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Successful treatment of rheumatoid meningitis with cyclophosphamide but not infliximab

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Rheumatoid meningitis is a rare but lethal disorder that occurs in an elderly population with longstanding rheumatoid arthritis (RA).¹ Although the majority of

patients experience neurological symptoms, up to 26% of the patients were asymptomatic in a case series study as identified by necropsy.¹ There is poor correlation between

Figure 1 Magnetic resonance images demonstrated abnormal gadolinium enhancement of the dura and leptomeninges, and hyperintense signal in the subarachnoid spaces before intravenous cyclophosphamide treatment (A, C). After 6 months of treatment with monthly intravenous cyclophosphamide and daily oral prednisone, almost complete resolution of these abnormal findings occurred (B, D). Coronal T₁ weighted images after administration of intravenous gadolinium contrast (A, B), and axial FLAIR images (C, D). (R, right; L, left).

Figure 2 A biopsy of the dura and underlying brain showed thickening of the dura and leptomeninges with chronic inflammation (A). The inflammatory exudate consists of mature lymphocytes, plasma cells, and histiocytes (B) surrounding an area of bland necrosis with acellular debris (C). Occasional multinucleated cells are also present in the exudate (D). Haematoxylin and eosin stain. Original magnification (A) $\times 50$; (B) $\times 400$; (C) $\times 200$; (D) $\times 600$.

the severity of synovitis and neurological symptoms, which therefore imposes a challenge in the diagnosis of this condition.¹ To date there are no established treatment regimens for rheumatoid meningitis, although most patients receive immunosuppressive agents. Although the anti-tumour necrosis factor (TNF) agents have been proved to provide significant relief for the articular manifestations of RA, their effectiveness for rheumatoid meningitis has not been reported.²

A 58 year old woman with previous diagnoses of fibromyalgia and osteoarthritis was referred to the rheumatology clinic of the Massachusetts General Hospital (MGH) with worsening polyarthritis of both hands, wrists, knees, and ankles while receiving daily rofecoxib, 25 mg. Before the visit she had undergone extensive investigation for a 6 month history of progressive neurological symptoms, including severe headaches, emotional lability, left facial numbness, slurred speech, weakness and numbness of the extremities, frequent falls, and seizures. Brain magnetic resonance imaging (MRI) showed enhancement of the leptomeninges over the right cerebral convexity (figs 1A and C). Brain biopsy at the MGH showed chronic pachymeningitis and leptomeningitis exhibiting an ill-defined granulomatous reaction with central necrosis and surrounding chronic active inflammation with numerous plasma cells, Russell bodies, and multinucleated giant cells (fig 2). Gram stain and cultures of the brain biopsy samples failed to show any organisms, nor were malignant cells identified.

At the MGH rheumatology clinic, her musculoskeletal examination, MRI of the hands showing scattered erosions in

the proximal carpal bones and distal radius, and laboratory findings (erythrocyte sedimentation rate 79 mm/1st h, C reactive protein 73.7 mg/l, rheumatoid factor 413 IU/ml, anti-cyclic citrullinated protein antibody 12 U (normal <20 U)) were consistent with seropositive RA. After exclusion of other autoimmune processes a diagnosis of RA and rheumatoid meningitis was made.³

Treatment was started with monthly intravenous infusions of cyclophosphamide, 600 mg/m² for 6 months, and daily oral prednisone, 40 mg for 2 weeks. Her prednisone was tapered to 15 mg over a 6 month period. Her neurological symptoms and brain MRI abnormalities completely resolved on this regimen (figs 1B and D). The polyarthritis recurred when her daily prednisone was tapered below 20 mg, but resolved after institution of infliximab. However, the neurological symptoms and brain MRI findings (MRI not shown) recurred 4 months after her cyclophosphamide was discontinued and after she had received three doses of infliximab within 3 months. A second course of intravenous cyclophosphamide and oral prednisone treatment was given and her brain MRI findings (MRI not shown) again resolved and the neurological symptoms remitted. The patient's polyarthritis recurred when her daily prednisone was tapered below 20 mg.

