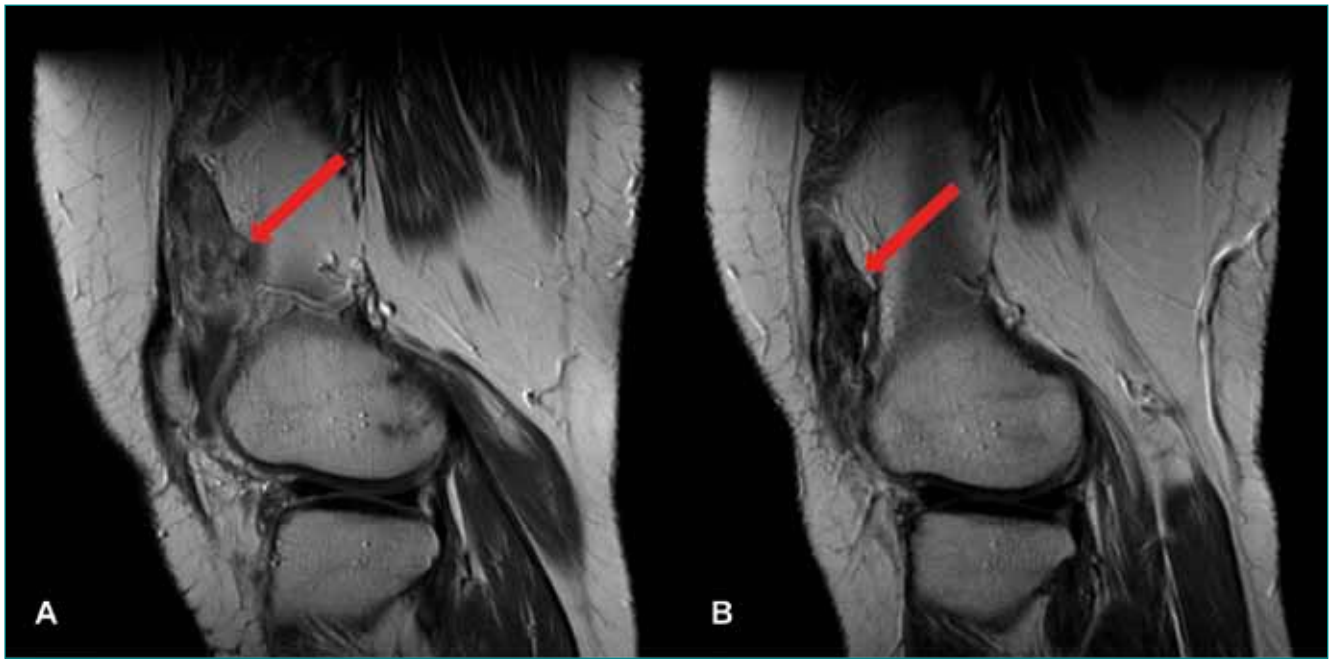

Fig. 1. Sagittal T1-weighted magnetic resonance imaging (MRI) performed on June 2011 revealed a 6-cm solid mass with irregular margins located in the lateral and medial side of the left knee characterized by non-homogeneous hypointense signal in T1-sequences (A). After 3 months' therapy, MRI showed a decrease in tumor size and a reduction in contrast enhancement (B).

