Case Report

Remitting Seronegative Symmetrical Synovitis with Pitting Edema Following Intravesical Bacillus Calmette-Guérin Instillation

STEPHANE MOULY, FRANCIS BERENBAUM, and GERARD KAPLAN

ABSTRACT. Remitting seronegative symmetrical synovitis with pitting edema (RS_3PE) is a rare syndrome of undetermined etiology occurring in the elderly. We describe the first case of RS_3PE in a HLA-B27 positive 65-year-old man following intravesical bacillus Calmette-Guérin (BCG) instillation for bladder carcinoma. He developed symmetrical arthritis and synovitis involving wrists, knees, ankles, and metatarsophalangeal joints, with marked pitting edema of the dorsa of both hands and feet, fever, and elevated acute phase reactants. Right knee effusion revealed nonspecific sterile inflammatory fluid. He responded dramatically to nonsteroidal antiinflammatory drugs. BCG instillation may have triggered active symmetrical synovitis via local T cell activation and a T-helper-1 (Th-1)/Th-2 inflammatory profile. (J Rheumatol 2001;28:1699–701)

Key Indexing Terms:
REMITTING SERONEGATIVE SYMMETRICAL SYNOVITIS WITH PITTING EDEMA
INTRAVESICAL BACILLUS CALMETTE-GUÉRIN HLA-B27
DRUG INDUCED DEPRESSION

Since 1985, over 60 cases of remitting seronegative symmetrical synovitis with pitting edema (RS_3PE) have been reported[1-6]. This syndrome may be due to environmental factors or as-yet unknown infectious agents[1]. Although RS_3PE has been described in patients with either *Escherichia coli* or *Campylobacter jejuni* infections[1,7], no association with *Mycobacterium tuberculosis* or bacillus Calmette-Guérin (BCG) has been reported. Aseptic arthritis following intravesical BCG instillation is a reactive oligoarthritis, associated with the HLA-B27 phenotype in 61% of cases and involving the knees in 80% of cases after 4 to 8 weeks of BCG immunotherapy[8]. Although soft tissue swelling with active synovitis during BCG induced arthritis has been reported once[9], typical RS_3PE has never been described. We report the first case of RS_3PE syndrome occurring 24 h after intravesical BCG instillation in a 65-year-old man treated for superficial bladder carcinoma.

CASE REPORT

A 65-year-old man was admitted for abrupt onset of polyarthritis following intravesical BCG instillation. Differentiated bladder polyps were diagnosed and removed in 1984, and moderately differentiated transitional cell bladder carcinoma developed. A 6 week course of weekly intravesical BCG vaccine was commenced in May 1997. His history was otherwise remarkable for hypertension, inferior acute myocardial infarction in 1985, and mild chronic obstructive pulmonary disease. Twenty-four hours after the last instillation (July 10, 1997), he experienced sudden tenderness, swelling, and limitation of motion initially involving his left foot, then his right wrist, both knees, and left ankle. Pain in the lumbar and cervical spine and conjunctivitis were also noted. Prior to admission, various nonsteroidal antiinflammatory drugs (NSAID), colchicine, aspirin, and a short course of prednisolone 30 mg/day had been prescribed, but without improvement. Major laboratory findings are summarized in Table 1.

Clinical examination on admission (July 25, 1997) revealed an unwell looking man (weight 78 kg, height 163 cm) with fever (38.6°C, 101.5°F), pulse 80/min, and blood pressure 135/80. There was evidence of synovitis in both ankles, knees (with moderate effusion), wrists, mediotarses, and left metatarsophalangeal joints associated with marked pitting edema of the dorsa of both hands and feet and bilateral painful conjunctivitis. Clinical examination was otherwise normal. Laboratory findings are summarized in Table 1. Blood chemistry tests including calcium, phosphorus, uric acid, and liver tests were normal (data not shown). Blood cultures and urinalysis (including absence of proteinuria) remained negative. Rheumatoid factor, Epstein-Barr virus serology, and antinuclear, LKM-1 and mitochondrial (M2) antibodies were negative. Cryoglobulinemia was absent. Complement fractions C3 and C4 were slightly elevated as well as serum immune complexes (1.9 g/l, 0.4 g/l, and 4.0 μg/ml, normal ranges 0.75–1.4, 0.1–0.34, and 0–1.5, respectively). This patient was HLA-B8 B27, DRB1*0301, DRB1*0801, 06, and DRB3*0101 positive. His right knee effusate was analyzed (Table 1). Radiographic findings including wrists, hands, knees, ankles, feet, lumbar spine, and pelvis were unremarkable. Ophthalmologic examination revealed bilateral keratoconjunctivitis. Abdominal and pelvic ultrasound examinations were normal, as were carcinoembryonic and prostate-specific antigens.

