Rheumatol Int (2011) 31:1383–1385
DOI 10.1007/s00296-009-1266-z

CASE REPORT

Unusual central nervous system involvement of rheumatoid arthritis: successful treatment with steroid and azathioprine

Asuman Sengoz Inan · Seval Masatlıoglu · Seyfi C. Ozyurek · Derya Engin · Ilknur Erdem

Received: 31 August 2009 / Accepted: 29 November 2009 / Published online: 15 December 2009

Abstract Central nervous system involvement of rheumatoid arthritis (RA) frequently develops in patients who had a long-term history of RA, irrespective of the disease activity of systemic arthritis, and it has a high mortality rate despite treatment. Since clinical symptoms and radiologic signs are rather nonspecific, in short of doing biopsy, the diagnosis of rheumatoid meningitis is one of exclusion. However, the strongly positive rheumatoid factor in the cerebrospinal fluid is quite specific. We here report a 70-year-old man who had not been diagnosed as RA before he was admitted with neurological findings, who was diagnosed as RA later and successfully treated with prednisolone and azathioprine.

Keywords Rheumatoid arthritis · Rheumatoid factor · Prednisolone · Azathioprine

A. S. Inan · S. C. Ozyurek · D. Engin
Department of Infectious Diseases and Clinical Microbiology, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey

S. Masatlıoglu
Department of Rheumatology, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey

I. Erdem
Department of Infectious Diseases and Clinical Microbiology, Namık Kemal University, Tekirdag, Turkey

A. S. Inan (✉)
Kazım Karabekir sk., Guneş Apt. No: 7/44, Erenkoy, Kadıköy, 34738 Istanbul, Turkey
e-mail: asumaninan@hotmail.com

Introduction

Nervous system involvement of rheumatoid arthritis (RA) is uncommon. It is usually the result of spinal cord compression due to subluxation of the cervical vertebrae; a cerebral infarct and/or hemorrhage due to vasculitis; or by direct involvement of central nervous system (CNS) structures by inflammatory cells. Characteristic pathologic findings are rheumatoid nodules in the CNS, pachymeningitis or leptomeningitis and vasculitis [1, 2]. Since the clinical symptoms and radiologic signs are rather nonspecific, short of doing a brain biopsy, the diagnosis is one of exclusion. In addition it is reported that the strongly positive rheumatoid factor in the cerebrospinal fluid (CSF) is quite specific [2–5]. We here report a patient who had not been diagnosed as RA before he was admitted with neurological findings, who was diagnosed as RA later and treated successfully.

Case report

A 70-year-old man was hospitalized with the complaints of fever, headache, nausea, vomiting and confusion of 5 days duration. He was living in a rural region of Turkey and had joint pains for 10 years. On admission he had a fever 38°C, nuchal rigidity, positive Kerning and Brudzinski signs. There was swelling in his metacarpophalangeal joints, radial deviation at the wrist with ulnar deviation of the digits and had swan-nack deformities of his fingers. Laboratory studies showed a leukocyte count of $11 \times 10^3/\mu l$ (neutrophils 73%, lymphocytes 22% and monocytes 5%), an erythrocyte sedimentation rate of 124 mm/h, a C-reactive protein of 6.5 mg/dl (normal <0.8 mg/dl). Rheumatoid factor was positive (108 IU/ml) in serum. Antinuclear

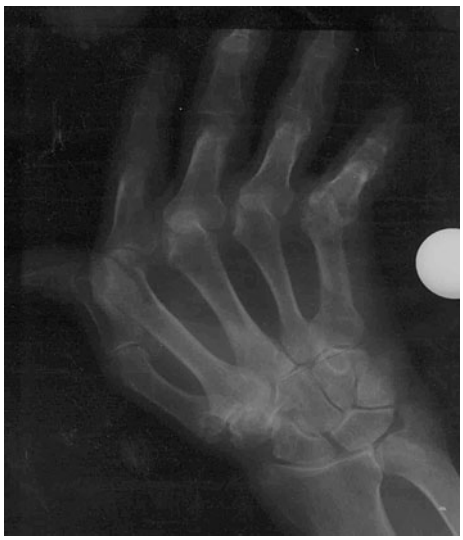

Fig. 1 X-ray of the hands: juxta-articular osteopenia, marginal erosions and narrowing of the joint spaces

antibody, antimyeloperoxidase antineutrophil antibody (MPO-ANCA), antiproteinase-3 antineutrophil antibody (PR3-ANCA) and angiotensin converting enzyme were within normal ranges. Computed tomography and magnetic resonance imaging of brain were normal. CSF analysis showed 140 cells/mm^3 (neutrophils 62%, lymphocytes 28%); protein 113 mg/dl; glucose 34 mg/dl (blood glucose 96 mg/dl) on his first hospital day. Ceftriaxone 2 × 2 g/day, ampicillin 4 × 3 g/day were administered. On the fourth hospital day, CSF analysis showed 148 cells/mm^3 (lymphocytes: 82%, neutrophils: 18%); protein: 267 mg/dl; glucose: 46 mg/dl (blood glucose: 96 mg/dl); rheumatoid factor was positive at 98 IU/ml. There was no improvement in his general condition and the clinical findings, and acyclovir 3 × 10 mg/kg/day and quadruple anti-tuberculous therapy (isoniazid, rifampicin, ethambutol and pyrazinamide) were initiated. Cytological examinations of the CSF did not show any malignant cells. Serology and cultures for bacteria, mycobacterium and fungi were negative, so were the polymerase chain reactions for Herpes simplex virus and *Mycobacterium tuberculosis*. The purified protein derived skin test was 0 mm and chest radiograph was normal.

