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Tumor Necrosis Factor α Blockade In Therapy-Resistant Pigmented Villonodular Synovitis

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Abstract

Pigmented villonodular synovitis (PVNS) is considered a neoplastic-like disorder of the synovium, histologically characterized by villonodular hyperplasia resulting in dense fibrosis and hemosiderin deposition. The pathogenesis of the disease is still unknown. We present a patient with severe therapy-resistant PVNS of the right knee joint. Several conventional treatment regimens, including open surgical synovectomy and intra-articular injections of yttrium 90 (⁹⁰Y) failed to control the disease. After finding marked TNF-α expression in arthroscopic synovial tissue samples, treatment with an anti-TNF-α monoclonal antibody (infliximab) at a dosage of 5 mg/kg was initiated. Additional courses with the same dosage administered 2, 6 and 14 weeks later, and bimonthly thereafter up to 52 weeks, resulted in control of signs and symptoms. Immunohistologic analysis at follow up identified a marked reduction in macrophage numbers and TNF-α expression in the synovium. To our knowledge, this is the first case, which describes treatment with TNF-α blockade of PVNS in a patient who is refractory to conventional therapy. This case report provides the rationale for larger controlled studies to further elucidate the efficacy of TNF-α blockade treatment in refractory PVNS.

Key words: Pigmented villonodular synovitis, TNF-α blockade treatment, Magnetic Resonance Imaging (MRI), immunohistochemistry.
Introduction

In 1941 Jaffe et al described pigmented villonodular synovitis (PVNS) as an inflammatory and reactive disease of synovial tissues caused by uncertain trauma of the joint. Since then localized and diffuse forms of synovial involvement have been reported. In general the disease is considered as a pre-malignant disease because of its effects on joint structures and integrity, although its exact etiology remains still unknown. Most common site affected is the knee but it can be present in any synovial joint. PVNS is a rare disease with an annual incidence of 1.8 and a prevalence of 9.2 patients per million population. Untreated it can result in severe joint damage with accompanying disability. Therefore, PVNS is treated aggressively; preferred treatment is surgical synovectomy (either arthroscopically or open), eventually followed by radiosynovectomy with intra-articular injection of $^{90}$Y. Nevertheless an important problem remains reoccurrence of disease after these treatment methods. A recurrence rate between 25 and 45% has been reported.

Recently, the presence of macrophages and related pro-inflammatory cytokines such as tumor necrosis factor (TNF)-$\alpha$ has been described in PVNS. These findings offer new insights into the pathomechanism of PVNS by suggesting that periarticular bone resorption and cartilage destruction which characterize PVNS may be related to the expression of pro-inflammatory cytokines, which in turn stimulate MMP production. As a consequence, TNF-$\alpha$ blockade might be a new therapeutic option in order to stop or at
least delay the destruction in refractory PVNS. Currently, no cases of TNF-α targeted treatment have been reported.

Case report

In 1994, a 22-year-old man, presented with monoarthritis of the right knee joint. The diagnosis localized form of PVNS was made by arthroscopy and confirmed by histological examination. In 1995 an open surgical synovectomy was performed because of persistent disease. The result of this treatment appeared to be unsatisfactory with recurrence of the disease in 1996. Magnetic Resonance Imaging (MRI) showed enhancing synovium surrounding the haemosiderin deposits indicating persistent synovitis located posterior in the knee joint and an intercondylar erosion with a diameter of 1 cm. Treatment with intra-articular injection of $^{90}$Y was performed. Due to unsatisfactory results of this procedure, patient was retreated 6 months later with intra-articular injection of $^{90}$Y in 1997. After this second intra-articular injection the disease reoccurred and was controlled by aspiration of synovial fluid and locally administered steroids. During the following years the disease affected activities of daily life (ADL) in such a way that patient had to cessate his profession as mechanic and switched to an administrative position. During these years radiological examination including plain X-rays, CT and MRI scanning was performed periodically. MRI scanning performed in 1998 showed progression of the disease posterior in the knee joint, progression of effusion and the existence of the already described intercondylar erosion with a diameter of still 1 cm. On MRI scanning at the end of 2002, just before treatment with anti TNF-
α was started, progressive damage was seen, characterized by hyperproliferative synovium in the complete knee joint, destruction of the cartilage, increase of the intercondylar erosion up to a diameter of 2 cm and occurrence of several other small erosions.

Because of this progressive radiological damage, persisting synovitis with effusion (70-80 ml) and progressive limitations in ADL, additional analysis into the local pathology was justified. Therefore an arthroscopy of the knee was performed to provide more insight in the pathogenesis of the disease and to evaluate possible treatment options (fig 1A). Subsequently multiple synovial samples were obtained as described previously.9 At routine histopathology classical histological features were observed with pigment depositions and an impressive infiltrate. Immunohistology revealed that this infiltrate mainly consisted of CD68+ macrophages (clone EBM11, DAKO, Glostrup, Denmark) with abundant presence of anti TNF-α (IP-300,Genzyme) (fig 2A).

In response to these findings and the lack of efficacy of conventional therapeutics, therapy with infliximab (5 mg per kg body weight) and methotrexate (10 mg/week) was started, which was well tolerated by the patient. Additional courses were administered 2,6,14 and 20 weeks later at the same dosage; later courses were administered at 8-week intervals up to 54 weeks.