He was treated with ketoprofen 100 mg IV once daily along with morphine sulfate 30 mg po twice daily for 3 days and experienced prompt improvement. Following ketoprofen treatment, aminotransferase serum

From the Department of Rheumatology, Saint-Antoine Hospital, Paris, France.

S. Mouly, MD; F. Berenbaum, MD, PhD; G. Kaplan, MD.

Address reprint requests to Dr. S. Mouly, General Clinical Research Center, Campus Box No. 7600, Room 3005 APCF, The University of North Carolina, Chapel Hill, NC 27599-7600. E-mail: smouly@email.unc.edu

Submitted June 22, 2000; revision accepted December 18, 2000.

Table 1. Biological findings over 3 months in a 65-year-old man with BCG induced RS_3PE.

	July 16, 1997	August 5, 1997	August 12, 1997	September 1, 1997
White blood cells (4000–10,000/mm^3)*	13,300	9800	11,900	11.800
Hemoglobin (130–180 g/l)*	144	110	103	106
Platelets (150,000–400,000/mm^3)*	299,000	639,000	535,000	669,000
Polymorphonuclear neutrophils (PMN) (4000–7000/mm^3)*	10,640	6000	9200	8260
ESR (< 20 mm/h)*	91	92	100	113
CRP (0–5 mg/l)*	240	179	140	NA
Joint fluid analysis				
Red cells, mm^3		760		8100
White cells, mm^3		1240		4200
PMN, %		86		34
Lymphocytes, %		5		12
Other, %		9		59
Culture**		Sterile		Sterile

*Numbers in parentheses indicate normal ranges.
**Including mycobacteria.
NA: Not available.

levels increased to 51 IU/l (1.5N, aspartate aminotransferase) and 135 IU/L (4N, alanine aminotransferase) and serum gamma-glutamyltransferase and alkaline phosphatases increased to 97 (2N) and 135 IU/l (1.5N), respectively. Morphine sulfate was withdrawn and ketoprofen replaced by indomethacin 50 mg po 3 times daily, resulting in rapid normalization of liver tests. Conjunctivitis improved with 2 weeks of local eyedrop treatment. One month later, he still complained of moderate pain with synovitis in ankles, knees, and wrists without pitting edema. The right knee effusate was again aspirated (Table 1), followed by local infiltration of 50 mg prednisolone. He also complained of forgetfulness, sleeplessness, irritability, inability to concentrate, and sad mood since introduction of indomethacin. The latter was replaced by meloxicam 7.5 mg once daily followed by complete resolution of joint pain, synovitis, knee effusions, and behavioral changes. No relapse or sequela has been reported to date and the patient completely withdrew from his treatment in November 1997.

DISCUSSION

Our patient had characteristic features of RS_3PE syndrome: male > 50 years of age, abrupt onset of seronegative symmetrical polyarthritis and synovitis involving wrists (55% of cases), knees (33% of cases) and ankles (26% of cases), prominent pitting edema of the dorsa of both hands and feet, fever, and elevated acute phase reactants[1-3,5,10,11]. While initial asymmetrical presentation has been observed in some patients with RS_3PE[6,7], bilateral keratoconjunctivitis, present in 25% of reactive arthritis including BCG induced arthritis[8], has never been reported. Although less frequent than HLA-B7, HLA-B27 has been observed in some patients with typical RS_3PE[2,10,11]. A short course of prednisolone given prior to admission provided no improvement, unlike most cases of this syndrome[3,5,10]. Our patient responded dramatically to NSAID treatment, and NSAID alone or in combination with hydroxychloroquine have been associated with prompt or more gradual response[2,11,12]. Moreover, atypical RS_3PE, especially when associated with cancer, has been shown to respond poorly to steroids[3,6]. Indeed, our patient had superficial bladder cancer. However, since the malignancy was well controlled at the time RS_3PE occurred, we believe that BCG instillation led to the development of this polysynovitis.

