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Intravenous treatment with immunoglobulins may improve chronic undifferentiated mono- and oligoarthritis

H.-D. Stahl, R. Pfeiffer, F. Emmrich

Institute of Clinical Immunology and Transfusion Medicine, University of Leipzig, Leipzig, Germany.

Hans-Detlev Stahl, MD, PhD; Robert Pfeiffer; Frank Emmrich, MD.

Please address correspondence and reprint requests to: H. D. Stahl, Institute of Clinical Immunology and Transfusion Medicine, University of Leipzig, Haertelstrassee 16-18, D-04107 Leipzig, Germany.
E-mail: stah@medizin.uni-leipzig.de

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ABSTRACT

We previously reported on 8 young patients with undifferentiated mono- and oligoarthritis whose synovial tissue tested positive for Parvovirus B19 DNA by PCR.

Three of these patients remained clinically undifferentiated and suffered from progressive inflammatory disease despite conventional therapy and repeated synovectomy. Intravenous treatment with immunoglobulin (0.4 g/kg body weight over 5 days) resulted in marked improvement in 2 of the 3 patients, allowing them to avoid repeated synovectomy during follow-up periods of 7 and 10 months, respectively.

Introduction

We previously investigated a group of 41 consecutive patients undergoing joint surgery and encompassing 16 patients with undifferentiated mono- and oligoarthritis, among whom 8 tested positive for Parvovirus B19 DNA in synovial tissues, as detected by polymerase chain reaction (PCR) (1). Arthritis improved spontaneously in 3 patients, but became persistent in 5 of 8 cases. Three young patients suffering from persistent undifferentiated mono- or oligoarthritis affecting the knee joints remained resistant to further therapy.

In recent years, treatment with high-dose intravenous immunoglobulin (IVIG) has emerged as a powerful method to control several inflammatory disorders, particularly if characterised by high antibody production and resistance to conventional treatment. These disorders include chronic arthritis (2) and some Parvovirus B19-associated conditions, including systemic vasculitis of childhood (3) and RA-like chronic arthropathy in adults (4). In the cases reported here, the resistance to conventional treatment and the possible Parvovirus-associated mechanism led to the decision of treatment with IVIG. As described in the following case reports, this resulted in marked improvement of joint swelling and humoral inflammation in 2 of 3 patients.

Case reports

Patient 1

A 17-year-old male (R.N.) presented with overnight onset of painless swelling of the right knee in January 1996. There was no history of eye inflammation, pain of the back, buttocks or heels, urethral discharge, skin rash, diarrhoea or family history of psoriasis. The patient was treated with repeated arthrocentesis (3 times during which 150, 85, and 50 ml of sterile synovial fluid were withdrawn, respectively), oral pulse prednisolone (100 mg initially, gradually reduced over 34 days), indomethacine (150 mg/day) and physical rest for 1 week. After transient improvement, the patient relapsed in April, June, and August 1996. At this time, he was referred to the Orthopaedic Department for diagnostic arthroscopy, which only disclosed unspecific inflammation. After another relapse of the knee monarthritis in August 1997, he was referred for synovectomy. The synovial tissue displayed unspecific inflammation at histological examination, and tested positive for Parvovirus B19 DNA upon PCR testing.

On first presentation to our Unit in January 1997, the right knee was markedly swollen, mildly warm and slightly painful on motion. The midpatellar circumference was +3 cm compared to the opposite side. There was no sign of eye inflammation or skin rash. Lumbar mobility was normal and the Mennel's test was negative. Blood tests showed a normal blood count, creatinine, electrolytes, C-reactive protein (CRP), and angiotensin converting enzyme. Antinuclear antibodies and rheumatoid factor (RF) were all negative. The antibody titers against various arthritis-associated virusa and bacteria, especially *Borrelia burgdorferi*, were unrevealing. X rays of the sacroileac joints were normal. The patient was HLA-B27 negative and HLA-DR4 positive.

The diagnosis of undifferentiated monoarthritis was made. Arthrocentesis was performed (130 ml sterile fluid; 13,000 leucocytes/μl) and Diclofenac prescribed (100 mg/day orally). In the following 9 months, the patient suffered 5 episodes of acute knee swelling. The last 3 episodes were treated with monthly arthrocentesis and injections of 4 mg cristalline dexamethason acetate. In June 1998, treatment with hydroxychloroquine (400 mg/day) and piroxicam (80 mg/day) was begun.