During the initial twenty weeks of treatment with anti TNF-α the knee was punctuated every 4 weeks for persisting effusion, without instillation of intra-articular corticosteroids. Initial volume was 80 ml and this gradually reduced to 30 ml. After the 4th infusion with infliximab at 20 weeks, no synovial fluid could be obtained and there
was a meaningful improvement in ADL. For example, patient was able to stand for several consecutive days again without experiencing any pain in the knee joint, which was impossible for him before treatment with infliximab. To evaluate the histological changes at 20 weeks, a second set of synovial biopsies was obtained by arthroscopy (fig 1B and 2B). A dramatic reduction in cellularity (baseline 1723 cells/mm², 20 weeks 732 cells/mm²) number of macrophages (baseline 1620 cells/mm²; 20 weeks 590 cells/mm²), estimated pigment (baseline IOD 5602/ mm²; 20 weeks 2108/ mm²) and TNF-α (baseline IOD 236134/ mm², 20 weeks 125450/ mm²) was seen.

Based on the response to treatment with infliximab, it was decided to continue treatment with infliximab bimonthly to control local disease activity. MRI scanning performed 10 months after treatment with infliximab showed neither progression nor regression of the synovial tumor mass but also no new or larger erosions in comparison with MRI scanning just before treatment. In conclusion patient experienced a good response on this therapeutic regime with infliximab up to 54 weeks of treatment, without any side effects.
Discussion

The presented case is to our knowledge the first to demonstrate the efficacy of infliximab treatment in refractory PVNS. After 20 weeks of infliximab treatment meaningful clinical improvement was observed together with an impressive reduction in number of synovial tissue macrophages.

TNF-α blockade was considered as a therapeutic option in our patient with refractory PVNS for several reasons. First, macrophages and related pro-inflammatory cytokines such as TNF-α have been reported to be important in PVNS.7,8 In our case this could be confirmed. Secondly, it has been demonstrated that in patients with rheumatoid arthritis (RA) infliximab reduces the number of inflammatory cells in synovial tissue as soon as 48 hours after initiation of treatment.10 In RA it has been demonstrated that there is a close relation between the magnitude of local inflammation and macrophages and their related cytokines.11,12 Therefore, targeting macrophages and related cytokines could be momentous in other diseases such as PVNS where macrophages are predominant cells.

In RA TNF-α is believed to play a key role in the pathogenesis.10 By finding large amounts of TNF-α in PVNS, one could hypothesize if TNF-α might play such a role in the pathogenesis of PVNS as well. Up to now PVNS is considered a neoplastic-like disorder of the synovium with synovitis as a secondary reaction in PVNS.2,4 Yudoh et al already suggested that the pathologic mechanism for growth of hypertrophic villi in PVNS seems to be different from synovial growth in RA.4 Synovial hyperplasia in PVNS might be due to up-regulation of synoviocyte proliferation as represented by activation of
telomerase, which is evident in the majority of tumor cell lines.\textsuperscript{4} From this point of view it is not surprising that treatment with TNF-\(\alpha\) blockade did not result in reduction of the synovial tumor mass as measured by MRI. However a marked decrease in macrophages and TNF-\(\alpha\) production might have stopped or at least delayed the destructive potency of this tumor in our patient.

In RA TNF-\(\alpha\) blockade results in immediate clinical improvement and reduced macrophage infiltration in the synovium.\textsuperscript{10} In our patient disease control was only achieved after a few months, with persisting effusion of the knee during the first months of treatment, unless the markedly higher dose of infliximab (5 mg/kg) in comparison with the dose used in a previous synovial biopsy study in RA patients (3 mg/kg). This slower disease control might have been caused by the greater hyperplasia of the synovium observed in our patient.

To our knowledge, this is the first case of successful treatment with TNF-\(\alpha\) targeted therapy resulting in clinical and histological disease control in refractory PVNS. Debulking surgery, eventually followed by intra-articular \(^{90}\text{Y}\) or radiation treatment, remains the first step for treatment of PVNS. Our report supports larger clinical studies with long-term follow-up in order to inform us on the effects of infliximab on structural damage and the possibility to delay significant surgery such as joint replacement in patients with PVNS with relapsing disease after open surgery and treatment with \(^{90}\text{Y}\).
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Figures

**Figure 1** Macroscopic examination of the synovium before (A) and after 20 weeks (B) of treatment with anti TNF-α.

A) Hypertrophied synovium with villous transformation and hemosiderin deposition

B) Reduction of hypertrophied synovium and hemosiderin deposition

**Figure 2** Pathological specimen of pigmented villonodular synovitis before (A) and after 20 weeks (B) of treatment with anti TNF-α.

A) Classical histological features were observed with pigment depositions and an impressive infiltrate, mainly consisting of macrophages with abundant presence of TNF-a with immunohistochemical staining for macrophages and TNF-α at baseline.

B) A dramatic reduction in cellularity, number of macrophages, estimated pigment and TNF-α after 20 weeks of treatment with anti TNF-α was seen.
Figure 1a
Figure 1 b
Figure 2

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