As far as we know, this is the first report of the recurrence of rheumatoid meningitis during treatment with the anti-TNF agent infliximab despite simultaneous resolution of symptomatic polyarthritis. Cyclophosphamide and prednisone had previously produced a complete response of neurological symptoms and MRI abnormalities, as reported in another patient.⁴ The reasons for recurrence of meningitis in our patient during infliximab treatment are unclear, but one possibility is restricted access of the agent—that is, monoclonal antibodies with high molecular weights, into the central nervous system through the intact blood-brain barrier. Although the penetration of infliximab across the blood-brain barrier has not been measured, the penetration of other therapeutic monoclonal antibodies is between 0.1% and 0.3% of serum levels in patients with leptomeningeal cancer.^{5–6} None the less, responses of central nervous system lymphoma to intravenous rituximab,⁷ metastatic breast cancer to trastuzumab,⁸ and neuro-Behçet's disease⁹ and neurosarcoidosis¹⁰ to infliximab have been reported. Conceivably, therefore, failure of treatment by infliximab is related to the ineffectiveness of an anti-TNF agent for the granulomatous disease of rheumatoid meningitis.¹¹ Rituximab or other monoclonal antibodies may have promising therapeutic effects for rheumatoid meningitis in the future as rituximab has been shown to be effective for different autoimmune diseases, including RA.¹² Further reports of the effect of these agents on the extra-articular manifestations of RA are needed.

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Successful use of rituximab in a patient with recalcitrant Churg-Strauss syndrome

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Churg-Strauss syndrome (CSS) is a disorder characterised by hypereosinophilia and systemic vasculitis occurring in people with asthma and allergic rhinitis. Corticosteroids in combination with a cytotoxic agent are the most effective treatment for CSS. Rituximab, a genetically engineered chimeric anti-CD20 monoclonal antibody has recently been tried with favourable responses in chronic immunological diseases.¹ Several published reports have shown its effectiveness in ANCA mediated vasculitides.^{2,3} We present a patient with CSS who responded well to rituximab after conventional treatments had failed.

A 49 year old, white male patient with a long history of asthma presented in 2000 with inflammatory polyarthritis, bilateral scleritis, and negative autoantibodies. He was managed as a patient with seronegative RA but was intolerant to methotrexate and sulfasalazine. His symptoms settled, only to recur in 2004 with polyarthralgia, vasculitic skin rash (fig 1), dyspnoea, microscopic haematuria, and mild proteinuria.

Repeat investigations showed a high absolute eosinophil count of $4 \times 10^9/L$, raised erythrocyte sedimentation rate (ESR) of 120 mm/1st h, and C reactive protein (CRP) of 181 mg/L, mildly raised creatinine, and a positive cANCA (anti-proteinase 3 (PR3) titre of 30 (normal <2)). High resolution computed tomography of his chest showed pulmonary infiltrates consistent with pulmonary vasculitis. A nasal biopsy showed chronic inflammation, with some areas suggestive of vasculitis, and eosinophilic infiltration. His skin biopsy showed leucocytoclastic vasculitis, and a renal biopsy disclosed minimal non-specific abnormalities. Based on the above,⁴ a diagnosis of CSS was made and treatment was started with prednisolone 40 mg and azathioprine.

His initial response was not sustained, requiring a change to cyclophosphamide in January 2005. Despite fortnightly pulses of cyclophosphamide (15 mg/kg) for 5 months, his condition continued to deteriorate. At this point, after reviewing the available publications on the use of rituximab in ANCA associated vasculitis,^{2,3} treatment was started with this drug. Although it was planned as a 4 week regimen at 700 mg/week (375 mg/m² body surface area) with 100 mg intravenous

methylprednisolone,² he required hospital admission after the second infusion, with bronchopneumonia and herpes zoster. This was treated appropriately, and his third infusion was given as a bolus on the 4th week (1 g). After this, his skin vasculitis cleared completely (fig 1) with normal ESR, CRP, absolute eosinophil count, anti-PR3 titres (fig 2), and undetectable B cells with normal T cell markers. He has been seen fortnightly since then (nearly 3 months), with no recurrence of skin vasculitis. Small increases in his eosinophil count ($(0.5-1.5) \times 10^9/L$) have occurred and treatment with oral prednisolone at a dose of 30 mg a day is continuing.

Based on the above, rituximab appears to be a promising treatment for induction of remission in CSS. The rationale behind the use of rituximab is based on three assumptions⁵: (a) ANCA has an important role in the pathogenesis of ANCA associated vasculitides; (b) treatment with rituximab can effectively deplete CD20 expressing precursors of ANCA-producing plasma cells; and (c) plasma cells producing ANCA are short lived, and transient depletion of their CD20+

Figure 1 Skin vasculitic changes before (above) and after (below) treatment with rituximab.