CASE REPORT

Rheumatoid disease: an unusual cause of relapsing meningoencephalitis

Sian K Alexander,[1] Maria Di Cicco,[2] Ute Pohl,[3] Alberto Cifelli[1]

[1]Department of Neurology, Queen's Hospital, Romford, UK
[2]Department of Rheumatology, Queen's Hospital, Romford, UK
[3]Department of Pathology, Queen's Hospital, Romford, UK

Correspondence to
Dr Sian K Alexander, siankathalexander@gmail.com

Accepted 18 December 2017

SUMMARY

A 73-year-old man presented with three episodes of dysphasia and disinhibited behaviour, a single seizure and transient ischaemic attack-like events characterised by right arm and/or leg weakness. These episodes were separated by month-long asymptomatic intervals. Medical history included rheumatoid arthritis, which was clinically quiescent on leflunomide.

Repeated cerebrospinal fluid examination showed a persistent lymphocytosis with mildly reduced glucose and elevated protein; oligoclonal bands and viral PCR were negative. MRI of the brain was initially normal, but 7 months after initial presentation revealed meningeal enhancement with bifrontal cortical hyperintensities on T2/fluid-attenuated inversion recovery. Brain biopsy demonstrated necrotising granulomatous meningitis with mixed T cell and B cell infiltrates and without evidence of vasculitis or infection. Serum anticyclic citrullinated peptide antibodies were strongly positive.

The diagnosis of rheumatoid meningoencephalitis was made on the basis of brain biopsy findings and serological evidence of active rheumatoid disease. Steroids and rituximab therapy were started leading to clinical stabilisation.

BACKGROUND

Rheumatoid meningitis (RM) with or without encephalitis is a rare manifestation of rheumatoid arthritis. It can occur, as in this case, in individuals with otherwise quiescent disease. It is characterised by an inflammatory CSF and radiological evidence of meningeal enhancement with or without underlying parenchymal signal change; however, radiological abnormalities may lag behind clinical disease by many months. Biopsy showed a necrotising granulomatous meningitis with mixed T and B cell infiltrates. Anti-CCP antibodies can helpfully raise suspicion of active rheumatoid disease, although they do not accurately correlate with disease activity.

Infective meningoencephalitis may mimic this condition, with similar clinical, laboratory and histopathological findings. In our patient, frontal lobe cerebritis secondary to sinus disease was a particular concern, and detailed microbiological investigations were undertaken to exclude it.

This case highlights a potential manifestation of rheumatoid disease which may be missed. Treatment is immunosuppression, in this case with steroids and rituximab, although the optimal regime is not established.

CASE PRESENTATION

A 73-year-old retired bricklayer presented to our department with a history of three episodes of expressive dysphasia, agitation and impulsivity, during which he was able to feed and mobilise independently. The dysphasia resolved and behavioural change spontaneously improved 2–4 days from onset. At the time of the first episode, he had a single tonic–clonic seizure. The episodes were separated by asymptomatic periods lasting months (there was a 6-month interval between first and second episodes, and a 1-month hiatus between second and third episodes). There were no fevers or night sweats, but the patient had lost weight over recent months and reported generalised malaise. Following the third episode, there was persistence of a mildly disinhibited manner and the patient also experienced spells of intermittent and spontaneously resolving left arm and leg weakness, lasting between one and a few hours.

Medical history included seropositive rheumatoid arthritis (which was clinically quiescent on leflunomide), mesenteric ischaemia, peripheral vascular disease, abdominal aortic aneurysm (5 cm diameter), chronic kidney disease stage 3, hypertension and hypercholesterolaemia. He was an ex-smoker with no alcohol history or illicit drug exposure and was living independently with his family. There was no relevant family history.

On physical examination at presentation, there was isolated expressive dysphasia and subtle disinhibition, without evidence of other neurological deficits, active synovitis, pulmonary, renal or other systemic disease.

INVESTIGATIONS

With each episode, the patient was evaluated with peripheral blood examination, chest X-ray, urinalysis, CT and then MRI of the brain, as well as lumbar puncture. Cerebrospinal fluid (CSF) analysis was abnormal from the first presentation with persistent lymphocytosis, mildly reduced glucose and elevated protein; oligoclonal bands were absent and viral PCRs negative (see table 1).