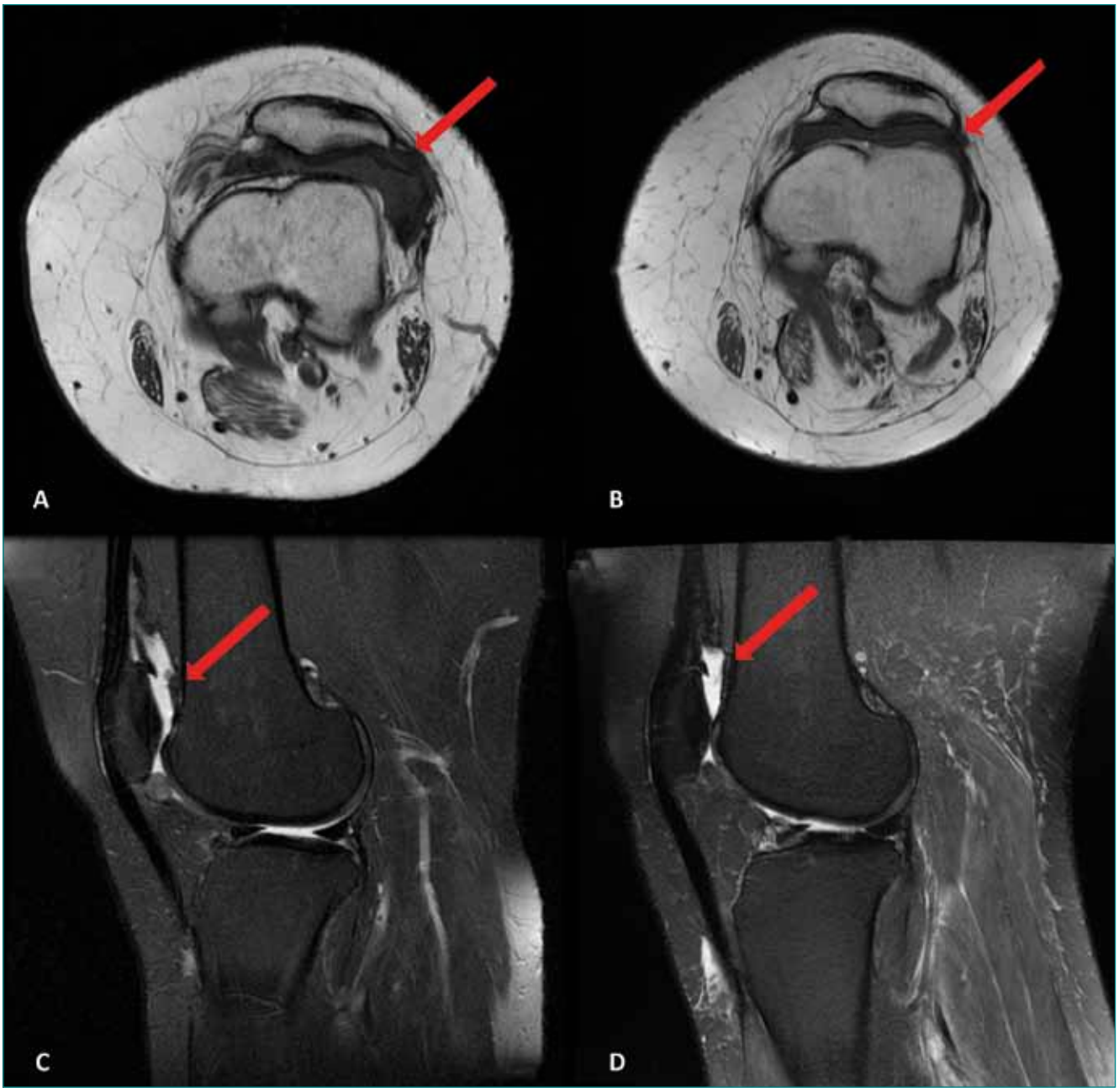

Fig. 2. Magnetic resonance imaging (MRI) performed on June 2014 (A, C) and after 6 months' therapy (B, D); images are axial T1-weighted (A, B) or sagittal STIR (C, D). Initial MRI (A, C) showed 5 solid nodules located near the trochlea of the femur characterized by hyperintensity in STIR and hypointensity in T1-weighted images with non-homogeneous contrast enhancement (arrow). After 6 months' therapy (B, D), MRI revealed complete regression of neoplastic lesions.

Conclusion

This case highlights the importance of a multidisciplinary approach to treatment of patients affected by a rare disease, such as PVNS. In patients with recurrent PVNS, imatinib therapy may facilitate resection, decreasing the morbidity associated with surgery that can potentially lead to functional impairment. Clinical decision making should be individualized based on each patient's clinical condition and requirements. The outcomes in our case indicate that a sustained response can be achieved with continuous imatinib therapy over a long time period, achieving tumor shrinkage and symptom improvement. Recently, Cassier et al. [10] presented a retrospective analysis on imatinib efficacy in PVNS, showing that disease control can persist even after interruption of therapy. The current case showed that the reintroduction of imatinib after a period of suspension did not appear to decrease tumor susceptibility to treatment because retreatment was associated with an improvement of symptoms and a disease regression in our patient with relapsed PVNS. However, there are currently no data available about the optimal duration of imatinib treatment in this setting. Moreover, given the median age of PVNS on-

set, the issue of patients wanting to have children at a time when they are receiving imatinib treatment is a relevant issue and there is little data on pregnancy outcomes during imatinib therapy [11-13]. Therefore, every decision has to be carefully discussed with the patient.

