

Central nervous system involvement as a major manifestation of rheumatoid arthritis

M. Zolcinski · S. Bazan-Socha · G. Zwolinska · J. Musial

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Abstract A 58-year-old woman with an 8-year history of seropositive rheumatoid arthritis was admitted with right hemiparesis, history of seizures, fever, weight loss and headaches. Her blood tests revealed the presence of rheumatoid factor, elevated C-reactive protein and anti-cyclic citrullinated peptide antibodies (>200 RU/ml). Examination of cerebrospinal fluid demonstrated pleocytosis (118 cells/mm³, predominantly lymphocytes) with elevated protein level (58 mg/dl); cultures were negative. Magnetic resonance imaging findings were suggestive for meningoencephalitis. Short course of high-dose corticosteroids and cyclophosphamide led to clinical improvement. Rheumatoid vasculitis was probably responsible for neurological symptoms.

Keywords Rheumatoid arthritis · Vasculitis · Central nervous system

Introduction

Neurovascular disease in the course of rheumatoid arthritis (RA) represents a form of rheumatoid vasculitis which involves mainly peripheral nervous system. Central nervous system (CNS) involvement presenting as pachymeningitis,

leptomeningitis or encephalitis is rare [1]. Symptoms due to cerebral vasculitis, amyloidosis and/or rheumatoid nodules may involve stroke, seizures or encephalopathy [2]. Establishing diagnosis is difficult as extra-articular manifestations of RA may exacerbate during remission of synovitis [3].

We present a case of a 58-year-old woman with an 8-year history of seropositive RA. She was well until the age of 50 when she fulfilled the clinical and laboratory ACR criteria of RA (i.e. morning stiffness, symmetric swelling of joints in both hands and feet, the presence of rheumatoid factor). No radiological signs of RA were seen in her joints. She had been treated with methotrexate and oral steroids for 6 months with an excellent response. Then she stopped treatment by herself and did not continue follow-up visits.

After 6 years of complete remission she was admitted with high-grade fever, gait imbalance whilst walking with a tendency to fall, weight loss, severe headaches followed by right hemiparesis and seizures. Blood tests revealed elevated rheumatoid factor (RF) and C-reactive protein (CRP) with low-grade normocytic anemia and normal leukocyte count. Her joints were not swollen, no signs of RA were seen on hand and feet X-rays, no subcutaneous rheumatoid nodules were found. Computed tomography of the head was unremarkable. Examination of cerebrospinal fluid demonstrated pleocytosis (118 cells/mm³ 65% of lymphocytes) and elevated protein level (58 mg/dl). Cultures for bacteria, tuberculosis and fungi were negative. The diagnosis of aseptic meningitis was made and the patient was treated with low dose steroids and antibiotics (as prophylaxis) for 3 weeks with some clinical and neurological improvement. She was discharged in a good health condition; no further treatment was ordered.

Fever and neurological symptoms (seizures, right-sided hemiparesis, speech disturbance) recurred 4 weeks after

M. Zolcinski · S. Bazan-Socha · J. Musial (✉)
Department of Internal Medicine,
Jagiellonian University School of Medicine,
Skawinska 8, 31-066 Krakow, Poland
e-mail: mmmusia@cyf-kr.edu.pl

G. Zwolinska
Department of Neurology,
Jagiellonian University School of Medicine,
Krakow, Poland

discharge. Her blood tests revealed the presence of RF, elevated levels of CRP (>160 mg/ml) and anti-cyclic citrullinated peptide antibodies (anti-CCP; >200 RU/ml), low titers of unspecific antinuclear antibodies (1:320) and anti-neutrophil cytoplasmic antibodies (1:80), exhibiting perinuclear pattern by indirect immunofluorescence (p-ANCA). Her C3, C4 complement components were normal. Magnetic resonance imaging (MRI) revealed a single abnormal high signal lesion in the left frontal lobe on FLAIR and T1-weighted sequences with diffuse edema and gadolinium-enhancement of the leptomeninges adjacent to left frontal lobe (Fig. 1). Based on clinical signs and laboratory findings a rheumatoid meningoencephalitis was suspected. One infusion of methylprednisolone (1,000 mg i.v.) followed by oral therapy (0.5 mg/kg/day) and continuous treatment with valproic acid were effective in controlling her symptoms. Repeated MRI (8 weeks later) showed a complete regression of the changes in the left frontal lobe with a remaining gadolinium-enhancement of the leptomeninges in the left hemisphere (Fig. 2). Initial immunosuppressive treatment was followed by intravenous pulse

cyclophosphamide (10 mg/kg) at 4-weekly intervals and daily oral methylprednisolone (0.5 mg/kg). After 3 months the patient is in a very good neurological condition, with no hemiparesis, fever or seizures.

Despite such an aggressive treatment the patient developed clinical signs of arthritis on both her hands, reaching the score of 4,54 (DAS28). Ultrasound examination of her hands revealed bilateral synovitis in metacarpophalangeal and proximal interphalangeal joints with two new erosions and a significant vascular flow acceleration seen using power Doppler/continuous Doppler (PD/CD) imaging.

