

Self-limited Rheumatoid Meningitis as a Presenting Symptom of Rheumatoid Arthritis

Vitaly Finkelshtein MD^{1,6}, Yair Lampl MD^{1,6}, Mordechai Lorberboym MD^{2,6}, Andrew Kanner MD^{5,6}, Dominique Ben-Ami Raichman MD^{3,6}, Ron Dabby MD^{1,6} and Amir Tanay MD^{4,6}

¹Departments of Neurology, ²Nuclear Medicine, and ³Radiology and ⁴Allergy, Immunology and Rheumatology Clinic, Wolfson Medical Center, Holon, Israel

⁵Department of Neurosurgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

⁶Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

KEY WORDS: rheumatoid arthritis (RA), meningitis, anti-cyclic citrullinated peptide antibodies (CCP), positron emission tomography-computed tomography (PET-CT), brain biopsy

IMAJ 2018; 20: 262–264

Central nervous system involvement in rheumatoid arthritis (RA) is a rare and treatable, yet potentially fatal, condition that is frequently recognized only by autopsy [1]. The condition may present as meningitis, vasculitis, or spinal cord lesions. Approximately 25 case reports were published during the last decades describing various clinical symptoms of this condition, including confusion, focal neurological deficits, seizures, stroke-like episodes, and Parkinsonism.

In this case report, we present a patient without any history of relevant systemic diseases who was diagnosed with a self-limited episode of rheumatoid meningitis (RM) and subsequently developed atypical sero-positive RA about 13 months later.

PATIENT DESCRIPTION

A 66 year old female without any history of chronic diseases, except for osteoporosis, presented with a 2 month history of constant mild right parietal headaches and transient paresthesia in the left leg. Her neurological examination was unremarkable except for slightly brisk tendon reflexes and a Babinski sign on the left side. She did

not have any symptoms of systemic inflammation or joint pain.

Brain magnetic resonance imaging (MRI) showed effacement of the sulci in the right upper parietal area with regional dural and leptomeningeal enhancement, high signal intensity in the sulci on fluid attenuated inversion recovery (FLAIR) sequence, and two small high-signal subcortical foci in this area on T2/FLAIR sequences. No restriction on diffusion-weighted imaging sequence was found [Figure 1A, 1B, 1C]. Total body computed tomography (CT) was normal. An electroencephalogram (EEG) showed right fronto-parietal epileptiform activity.

Following the neuroimaging and EEG findings, treatment with lamotrigine was initiated. During the lamotrigine dose escalation period, the patient experienced two short-lasting focal seizures in the left extremities. In the subsequent 2 month period, her headache was resolved and no additional seizures occurred.

The patient was followed by the neurology and rheumatology clinics. Follow-up brain MRI, approximately 3 months after the patient's initial presentation, did not indicate any changes compared to the previous study, but the radiological differential diagnosis included meningeal melanoma. A whole body positron emission tomography-computerized tomography (PET-CT) with 15 mCi fluorodeoxyglucose (FDG) and an intravenous contrast medium showed increased FDG intensity in the right parietal cortex. A CT scan of this area exhibited hyperdense changes with effacement of the sulci and dural enhancement. No significant edema or mass effect and no

pathological uptake in the rest of the body were noted.

Dermatological and gynecological examinations did not indicate any pathology.

An open biopsy of the right parietal meninges and brain cortex revealed yellowish subarachnoid plaques. A histologic examination showed fragments of the arachnoid membrane and cortex exhibiting chronic inflammation, plasma cells, numerous Langerhans giant cells, and a necrotizing granulomatous reaction. No evidence of malignancy was found. Periodic acid–Schiff, Gomori Methenamine–Silver, Ziehl–Neelsen, and Gram stains were negative, as were tuberculosis polymerase chain reaction and cultures and fungal cultures.

Primary neurosarcoidosis was considered. Laboratory investigations revealed normal blood chemistry and normal levels of erythrocyte sedimentation rate; C-reactive protein; angiotensin converting enzyme; anti-neutrophil cytoplasmic antibodies; anti-nuclear antibody; complement 3; complement 4; serum immunofixation test; cryoglobulins; and serum immunoglobulin (Ig) levels of IgA, IgM, IgG2, IgG3, and IgG4. Total IgG and IgG1 levels were slightly reduced. Urine analysis was normal, including calcium level.

Rheumatoid factor (RF) level in repeated examinations was elevated at 23, 25 IU/ml (normal < 14 IU/ml), whereas anti-cyclic citrullinated peptide (CCP) levels were markedly elevated at 266 U/ml (normal < 20 U/ml).

