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Rheumatoid leptomeningitis presenting with an acute neuropsychiatric disorder

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MANUSCRIPT TITLE PAGE

Title:

Rheumatoid leptomeningitis presenting with an acute neuropsychiatric disorder

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Michal Lubomski: involved in the inpatient management of the patient, study concept, literature review and writing of the manuscript.

Joanne Sy: involved in the reporting of the histopathology, study concept and writing of the manuscript.

Michael Buckland: involved in the reporting of the histopathology, study concept and writing of the manuscript.

Andie S. Lee: involved in the inpatient management of the patient and writing of the manuscript.

Bethan Richards: involved in the inpatient management of the patient and writing of the manuscript.

Elizabeth Thompson: involved in the reporting of MRI imaging and writing of the manuscript.

Michael Fulham: involved in reporting of PET imaging and writing of the manuscript.

Nora Breen: involved in the inpatient management of the patient and writing of the manuscript.

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Title:

Rheumatoid leptomeningitis presenting with an acute neuropsychiatric disorder

Abstract:

Leptomeningitis is a rare central nervous system manifestation of rheumatoid arthritis (RA), generally in patients with established chronic rheumatoid disease. We report a 41-year-old man without previous RA or psychiatric disorder presenting with an acute neuropsychiatric disturbance and polyarthralgia.

MRI brain showed asymmetric bi-frontal leptomeningitis, confirmed on (¹⁸F)-fluoro-D-glucose-positron emission tomography. Other investigations revealed highly positive serum and CSF anti-cyclic citrullinated peptide. A leptomeningeal biopsy showed necrotising leptomeningeal inflammation with ill-defined granulomas and lymphoplasmacytic infiltrate without organisms. Prolonged high-dose corticosteroids and then rituximab resulted in recovery.

Chronic leptomeningitis can present with an acute neuropsychiatric disorder. We highlight that early rheumatoid disease can, rarely, cause a chronic leptomeningitis, reversible with immunotherapy.

Key words:

Rheumatoid Meningitis; Leptomeningitis; Pachymeningitis; Neuropsychiatric disturbance; Rheumatoid Arthritis

Introduction:

Leptomeningitis is a rare manifestation of central nervous system involvement in rheumatoid arthritis (RA), usually presenting with focal neurological signs in patients with established disease. We report a patient with only a short history of polyarthralgia, who presented with an acute neuropsychiatric disturbance, and a chronic fronto-temporal leptomeningitis, which turned out on serology and biopsy to reflect rheumatoid disease. He was successfully treated with corticosteroids and rituximab. Four months later, he began a graded return to work.

Clinical Summary:

A previously well 41-year-old man of Nicaraguan origin was brought to the Emergency Department by co-workers, concerned about a four-day deterioration in mental state. His psychiatric symptoms included elevated and irritable mood; increased energy and reduced sleep; out of character risk-taking; grandiose and persecutory delusions; and plans to spend large sums of money on a sports car and property development. This was preceded by several months of reduced frustration tolerance, as reported by his wife. He complained only of chronic headache and migratory palindromic, large and small joint polyarthritis for 18-months, self-treated with indomethacin for a few weeks due to suspected gout. He was a non-smoker with a social alcohol consumption and denied recreational drug use. Much later it emerged that three-months before this he had seen a private neurologist about transient sensory symptoms and leg weakness. MRI brain showed early leptomeningeal changes, however he did not reveal this to his family and failed to attend his scheduled follow-up consultations, in hindsight likely due to early executive dysfunction.