For the time being the patient refuses treatment with classic disease modifying drugs.

Discussion

The severe neurological symptoms in our patient were most probably caused by rheumatoid involvement of the CNS. Such manifestations of RA may include vasculitis, cerebral pachymeningitis, leptomeningitis, chorioid plexus

Fig. 1 MRI images. High signal lesion in the left frontal lobe on FLAIR and T1-weighted sequences with diffuse edema and gadolinium-enhancement of the leptomeninges adjacent to left frontal lobe

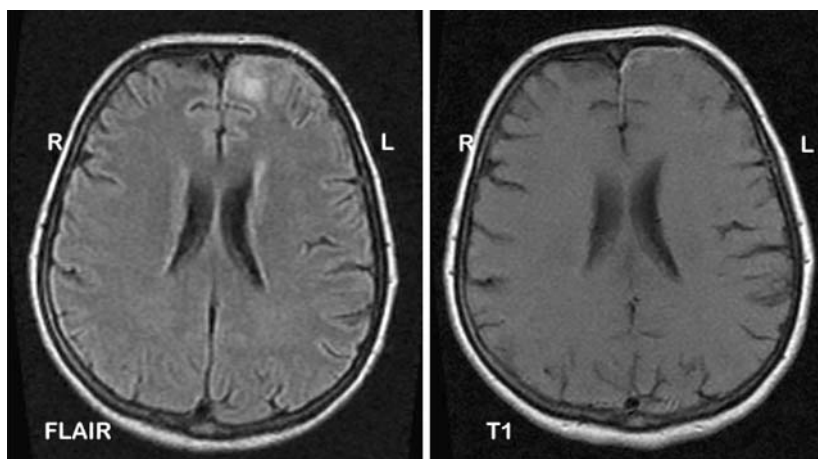
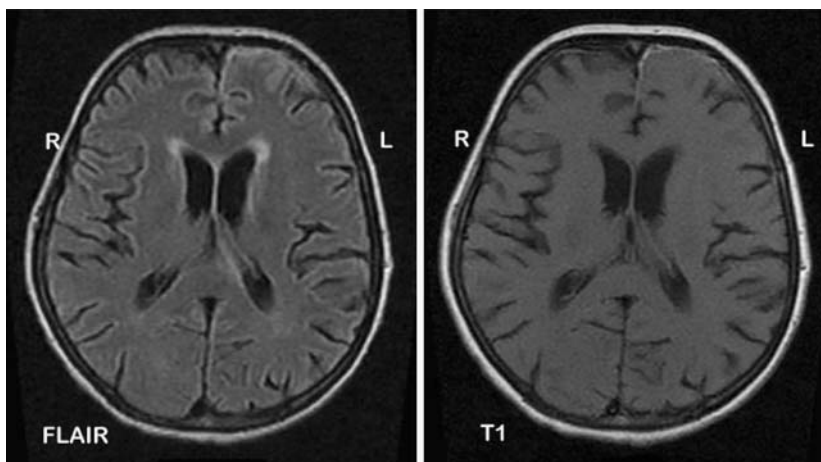


Fig. 2 Repeated MRI images (after 8 weeks of treatment with methylprednisolone). Complete regression of the abnormal high signal lesion in the left frontal lobe with a remaining gadolinium-enhancement of the leptomeninges in the left hemisphere



infiltration, myelopathy secondary to atlanto-axial subluxation, rheumatoid infiltration of the spinal dura or cerebral complications induced by hyperviscosity associated with high titers of RF [3, 4]. The clinical symptoms, MRI findings, high titers of RF and anti-CCP and finally good response to immunosuppressive therapy support the diagnosis of meningoencephalitis in our patient, most likely caused by rheumatoid vasculitis. Positive antinuclear antibodies possibly predisposed her to the development of rheumatoid vasculitis [5]. The disappearance of brain abnormality and good response to high dose steroids is typical for CNS rheumatoid vasculitis [3]. For these reasons, no brain or meningeal biopsies were performed. These procedures were previously described in CNS rheumatoid vasculitis [8, 9], but seemed unethical in the patient described.

High signal brain lesions with enhancement of the leptomeninges in MRI were previously reported in a setting of long-lasting joint-deforming RA [6, 7, 8]. They are usually accompanied by other manifestations of rheumatoid vasculitis, such as subcutaneous nodules, peripheral neuropathy and cutaneous vasculitis. Our patient is an example of a predominant rheumatoid CNS involvement with no other extra-articular pathology. During the time the patient developed neurological symptoms there were no clinical signs of active arthritis. Arthritic manifestations developed, however, after a 3-month immunosuppressive treatment. The observation that cyclophosphamide and steroids may worsen, or at best have no effect on rheumatoid synovitis in RA vasculitis patients, has been described previously [10, 11].

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