Considering the positive RF and anti-CCP levels, the brain and meningeal biopsies were reviewed and the patho-

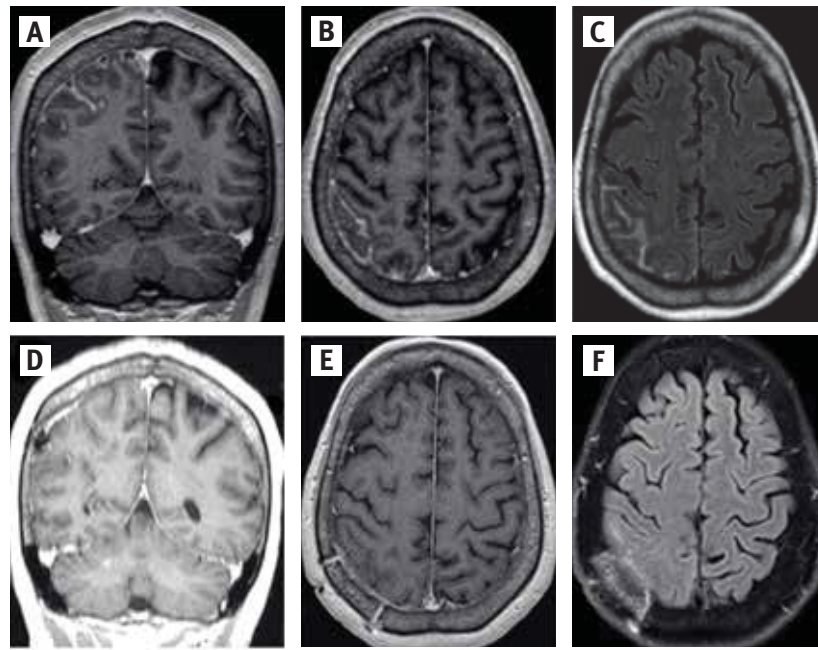
logical conclusion was that the observed non-specific, granulomatous process in the meninges may be compatible with rheumatoid leptomeningitis.

Follow-up brain MRI [Figure 1D, 1E, 1F] and PET-CT performed 3 and 9 months after the biopsy, showed substantial improvement. There were no pathological findings on the PET-CT and no gyral enhancement on the MRI. Lumbar puncture and cerebrospinal fluid (CSF) analysis performed 9 months after the onset of symptoms showed normal cell counts as well as normal protein and glucose levels.

One year after the patient's initial presentation, she reported pain and limitation of range of movement in her left shoulder that lasted for several days, which was followed by similar symptoms in her right shoulder, and again, in her left shoulder accompanied by pain and swelling of her right wrist and dorsal aspect of her right hand lasting for 2 days. These episodes responded only partially to treatment with non-steroidal anti-inflammatory drugs and each resolved after a few days. A review of her medical history revealed that 18 months earlier the patient had had an episode of pain and flexion deficit in her right third finger that had lasted several days.

A physical examination performed more than 1 year after the neurological presentation was notable for some tenderness in the wrist and metacarpophalangeal and proximal interphalangeal joints on the right side, without swelling. The left shoulder was not swollen but moderate pain could be elicited at the end of all movement ranges. At that point, considering the rheumatoid nodule-like localized granulomatous lepto-meningitis and positive rheumatoid serology (both RF and anti-CCP), the patient was thought to have a clinical course compatible with palindromic rheumatism. A diagnosis of seropositive RA with preceding extra-articular manifestation of RA was made. The patient started taking oral methotrexate 12.5 mg, once weekly, which was well tolerated. On follow-up 9 months later she was asymptomatic regarding her articular as well as her extra-articular manifestations.

Figure 1. Initial brain magnetic resonance imaging at case presentation showed effacement of the sulci in the right upper parietal area with regional dural and leptomeningeal enhancement [A,B] and a high signal in the sulci on FLAIR sequence [C]. Follow-up studies showed a substantial improvement [D,E,F]



DISCUSSION

RM is a rare and severe complication of RA, and its pathogenesis remains unclear. The diagnosis of this condition is difficult. It is usually made by exclusion and requires neuroimaging, CSF studies, extensive blood studies, and a brain biopsy. Any of the aforementioned tests may show only non-specific changes. MRI findings usually exhibit non-specific meningeal thickening and contrast enhancement [2]. CSF studies may be normal or show non-specific lymphocytic pleocytosis with protein elevation. The significance of increased RF in the CSF is unclear [3]. Brain and meningeal biopsy shows granulomatous inflammation with multifocal necrosis and meningeal vasculitis.

There is no consensus about the treatment of RM. In most reported cases the patients were treated empirically by a combination of corticosteroids and immunosuppressive drugs (methotrexate, azathioprine, cyclophosphamide) or with infliximab.

The majority of case reports describe patients with a previous history of RA. We

found only two cases in which the neurological involvement preceded the diagnosis of classic RA. In one case the patient had a history of arthralgia [4], in the other case RA manifestations occurred 2 months after pachymeningitis was diagnosed [5].