Radiographs of the hands demonstrated juxta articular osteoporosis, marginal erosions and narrowing of the joint spaces of all metacarpophalangeal, proximal interphalangeal and carpal joints, bilaterally (Fig. 1). He was diagnosed as having RA. On the seventh hospital day, somnolence, nuchal rigidity, Kerning and Brudzinski signs were still present. A dural biopsy was considered but was not done both due to his poor general condition and the reluctance of the family members to give permission. He was diagnosed as having CNS involvement due to RA. Intravenous methylprednisolone (1,000 mg/day for three consecutive days) was initiated. His clinical findings improved dramatically on the third day of the treatment. Oral prednisolone (1 mg/kg/day) was administered for 1 month, azathioprine 3 × 50 mg was added, and then prednisolone was gradually tapered. Control cranial MRI with contrast was evaluated as normal after 1 month of his hospital discharge. On follow-up (3, 6 and 12 months later), the patient was still doing well. CSF

Table 1 Summary of CNS investigation results

	Cells	Protein (N: 15–45 mg/dl)	Glucose/Blood Glucose (N: 40–70 mg/dl per 76–110 mg/dl)	RF (N: <20 IU/ml)	Others
On admission	140 (neutrophils 62%)	113	34/96		Brucella agg, RPR, Gram stain, Indian ink stain, Ziehl –Neelsen stain, latex agglutination tests were negative. Mycobacterium and fungal cultures, PCR for *M. tuberculosis* and HSV were resulted as negative
On the 4th day	152 (lymphocytes 82%)	265	36/91	98	Gram stain, Indian ink stain, Ziehl – Neelsen stain, latex agglutination tests were negative
On the 8th day	148 (lymphocytes 78%)	220	32/92	96	Brucella agg, RPR, Gram stain, Indian ink stain, Ziehl –Neelsen stain, latex agglutination tests were negative
On the 21st day	34 (lymphocytes 84%)	138	60/110	30	Brucella agg, RPR, Gram stain, Indian ink stain, Ziehl –Neelsen stain, latex agglutination tests, Mycobacterium and fungal cultures were negative
1 year later	0	60	64/110	<20	Gram stain, Indian ink stain, Ziehl – Neelsen stain, latex agglutination tests were negative

cell count protein and glucose levels and RF were within normal ranges at 12 months (Table 1). Now, 5 years later, he is still free of any symptoms of CNS disease. His RA is also in good remission.

Discussion

CNS involvement is a rare but a serious presentation of RA. We are aware of only a limited number of case reports of RA meningitis in the English literature [1, 6]. A definite diagnosis of CNS rheumatoid disease is in general difficult without autopsy, since there are very few clinical markers specific for this manifestation. In short of doing biopsy, the diagnosis of rheumatoid meningitis is one of exclusion. However, rheumatoid factor in the CSF is often used as a diagnostic marker and a strongly positive result is highly indicative [2–5].

Our patient apparently had rheumatoid meningitis mainly based on the clinical findings and his response to treatment. Rheumatoid meningitis frequently develops in patients who had a long term history of RA, irrespective of the disease activity of their systemic arthritis [1, 2]. It has a high, 70%, mortality rate despite treatment [2]. There is some evidence that steroids alone may not be sufficient and other agents should be added to treatment [6–9]. Because methotrexate can cause rheumatoid nodulosis on the extremities and leptomeninges, it is best avoided [7, 10].

References

1. Bathon JM, Moreland LW, DiBartolomeo AG (1989) Inflammatory central nervous system involvement in rheumotoid arthritis. Semin Arthritis Rheum 18:258–266
2. Kato T, Hoshi K, Sekijima Y, Matsuda M, Hashimato T, Otani M, Suzuki A, Ikeda S (2003) Rheumatoid meningitis: an autopsy report and review of the literature. Clin Rhematol 22:475–480
3. Tan HJ, Raymond AA, Phadke PP, Rozman Z (2004) Rheumatoid pachymeningitis. Singapore Med J 45(7):337–339
4. Markenson JA, McDougal JS, Tsairis P, Lockshin MD, Christian CL (1979) Rheumatoid meningitis: a localised immune process. Ann Intern Med 90:786–789
5. Kanemoto M, Ota Yasuhiro, Karahashi T, Nozue N (2005) A case of idiopathic hypertrophic cranial pacymeningitis manifested only by positive rheumatoid factor and abnormal findings of the anterior falx. Rheumatol Int 25:230–233
6. Starosta MA, Brandwein SR (2007) Clinical manifestation and treatment of rheumatoid pachymeningitis. Neurology 68:1079–1080
7. Yücel AE, Kart H, Aydın P, Ağildere AM, Benli S, Altinörs N, Demirhan B (2001) Pachymeningitis and optic neuritis in rheumatoid arthritis: successful treatment with cyclofosfamide. Clin Rheumatol 20:136–139
8. Chou RC, Henson JW, Tian D, Hedley-Whyte ET, Reginato AM (2006) Successful treatment of rheumatoid meningitis with cyclofosfamide but not infliximab. Ann Rheum Dis 65:1114–1116
9. Claassen J, Dwyer E, Maybaum S, Elkind MSV (2006) Rheumatoid leptomeningitis after heart transplantation. Neurology 66:948–949
10. Karam NE, Roger L, Hankins LL, Reveille JD (1994) Rheumatoid nodules of the meninges. J Rheumatol 21:1960–1963