Brain MRI was abnormal for the first time 7 months after the initial symptoms and demonstrated (as shown in figure 1) localised T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensity in both frontal cortices, more extensive on the right, with local oedema. There was modest parenchymal as well as leptomeningeal enhancement. At this time, cognitive assessment

To cite: Alexander SK, Di Cicco M, Pohl U, *et al*. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2017-222587

Table 1 Cerebrospinal fluid (CSF) results

	March 2016	September 2016	October 2016
White cell count (/cm^3)	32	100	18
% lymphocytes	90	28	100
CSF glucose (mmol/L)	2.6	3.1	2.5
Serum glucose (mmol/L)	4.8	5	4.8
Protein (g/L)	0.69	1.03	0.74
Viral PCR (herpes simplex, varicella zoster, Epstein Barr, enterovirus, cytomegalovirus)	Negative	Not done	Not done
Cytology	No malignant cells	Scant	No malignant
Lactate dehydrogenase (IU/L)	<50	Not done	Not done

revealed marked impairment on tests of memory and fluency (Addenbrooke's Cognitive Examination—III total score 68/100; subscores: attention 18/18; memory 8/26; fluency 5/14; language 26/26; visuospatial 11/16).

The radiological appearances were non-specific for infective or inflammatory causes of focal meningoencephalitis. Incidental sinus mucosal thickening was seen on the MRI of the brain, and CT of the sinuses was consistent with chronic sinusitis as well as a possible skull base defect. The patient underwent a sinus washout and sinoplasty, at which purulent-looking secretions were noted. *Staphylococcus haemolyticus* was cultured from this site but considered to have no significance by a Consultant Microbiologist and other microbial cultures were negative. Pan-fungal PCR was negative from sinus washout. HIV, lyme, syphilis and Brucella serology, and blood cultures were negative. Interferon-gamma release assay (Quantiferon) testing was negative. CT chest, abdomen and pelvis showed no evidence of systemic infection or malignancy.

The patient received empirical antibiotic treatment with intravenous ceftriaxone for 3 weeks followed by meropenem for 3 weeks, to which the cultured *S. haemolyticus* was fully sensitive. Leflunomide was stopped. There was no clinical or radiological improvement, which prompted a right frontal brain and meningeal biopsy. Histopathological analysis of the specimens found evidence of a necrotising, moderately granulomatous meningitis (as shown in figure 2). The leptomeninges were thickened, fibrosed and inflamed with focal areas of necrosis which were surrounded by a predominantly chronic inflammatory infiltrate with accumulations of T and B lymphocytes, plasma cells, macrophages and occasional multinucleate giant cells. In the brain parenchyma, reactive astrocytosis and chronic inflammatory infiltrates were observed. There were no features of vasculitis. While there was granulomatous inflammation of the meninges, there were no discrete and well-formed granulomata in the meninges or brain. There was no evidence of infection (including negative 16S and 18S PCR). IgG4 staining was negative.

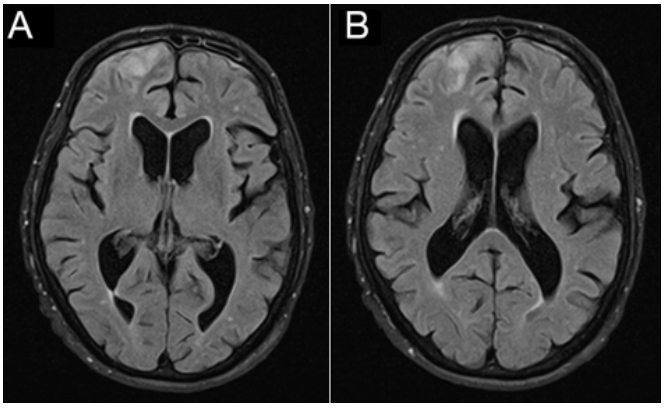

Figure 1 Axial fluid-attenuated inversion recovery MRI brain images demonstrated cortical hyperintensity in the frontal lobes, more prominent on the right. There was modest bilateral frontal intraparenchymal and leptomeningeal contrast enhancement (not shown).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for focal meningoencephalitis is broad, including infective, inflammatory and neoplastic aetiologies. Long-term exposure to immunosuppression (leflunomide and previously methotrexate) led us to include atypical microorganisms and unusual presentations of conventional pathogens.