On examination he was afebrile, without focal neurological signs, normal fundi and a supple neck. He was agitated, disinhibited and irritable, with pressured speech, mild thought disorder, persecutory and grandiose delusions. He could not recall recent events and was disorientated in time. His right elbow was swollen and painful. There were no nodules, rashes, nail changes or lymphadenopathy. All tests for drug-induced, infective or toxic/metabolic causes were negative (Supplementary Table 1). Brain

MRI showed leptomeningeal enhancement over both hemispheres especially the right frontal lobe (Figure 1:A,B) confirmed on neurological FDG-PET/CT with markedly increased glucose metabolism over the right frontal and temporal cortices (SUV 20.4 compared to 13.3 on the left), Figure 1:E,F). Neuropsychological evaluation confirmed behavioural and executive dysfunction with impaired mental flexibility, disinhibition, impulsivity and perseveration. Language, attention, visuospatial skills and memory remained preserved. Whole body PET/CT showed increased uptake in the right elbow (SUV 10.4, left elbow 2.1) consistent with inflammation, with moderately avid lymph nodes in the right axilla and supraclavicular fossa (Figure 1:G). EEG showed no focal slowing or epileptiform features. Examination of fresh CSF showed only one mononuclear cell, no organisms, protein 0.39g/L (N=0.15-0.45), glucose 3.4 mmol/L (N=2-4), normal cytology and flow cytometry. Ultrasound of the right elbow confirmed synovitis. A right supraclavicular lymph node biopsy showed only reactive changes, no granulomas; acid-fast smears, tuberculosis (TB) polymerase chain reaction (PCR) and mycobacterial cultures were negative. Serum anti-cyclic citrullinated peptide (CCP) antibody was >600U/mL (N<10); CSF anti-CCP was strongly positive. Rheumatoid factor was 8 IU/mL (N<15) and a vasculitic screen was unremarkable. Interferon-gamma release assay (IGRA) was positive suggesting TB, latent or active. A biopsy of the leptomeninges and the right frontal cortex showed necrotising inflammation with ill-defined granulomas and a dense lymphoplasmacytic infiltrate involving the leptomeninges (Figure 2:A,B,C). The underlying cortex showed rare superficial vessels with mild perivascular lymphocytic inflammation but was otherwise uninvolved. There was no evidence of vasculitis. No acid-fast bacilli, fungi or treponemes were identified on special stains. Tissue flow-cytometry showed a polyclonal plasma cell population with no evidence of a lymphoproliferative disorder. Immunohistochemistry showed no evidence of IgG4-related disease. TB-PCR and mycobacterial cultures were negative, even after three-months. The histological diagnosis favoured rheumatoid meningitis.

Treatment included three-day pulse 1g IV methylprednisolone with a high-dose oral prednisolone taper over six-months, with empirical cover for possible active TB with rifampicin, isoniazid, pyrazinamide and ethambutol. Two-doses of 1g IV rituximab, one-month after initiating steroids resulted in sustained improvement of neuropsychiatric and joint symptoms. B-cell monitoring showed adequate depletion

post rituximab. Oral olanzapine and diazepam, both 10mg twice daily assisted in the management of psychotic symptoms and behavioural disturbance in the setting of an acute neurological ward. Initial management also required the use of the relevant local mental health legislation with one-to-one nursing to reduce the risk that he would abscond. Capacity to make medical decisions was monitored and substitute decision-making was not required. After two-months he was discharged home with resolution of manic and psychotic symptoms, headache and synovitis but with persisting executive dysfunction. He continued on 60mg prednisolone daily and a weaning dose of olanzapine. A progress MR scan at three-months (Figure 1:C,D) showed marked reduction in leptomenigeal enhancement and thickening. Progress neuropsychological evaluation at four-months showed resolution of impulsive and disinhibited behaviour although he continued to show reduced mental flexibility. He began a graded return to work at that time but not yet to his previous level of authority and responsibility.

Discussion:

This patient's acute neuropsychiatric disturbance was due to frontal lobe cortical inflammation secondary to leptomenigitis. Lack of prior mental health history, normal metabolic/toxicology investigations, unremarkable CSF and asymmetric bifrontal leptomenigeal enhancement on MRI indicated an inflammatory or infiltrative leptomenigitis/pachymenigitis. Lymphoma, IgG4-related disease, TB, granulomatosis with polyangiitis, neurosarcoidosis, neurosyphilis and meningeal metastases were all considered (1), but migratory inflammatory arthritis and headache favoured rheumatoid meningitis and was supported by serum and CSF anti-CCP as well as the meningeal histology. The leptomenigeal granulomas were distinct from sarcoid which are typically well formed, not necrotic and do not have a large lymphoplasmacytic inflammatory component. As the IGRA suggested TB exposure, TB meningitis was considered although TB-PCR and repeat CSF analysis could not identify active meningeal TB and mycobacterial cultures were negative after three-months. After two-months of initial TB treatment, he continued on three-times weekly rifampicin and isoniazid to complete twelve-months treatment. The improvement in neuropsychiatric and joint symptoms and MRI reflected intensified treatment with rituximab coupled with a sustained slow taper of steroids, rather than TB treatment.