In August 1998, the patient developed NSAID-induced gastritis documented by gastroscopy. He was successfully treated with omeprazol (20 mg orally per day) and sucralfat (3 g orally per day over 4 weeks). The arthritis of the right knee relapsed, necessitating arthrocentesis 4 times in 10 days (synovial fluid sterile; 11,100-23,900 leucocytes/µl). The CRP was 192.2 mg/l. In this difficult clinical situation, we commenced treatment with IVIG (Polyglobin™ 0.4 g/kg body wt for 5 days). The swelling of the right knee improved only mildly (+2.5 cm midpatellar circumference compared to the left side); however, the leucocyte count in the synovial fluid dropped to 7,300/µ1 and the serum CRP to 13.5 mg/l. Two weeks after the first treatment, a second IVIG cycle was instituted.

Over the ensuing 2 1/2 months the midpatellar circumference of the right knee decreased to +1 cm compared to the left side and the CRP became negative. No relapse of joint swelling was observed in the following 10 months.

Patient 2

A 21-year-old male (R.R.) was referred to our Unit in January 1998 with persistent swelling of the left knee and, to a lesser extent, of the right knee. When his history was taken, the patient reported sudden swelling of the right knee in November 1989, at age 13; at that time the diagnosis of undifferentiated arthritis was made. Treatment included arthrocentesis, local injections with corticosteroids and systemic administration of NSAID, all without effect. Eventually, synovectomy was performed in 1994, and the patient remaining symptom-free for 4 1/2 years. Three months before presentation, and without any history of back, buttock or heel pain, eye symptoms, diarrhoea, urethral discharge, psoriasis, or signs of infection, the patient experienced sudden pain and swelling of the left knee, associated with fatigue and morning stiffness lasting 10 minutes.

Diagnostic arthroscopy demonstrated unspecific synovitis. PCR testing of synovial tissue tested positive for Parvovirus B 19 DNA. The clinical examination revealed swollen but painless knees bilaterally (midpatellar circumference: 35.5 cm on the right side and 37 cm on the left) and no other abnormalities. Blood tests demonstrated a normal cell count, creatinine, electrolytes and angiotensin converting enzyme. CRP was elevated (38.6 mg/l) and urine testing was normal. Antibodies against various arthritis-associated viral and bacterial pathogens, especially *Borrelia burgdorferi*, was unrevealing. Rheumatoid factor and antinuclear antibodies were negative; HLA-B27 and HLA-DR1 were positive. Urethral swabs were negative for gonoccocci and *Chlamydia tracomatis*, as documented by the ligase chain reaction. There were no radiological signs of sacroiliitis.

The diagnosis of undifferentiated oligoarthritis was made in January 1998. Treatment consisted of repeated arthrocentesis (synovial fluid sterile; 14,500-25,500 leucocytes/µl) and intra-articular injection of crystalline dexamethason acetate (4 mg). In March 1998 oral treatment with sulfasalazine (0.5 g twice daily), prednisolone (7.5 mg/day) and NSAIDs was begun. However, the joint swelling worsened in the following 6 months (midpatellar circumference 40 cm on the right and 38.5 cm on the left). In this difficult clinical situation, we commenced treatment with IVIG (Polyglobin™ 0.4 g/kg body weight over 5 days) accompanied by arthrocentesis of both knee joints. The serum CRP fell to 18.8 mg/l within one week. There was no relapse of swelling and the patient reported reduced pain and fatigue. One month after IVIG, joint swelling recurred (39 cm at midpatellar circumierence on both sides). However, the CRP was only mildly elevated (22.6 mg/l). We instituted another cycle of IVIG complemented by arthrocentesis of both knees. Two months thereafter, both knees displayed a reduced midpatellar circumference (37.5 cm right and 36.5 cm left) and the CRP had dropped to 9.9 mg/l. There was no local warmth and the patient experienced neither pain in the knees nor stiffness in the morning. He remained stable during a follow-up of 7 months.

Patient 3

This 19-year-old male (S.E.) was referred to our department in October 1997 because of intermittent swelling of his right knee for the last 14 months. His medical history included a sudden onset of monoarthritis following some days of hiking in August 1995. At that time the joint was warm and painful on movement. Despite treatment with Diclofenac, joint swelling persisted and the patient was referred for arthroscopy. Mechanical causes were excluded but macroscopically the synovia was markedly proliferated and inflamed. Biopsy revealed histologically unspecific synovitis. Crystalline glucocorticosteroids were administered intra-articularly and the patient remained free of symptoms for 6 months. Eventually, swelling of the right knee recurred in April 1996. Repeated arthrocentesis and intraarticular administration of crystalline corticosteroids did not control the inflammation. Synovectomy was performed in August 1996. Histology again revealed unspecific synovitis, and PCR testing of synovial tissues was positive for Parvovirus B19 DNA. The patient had been free of symptoms for 6 months before presenting to our outpatient department. There was no history of trauma, heel pain, eye symptoms, diarrhoea, urethral discharge, tick bite, psoriasis or signs of recent infection prior to the onset of arthritis. However, the patient reported episodes of back pain after work or late in the afternoon.