The pathogenic mechanism linking RS_3PE syndrome and intravesical BCG instillation is unclear. An infectious agent that triggers synovitis and pitting edema in a genetically programmed host has been postulated but never been confirmed[1,12]. High levels of interleukin 6 (IL-6) in one case and both IL-6 and tumor necrosis factor-α (TNF-α) in another have been reported, both having underlying malignancies[4]. Cytokine levels returned to normal after complete remission of the articular manifestations. In these 2 cases, the underlying malignancy may have triggered RS_3PE syndrome via an inflammatory process involving mainly IL-6. Similarly, a mixed synovial membrane T-helper 1 (Th1)/Th2 cytokine response involving IL-4, transforming growth factor-ß, interferon-γ, IL-8, IL-1, and TNF-α but not IL-6 was found in intravesical BCG induced arthritis[8,13]. Both RS_3PE and BCG induced arthritis can lead to hyperplastic synovitis with villous formation, diffuse edema, and infiltrate containing polymorphonuclear and T lymphocytes[9,12,13]. Taken together, these findings suggest a predominant T cell mediated immunological phenomenon. Although neither synovial biopsy nor proinflammatory cytokine levels were available from our patient, we postulate that BCG induced an immunogenic response in highly active synovial T cells leading to dramatic symmetrical polysynovitis with pitting edema.

NSAID induced mental disorders have been described in at least 35 cases, most with underlying psychiatric diseases[14]. Our patient, free of an underlying psychiatric condition, developed indomethacin induced depressive

symptoms, which rapidly resolved when indomethacin was replaced with meloxicam. While indomethacin was responsible for 25% of the reported NSAID induced psychiatric disorders, oxicams (e.g., piroxicam) induced only one episode[14], suggesting a structurally determined side effect. Increased levels of TNF-α following BCG therapy[8,13] could also have impaired indomethacin metabolism, leading to prolonged blood levels and associated adverse events[14,15].

In conclusion, RS_3PE may occur secondary to intravesical BCG instillation. Whether RS_3PE is caused by environmental factors or infectious agents is unknown; this requires further investigation that should focus on microorganisms capable of stimulating T cell inflammatory response and cytokine profile characterization during the acute phase of this syndrome.

REFERENCES

1. McCarty DJ, O'Duffy JD, Pearson L, Hunter JB. Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. JAMA 1985;254:2763-7.
2. Schaeverbeke T, Fatout E, Marcé S, et al. Remitting seronegative symmetrical synovitis with pitting oedema: disease or syndrome? Ann Rheum Dis 1995;54:681-4.
3. Olivé A, Del Blanco J, Pons M, Vaquero M, Tena X, Catalan Group for the Study of RS3PE. The clinical spectrum of remitting seronegative symmetrical synovitis with pitting edema. J Rheumatol 1997;24:333-6.
4. Sibilia J, Friess S, Schaeverbeke T, et al. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE): A form of paraneoplastic polyarthritis? J Rheumatol 1999;26:115-20.
5. Cantini F, Salvarani C, Olivieri I, et al. Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome: a prospective follow-up and magnetic resonance imaging study. Ann Rheum Dis 1999;58:230-6.
6. Cantini F, Salvarani C, Olivieri I. Paraneoplastic remitting seronegative symmetrical synovitis with pitting edema. Clin Exp Rheumatol 1999;17:741-4.
7. Michaels RM, Hochman RF. Remitting seronegative symmetrical synovitis with pitting edema [letter]. JAMA 1986;255:2444.
8. Buchs N, Chevrel G, Miossec P. Bacillus Calmette-Guérin induced aseptic arthritis: An experimental model of reactive arthritis [editorial]. J Rheumatol 1998;25:1662-5.
9. Hughes RA, Allard SA, Maini RN. Arthritis associated with adjuvant mycobacterial treatment for carcinoma of the bladder. Ann Rheum Dis 1989;48:432-4.
10. Olivieri I, Salvarani C, Cantini F. Remitting distal extremity swelling with pitting edema: A distinct syndrome or a clinical feature of different inflammatory rheumatic diseases? [editorial]. J Rheumatol 1997;24:249-52.
11. Chaouat D, Perier JY, Le Parc JM, Belange G. Polyarthrite subaiguë œdémateuse bénigne du sujet âgé. Neuf observations [Subacute oedematous polyarthritis of the elderly. Nine cases]. Presse Med 1990;19:1705-8.
12. Olivo D, D'Amore M, Lacava R, et al. Benign edematous polysynovitis in the elderly (RS3PE syndrome). Clin Exp Rheumatol 1994;12:669-73.
13. Smith MD, Chandran G, Parker A, et al. Synovial membrane cytokine profiles in reactive arthritis secondary to intravesical Bacillus Calmette-Guérin therapy. J Rheumatol 1997;24:752-8.
14. Jiang HK, Chang DM. Non-steroidal anti-inflammatory drugs with adverse psychiatric reactions: Five case reports. Clin Rheumatol 1999;18:339-45.
15. Williams ML, Bhargava P, Cherrouk I, Marshall JL, Flockhart DA, Wainer IW. A discordance of the cytochrome P450 2C19 genotype and phenotype in patients with advanced cancer. Br J Clin Pharmacol 2000;49:485-8.