Infective

Viral meningoencephalitis, in particular herpes simplex virus (HSV), is a common cause of acute behavioural disturbance, often with seizures and similar CSF findings (lymphocytic CSF, normal/slightly low glucose and normal/slightly elevated protein). However, the frontal distribution of disease and the absence of temporal lobe involvement are unusual for this condition, and the pattern of recurrent episodes and negative HSV CSF PCR made it extremely unlikely. Other viral aetiologies (varicella zoster and enteroviruses) excluded by CSF PCR.

Bacterial or fungal infection, especially by direct spread from chronic sinusitis, was a specific concern in our patient, particularly as he had received several short courses of third generation cephalosporin treatment with earlier presentations. The negative 16S and 18S PCR on intraoperative and biopsied tissue was diagnostically very helpful. Tuberculosis (TB) usually presents with an indolent course and lymphocytic CSF, but usually causes a basal meningitis and more pronounced biochemical abnormalities in the CSF. Moreover, interferon-gamma release assay (Quantiferon), Ziehl-Nielsen stains and TB cultures were negative.

Neoplasia

Weight loss, malaise and non-response to empirical antibiotic therapy could be indicative of an underlying systemic malignancy with neoplastic or paraneoplastic central nervous system (CNS) effects. Malignant cells were not visualised in the CSF or brain tissue. Cross-sectional imaging of the thorax and abdomen did not demonstrate any abnormalities. Paraneoplastic antibodies (Hu, Ri, Yo, amphiphysin/collapsin response mediator protein 5 and glutamic acid decarboxylase) were not detected.

Inflammatory

CNS vasculitis was a consideration, although the radiological findings were atypical for this and vasculitic features were absent in affected brain parenchyma on biopsy. In addition, antineutrophil cytoplasmic antibodies, connective tissue antibodies and antiphospholipid antibodies all tested negative. Antibody-mediated disease can present subacutely with diverse manifestations; however, antibodies against a range of neuronal epitopes were negative (contactin-associated protein (Caspr-2), **leucine** -rich glioma inactivated **1 protein** (Lgi-1), N-Methyl-D-aspartate (NMDA), gamma-aminobutyric acid B

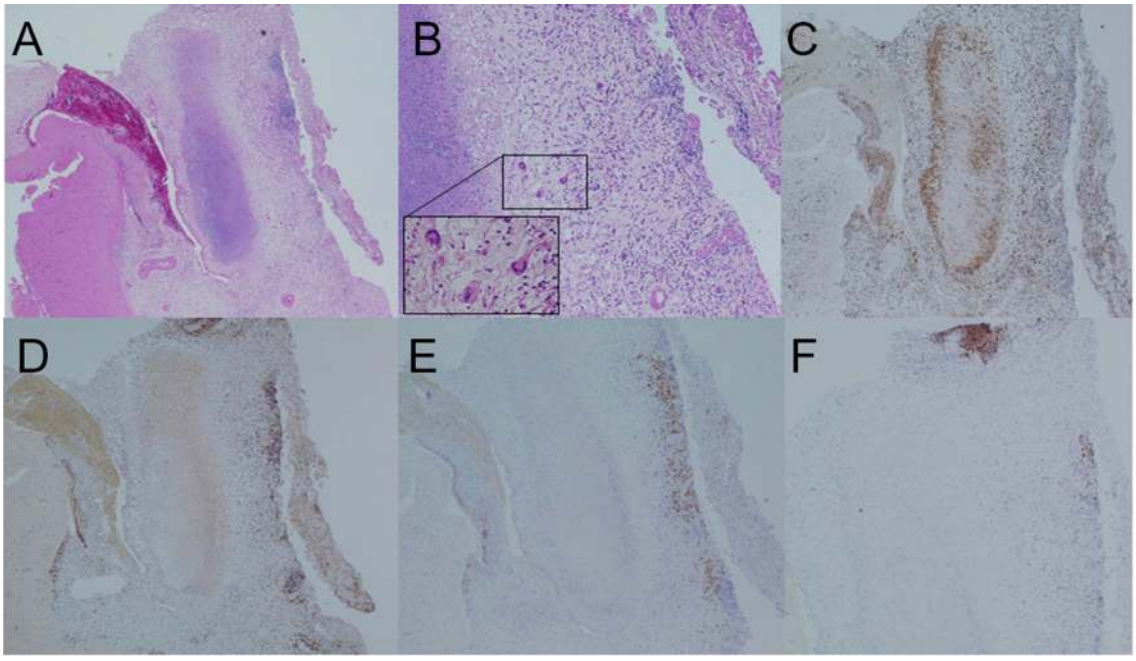

Figure 2 Histopathology of the brain/meningeal biopsy showed (A and B) thickened leptomeninges with focal necrosis surrounded by a mixed chronic inflammatory/moderately granulomatous infiltrate (H&E; ×20 and ×100, respectively). Immunohistochemistry revealed occasional multinucleate giant cells (B, insert, ×200); (C) numerous CD68 positive histiocytes/macrophages (×40); peripheral groups of (D) CD3 positive T cells (×40) and (E) CD138 positive plasma cells (×40), as well as focal collections of (F) CD20 positive B cells (×40).