On examination, the right knee was warm and swollen, measuring +2 cm at the midpatellar circumference compared to the left side. There was moderate pain at 150° flexion. The forehead displayed a erythematous rash atypical for psoriasis. The remainder of the physical examination was normal. Blood testing demonstrated a normal blood count, creatinine, electrolytes and angiotensin converting enzyme. The CRP was mildly elevated (6.9 mg/l). The urine was normal and antibody titers against arthritis-associated viral and bacterial pathogens especially *Borrelia burgdorferi* was unrevealing. Rheumatoid factor and antinuclear antibodies tested negative. The patient was HLA-B27 negative but HLA-DR1 positive. Biopsy taken from the skin forehead was consistent with seborrhoic dermatitis. Magnetic resonance imaging of the iliosacral joint was normal.

The diagnosis of undifferentiated mono-

arthritis was made. Treatment consisted of arthrocentesis (synovial fluid sterile; 11,000 leucocytes/µl) accompanied by the intra-articular administration of 4 mg dexamethason acetate. Diclofenac as needed was prescribed. Over the ensuing 12 months, the monoarthritis relapsed 4 times, with symptom-free intervals of 1-6 months. Each episode was treated with arthrocentesis (synovial fluid sterile; 7,000-11,000 leucocytes/µl), injection of 4 mg dexamethason acetate, and Diclofenac 50 mg once daily. The CRP remained slightly elevated (7 mg/l).

In November 1998 the patient presented to our Unit with swelling of the right knee (+2 cm midpatellar circumference on the right compared to the left side). We commenced treatment with IVIG (Polyglobin™ 0.4 g/kg body weight over 5 days) preceded by athrocentesis. Six days later the joint swelling relapsed. On day 21 arthrocentesis was again required and a second cycle of IVIG was instituted. The joint swelling recurred on day 24 (+2 cm in the right midpatellar circumference compared to the left side). However, the patient reported no morning stiffness and no requirement for NSAIDs. There were no changes in the CRP, ESR or leucocytes in the synovial fluid. The joint swelling persisted over the ensuing 8 months.

Discussion

We report here the successful treatment with IVIG of 2 young patients out of 3 suffering from persistent undifferentiated mono- and oligoarthritis affecting the knee joints, and in whom synovial tissue had tested positive for Parvovirus B19 DNA. This result is consistent with the beneficial response to IVIG reported by others, e.g. in RA-like chronic arthropathy in adults (4) and in Parvovirus B19-associated systemic vasculitis of childhood (3). The marked improvement of joint swelling and humoral inflammation in our 2 patients was in clear contrast to the minimal improvement shown by the third patient, which was limited to the fact that NSAIDs were no longer required during a follow-up period of 8 months.

A possible factor underlying the different response to therapy was the clinical status of the patients immediately before IVIG therapy. The 2 responsive patients had a acute inflammatory syndrome with high serum CRP (38.6 and 192.2 mg/ml, respectively) and synovial fluid leucocytosis in the arthrocentesis immediately preceding IVIG therapy (11,000-23,900 and 14,500-25,500, respectively). The unresponsive patient, in contrast, had a CRP of 7 mg/ml only, a synovial fluid leucocytosis between 7,000 and 11,000/µl and the histological examination of his skin lesion tended to exclude psoriasis. Thus, the immunoregulatory effect of IVIG may be exerted best in undifferentiated arthritis in the acute phase, when activation of the inflammatory cascade offers more defined and/or multiple targets for the action of high-dose IG. Several mechanisms have becn proposed to explain the immunomodulatory action of IVIG, such as idiotypic anti-idiotypic interactions with restoration of network regulation, antibodies to cell surface antigens, inhibition of T- and B-cell activation (including regulation of the cytokine produktion) (5), and, possibly, the involvement of an intracellular FC mechanism resulting in degradation of unbound pathogenic antibody (6).

In our 3 patients with oligo- or monoarthritis, notably, there was no evidence of high antibody levels. Whether the presence of Parvovirus B19 DNA in their synovial tissue played a role remains unclear. For ethical reasons, it was impossible to repeat the synovial biopsies in order to answer the critical question of whether the IVIG-induced clinical improvement was associated to clearance of Parvovirus B 19 DNA from the synovial tissues. However, Finkel *et al.* (1994) and Takahashi *et al.* (1998) reported IVIG treatment to be associated with a decrease of Parvovirus B19 positive cells in vasculitic lesions and bone marrow, respectively. Therefore, it is conceivable that the efficacy of the treatment in our patients might be related to the presence of anti-Parvovirus antibodies in the IVIG. However, the findings of the present study require confirmation in a larger number of patients with undifferentiated mono- or oligoarthritis.

The beneficial effect of IVIG in cases of unremitting undifferentiated monoarthritis indicates that this treatment may be an option if resistance to other established forms of treatment poses a problem in the clinical setting.

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