Rheumatoid meningitis more often involves the pachymeninges rather than the leptomeninges and appears granulomatous, occasionally with rheumatoid nodules and features of vasculitis. A confident diagnosis can only be made from tissue biopsy (2). There is inflammation with fibrinoid necrosis surrounded by lymphocytes and epithelioid histiocytes, with variable plasma cell infiltrate (1). Recent reviews of 29 (1) and 48 (2) rheumatoid meningitis patients suggest focal neurological changes, hemiparesis or hemi-sensory changes mimicking stroke or focal epilepsy are the usual presenting features (3), with about 2/3 of cases demonstrating asymmetric meningeal involvement on MRI (1). Most rheumatoid meningitis patients were known to have RA long before they developed leptomeningitis; ten reports suggest a neuropsychiatric disturbance, coinciding with seizures, myoclonus or hemiparesis (2). Only six reports document neurological manifestations without prior RA, with joint symptoms occurring with or soon after the onset of rheumatoid meningitis (2, 4-6).

Consensus about the treatment of rheumatoid meningitis is lacking. Corticosteroids and other disease-modifying immunosuppressive agents have been reported, including methotrexate, cyclophosphamide (2, 7), as well as tumour necrosis factor-alpha antagonists (8). This is the third reported case of rheumatoid meningitis successfully treated with rituximab (8, 9). The treatment was complicated by evidence of previous TB exposure. However, lack of systemic involvement, normal CSF parameters and strongly positive serum and CSF anti-CCP favoured rheumatoid meningitis over TB meningitis. We found no previous reports of rheumatoid meningitis presenting as an isolated acute neuropsychiatric disturbance, responsive to immunotherapy.

This case illustrates that rheumatoid disease needs to be considered in patients presenting with leptomeningitis, even in those without established RA. Clinical evaluation of joint symptoms and signs, anti-CCP (as well as rheumatoid factor) and then meningeal biopsy will confirm the diagnosis. The clinical features of this case crossed numerous disciplines, highlighting the importance of cooperation and collaboration between specialties.

Conflicts of Interest and Disclosures:

All authors declare no disclosures.

Highlights:

- Rheumatoid disease is a rare cause of leptomeningitis and can occur before a diagnosis of rheumatoid arthritis is made.
- Rheumatoid leptomeningitis can rarely present as an acute neuropsychiatric disorder.
- Rheumatological history, examination and a meningeal biopsy need to be considered in the investigation of patients with leptomeningitis.
- Intensive immunotherapy can reverse the leptomeningitis and associated neurological features.

Figure Legends:

Figure 1:

MR scan: **A)** coronal enhanced image shows asymmetric leptomeningeal thickening and enhancement over both frontal lobes; **B)** sagittal enhanced image shows leptomeningeal enhancement over right hemisphere. Progress three month MR scan **C)** coronal and **D)** sagittal enhanced images showing reduction in leptomeningeal enhancement and thickening.

FDG PET-CT scans: **E)** transaxial image shows markedly increased metabolism overlying right infero-mid frontal lobe; **F)** sagittal image shows extensive right frontal metabolism; **G)** whole body projection image shows markedly increased uptake in the right elbow (SUV 10.4l) consistent with inflammation. Also moderately increased glucose avid lymph nodes in the right axilla and supraclavicular fossa.

Figure 2:

A) Dense leptomeningeal inflammation and mild superficial cortical perivascular lymphocytosis (magnification 4x). **B)** Occasional necrotising granulomas with neutrophils (magnification 40x). **C)** Numerous multinucleated giant cells and dense lymphoplasmacytic inflammation (magnification 40x).

Supplementary Table 1:

Investigation Results

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