New agents under investigation with the aim of improving PVNS treatment and reducing the need for aggressive surgery in this setting include emactuzumab (RG7155) [14], a novel anti-CSF-1R antibody, and PLX3397 [15], a selective CSF-1R kinase inhibitor.

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Commentary

Tenosynovial giant cell tumor, localized and diffuse type (TGCT), is a rare neoplasm involving the synovium and tendon sheaths that typically presents in young and middle-aged adults of both sexes. Data on TGCT incidence and prevalence are very limited. In the United States, the estimated annual incidence of the diffuse and localized variants of the tumor is 1.8 and 9.2 cases per million, respectively [1]. The diffuse form of the tumor is also called pigmented villonodular synovitis (PVNS). PVNS is usually a monoarticular process that involves the bone, soft tissue, synovium or tendon sheath of large joints. The diagnosis of PVNS is definitively made from pathologic evaluation. However, features highly suggestive of the disease may be found on radiologic imaging, including computed tomography and magnetic resonance imaging. Tumor cells have spindle features and carry a genetic translocations linking the collagen 6A3 gene (on 2q35) with the CSF-1 gene (on 1p13) that is responsible for the release of CSF-1. CSF-1 attracts to the tumor site the inflammatory cell component of the tumor expressing CSF-1R. This population of cells is made by mononuclear and multinucleated giant cells and is predominant in the tumor mass. PVNS is usually a locally aggressive and slow-growing disease. Symptoms initially may be minimal, but as the tumor mass expands within the fixed confines of the intra-articular space and surrounding tissue, pain, stiffness, and swelling can become severe and result in marked functional limitation. In addition, exceptional cases with distant metastases have been described [2].

The current standard of care is the surgical resection of the tumor. Patient outcome after surgery

depends mostly on quality of surgical resection. This depends on multiple factors, including the location and extent of disease. The overall recurrence rate for patients with focal localized disease is low, ranging from 0% to 6%; however, in patients with diffuse forms of the disease, recurrence is considerably more common, estimated at >40%. Thus, diffuse disease carries a significant risk of multiple recurrences, and affected patients often have more extensive involvement and a lower likelihood of success with further surgery. Moreover, surgical resection may involve removal of major tendons, neurovascular structures, or limbs, leading to significant postsurgical morbidity [3]. Thus, there is a need for an effective medical therapy to treat patients with locally-advanced and/or recurrent PVNS. Currently there are no systemic pharmacological agents approved for the treatment of TGCT. However, in recent years, imatinib has been shown to be active based on its ability to inhibit CSF-1R [4-6]. On this basis, it is considered an option for symptomatic or progressive PVNS patients not suitable for surgical resection (i.e. locally-advanced cases). The case described above nicely shows the prolonged benefit achieved with imatinib in a locally-advanced PVNS patient. In this patient, imatinib treatment was associated with an improvement in symptoms and a decrease in tumor size. The tumor progressed after several months when imatinib was discontinued, but a new response was observed soon after re-initiation of therapy. These observations are consistent with an update to clinical trial data presented by Cassier during the 2015 ASCO Annual Meeting [7]. In that retrospective series of 49 PVNS cases treated with imatinib 400 mg/day, the overall response rate by RECIST was 20% (4% complete response, 16% partial response, 37% stable disease). At a median follow-up of 18 months, median progression-free survival nota had not been reached, thus confirming that responses are durable. Interestingly, symptom control persisted beyond imatinib. It should be noted that two cases with metastatic disease appeared to be resistant to imatinib. Unfortunately, it is unlikely that imatinib will be investigated for PVNS setting in formal prospective clinical trials. However, new CSF-R1-inhibitors (both small molecules and monoclonal antibodies) are under development [8,9]. The activity of these agents in TGCT looks to be very promising based on data from phase 1/2 studies. A confirmatory international randomized phase 3 study on the CSF-R1-inhibitor PLX3397 is ongoing in advanced PVNS patients with symptomatic disease.

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