The presented case of RM is unusual in several aspects. First, it was a self-limited event and the patient was treated symptomatically with lamotrigine only. Second, RM diagnosis, which was based on positive findings in both the meningeal and brain biopsies as well as on constant positive RF and anti-CCP serum levels, was done 13 months before the development of the clinical picture of RA. Third, PET-CT with FDG showed positive findings during the acute phase of RM that disappeared in the follow-up study. To the best of our knowledge, this is the first description of pathological PET-CT findings in RM.

CONCLUSIONS

Following our experience in this case study, we recommend including PET-CT, anti-

CCP, and RF to the investigation of patients with meningitis of unclear etiology.

Correspondence

Dr. V. Finkelshtein

Dept. of Neurology, Wolfson Medical Center,
Holon 58100, Israel

Phone: (972-3) 502-8512

Fax: (972-8) 947-0891

email: vitality7@bezeqint.net

References

1. Bathon JM, Moreland LW, DiBartolomeo AG. Inflammatory central nervous system involvement in rheumatoid arthritis. *Semin Arthritis Rheum* 1989; 18: 258-66.
2. Cianfoni A, Falcone C, Faustini F, et al. Rheumatoid leptomeningitis: magnetic resonance imaging and pathologic findings – a case report. *J Neuroimaging* 2010; 20: 192-4.
3. Kim HY, Park JH, Oh HE, Han HJ, Shin DI, Kim MH. A case of rheumatoid meningitis: pathologic and magnetic resonance imaging findings. *Neurol Sci* 2011; 32: 1191-4.
4. Duray MC, Marchand E, Gohy S, Weynand B, De Coene B, Laloux P. Granulomatous meningitis due to rheumatoid arthritis. *Acta Neurol Belg* 2012; 112: 193-7.
5. Shibahara T, Matsushita T, Matsuo R, et al. Anti-Cyclic Citrullinated peptide antibody-positive meningoencephalitis in the preclinical period of rheumatoid arthritis. *Case Rep Neurol* 2016; 8:156-60.

Capsule

For cancer, think globally, act locally

Systemic immunotherapy in cancer treatment can have major side effects because it stimulates the entire immune system and is not necessarily tumor-specific. Surgery, a classic mainstay of cancer treatment, has the drawback of temporarily suppressing the immune response at the site of tumor resection. To address both concerns, **Park** et al. designed hydro-

gel scaffolds to gradually release agonists of innate immunity. They implanted these scaffolds into mice at the sites of tumor resection. This approach was safe and more effective than systemic or even locally injected immunotherapy.

Sci Transl Med 2018; 10, eaar1916

Eitan Israeli

Capsule

Regeneration of the entire human epidermis using transgenic stem cells

Junctional epidermolysis bullosa (JEB) is a severe and often lethal genetic disease caused by mutations in genes encoding the basement membrane component laminin-332. Surviving patients with JEB develop chronic wounds to the skin and mucosa, which impair their quality of life and lead to skin cancer. **Hirsch** and colleagues showed that autologous transgenic keratinocyte cultures regenerated an entire, fully functional epidermis on a 7 year old child suffering from a devastating, life-threatening form of JEB. The proviral integration pattern was maintained in vivo and

epidermal renewal did not cause any clonal selection. Clonal tracing showed that the human epidermis is sustained not by equipotent progenitors, but by a limited number of long-lived stem cells, detected as holoclones, which can extensively self-renew in vitro and in vivo and produce progenitors that replenish terminally differentiated keratinocytes. This study provides a blueprint that can be applied to other stem cell-mediated combined ex vivo cell and gene therapies.

Nature 2017; 551: 327

Eitan Israeli

Capsule

A gammaherpesvirus provides protection against allergic asthma by inducing the replacement of resident alveolar macrophages with regulatory monocytes

The hygiene hypothesis postulates that the recent increase in allergic diseases such as asthma and hay fever observed in Western countries is linked to reduced exposure to childhood infections. **Machiels** et al. investigated how infection with a gammaherpesvirus affected the subsequent development of allergic asthma. The authors found that murine herpesvirus 4 (MuHV-4) inhibited the development of house dust mite (HDM)-induced experimental asthma by modulating lung innate immune cells. Specifically, infection with MuHV-4 caused the replacement of resident

alveolar macrophages (AMs) by monocytes with regulatory functions. Monocyte-derived AMs blocked the ability of dendritic cells to trigger a HDM-specific response by the T_H2 subset of helper T cells. These results indicate that replacement of embryonic AMs by regulatory monocytes is a major mechanism underlying the long-term training of lung immunity after infection.

Nature Immunol 2017; 18: 1310

Eitan Israeli