(GABA-B) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors). Behcet's disease was entertained in the differential diagnosis in light of the history of mesenteric ischaemia: the patient did not have ocular, optic nerve or skin involvement, nor mucosal ulceration and HLA-B51 was negative. IgG4 disease can cause a pachymeningitis, although almost always in the presence of systemic manifestations, but immunoglobulin levels were normal and IgG4 deposition was absent on the brain and meningeal biopsy.

The diagnosis of RM was suspected on the basis of the clinical characteristics of previously published case reports, serological evidence of rheumatoid disease (rheumatoid factor 45 (normal range 0–14 units/ml) and anticyclic citrullinated peptide (CCP) antibodies >340 (normal range 0–7 units/ml)) and ultimately supported by the cerebral biopsy findings.

Learning points

- Rheumatoid arthritis is a multisystem disease that can rarely cause meningitis and meningoencephalitis.
- Rheumatoid meningoencephalitis can occur in the absence of signs of systemic rheumatoid disease activity.
- Inflammatory cerebrospinal fluid findings in an individual with diagnosed or suspected rheumatoid arthritis should raise suspicion for this diagnosis. Clinical disease may precede MRI changes by many months. Rheumatoid factor and elevated cyclic citrullinated peptide antibodies may be present but do not accurately correlate with disease activity.
- Treatment is immunosuppression, although the optimal regime is not established. Steroids, cyclophosphamide and rituximab may all be effective. The limited evidence available suggests that tumour necrosis factor alpha blockade is not effective in preventing or treating rheumatoid meningoencephalitis.

TREATMENT

Leflunomide was restarted. High-dose steroids and rituximab therapy were commenced.

OUTCOME AND FOLLOW-UP

The patient's condition has stabilised, with no further relapses 6 months after diagnosis and initiation of treatment. The mildly disinhibited behaviour has persisted. He continues to live independently with his family.

DISCUSSION

RM is a rare complication of systemic rheumatoid disease. The largest case series is by Bathon *et al*, who reported death in 17 of 19 cases.[1] Subsequent publications have described effective treatment and better outcomes: in these reports (which are typically single cases) steroids and/or cyclophosphamide or methotrexate have been used with success.[2–6] The optimal agent and duration of immunosuppression are not established. Of note, one patient's CNS symptoms developed,[4] and another patient relapsed,[2] on tumour necrosis factor alpha blockade, indicating that these therapies may not be as effective as other drugs (or could even be counterproductive) in treating RM. Other cases describe the emergence of CNS rheumatoid disease in the absence of active synovitis, similarly to our case.[5 6]

Acknowledgements The authors thank the colleagues who contributed to this patient's care, including Neurology registrar Dr Stevan Wing, Rheumatology registrar Dr Muhammad Shipa and Microbiology colleagues, especially Dr Sandra Lacey.

Contributors SKA drafted the paper. UP contributed to the neuropathology information. MDC, UP and AC revised the paper. All authors contributed to the clinical care of the patient.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Bathon JM, Moreland LW, DiBartolomeo AG. Inflammatory central nervous system involvement in rheumatoid arthritis. *Semin Arthritis Rheum* 1989;18:258–66.
2 Chou RC, Henson JW, Tian D, *et al*. Successful treatment of rheumatoid meningitis with cyclophosphamide but not infliximab. *Ann Rheum Dis* 2006;65:1114–6.
3 Nihat A, Chinthapalli K, Bridges L, *et al*. Rheumatoid meningitis. *Pract Neurol* 2016:1–3.
4 Huys AC, Guerne PA, Horvath J. Rheumatoid meningitis occurring during adalimumab and methotrexate treatment. *Joint Bone Spine* 2012;79:90–2.
5 Chowdhry V, Kumar N, Lachance DH, *et al*. An unusual presentation of rheumatoid meningitis. *J Neuroimaging* 2005;15:286–8.
6 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.