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LETTER TO THE EDITORS

Neurosarcoidosis in a patient treated with tumor necrosis factor alpha inhibitors

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Dear Sirs,

We describe the case of a 36-year-old Caucasian man with a 9-year history of HLA-B27-positive ankylosing spondylitis, who presented with new seizures. He had a non-focal neurological exam. Blood tests showed mild leukocytosis and elevation in liver transaminases. Initial head CT showed hypodensity in the left frontal subcortical white matter. MRI of the brain showed leptomeningeal enhancement and several hyperintense lesions (Fig. 1a–c). He had been on adalimumab (Humira®) for 3 years, but this was discontinued as a repeat MRI showed progression and increased size of the lesions 1 month later. He was then treated with intravenous Solu-Medrol at 1 g/day for 5 days with prednisone taper and maintained on methotrexate. CSF studies showed mild lymphocytic leukocytosis and elevated protein. EEG showed bihemispheric slowing; left worse than right. Brain biopsy showed well-formed non-caseating granulomas consistent with neurosarcoidosis (Fig. 2a–c). Leading up to this presentation, he had also been treated with etanercept (Enbrel®) for 2 years prior to adalimumab. Tumor necrosis factor alpha inhibitors (TNFAIs) include etanercept (Enbrel®)—a TNFα p75 soluble receptor fusion protein; and adalimumab (Humira®) and infliximab (Remicade®)—both monoclonal antibody to TNFα. Despite the efficacy of TNFAIs in many autoimmune arthropathies and refractory sarcoidosis, treatment with these agents may have a paradoxical effect, as seen in this case.

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Neurosarcoidosis, in the presence of multisystem organ involvement and neurologic deficits, has an incidence of approximately 1 per 100,000 and is present in 5 % of systemic sarcoidosis cases [1]. It has been found strictly confined to the CNS in approximately 0.2 per 100,000. CNS involvement usually reveals granulomatous infiltration of the meninges and parenchyma, most prominent at the base of the brain [2, 3]. The etiology of sarcoidosis remains unknown; however, it may possibly be linked to genetic susceptibility with increased Th1 immune response to environmental factors [4]. TNFα is one of the main cytokines responsible for initiation and formation of granulomas; therefore, besides cytotoxic drugs such as methotrexate, azathioprine, and cyclosporine, TNFAIs have been used in some refractory cases of sarcoidosis [5, 6]. Combination treatment with mycophenolate mofetil and infliximab was shown to be effective in treating neurosarcoidosis [7]. Considering this known pathological correlation and efficacy of TNFAIs, it is somewhat surprising and paradoxical that TNFAIs would cause granulomatosis.

Tong et al. [8] summarized a total of 37 cases of sarcoid-like granuloma development after TNFAIs therapy. This phenomenon was reported in all three TNFAIs, suggesting this is a "class effect" [8–10]. Almost all cases are peripheral sarcoidosis of the lungs and skin [8]. There was only one case of neurosarcoidosis reported in a 41-year-old female being on infliximab and methotrexate for rheumatoid arthritis [11]. In our case, the temporal relationship between neurosarcoidosis development while being on etanercept and adalimumab, and resolution of the disease while being off the agents, is highly suggestive of causality. We did not rechallenge the patient with another TNFAI as there has been previous reports on recurrence of sarcoid-like granulomas with rechallenging [8, 12].

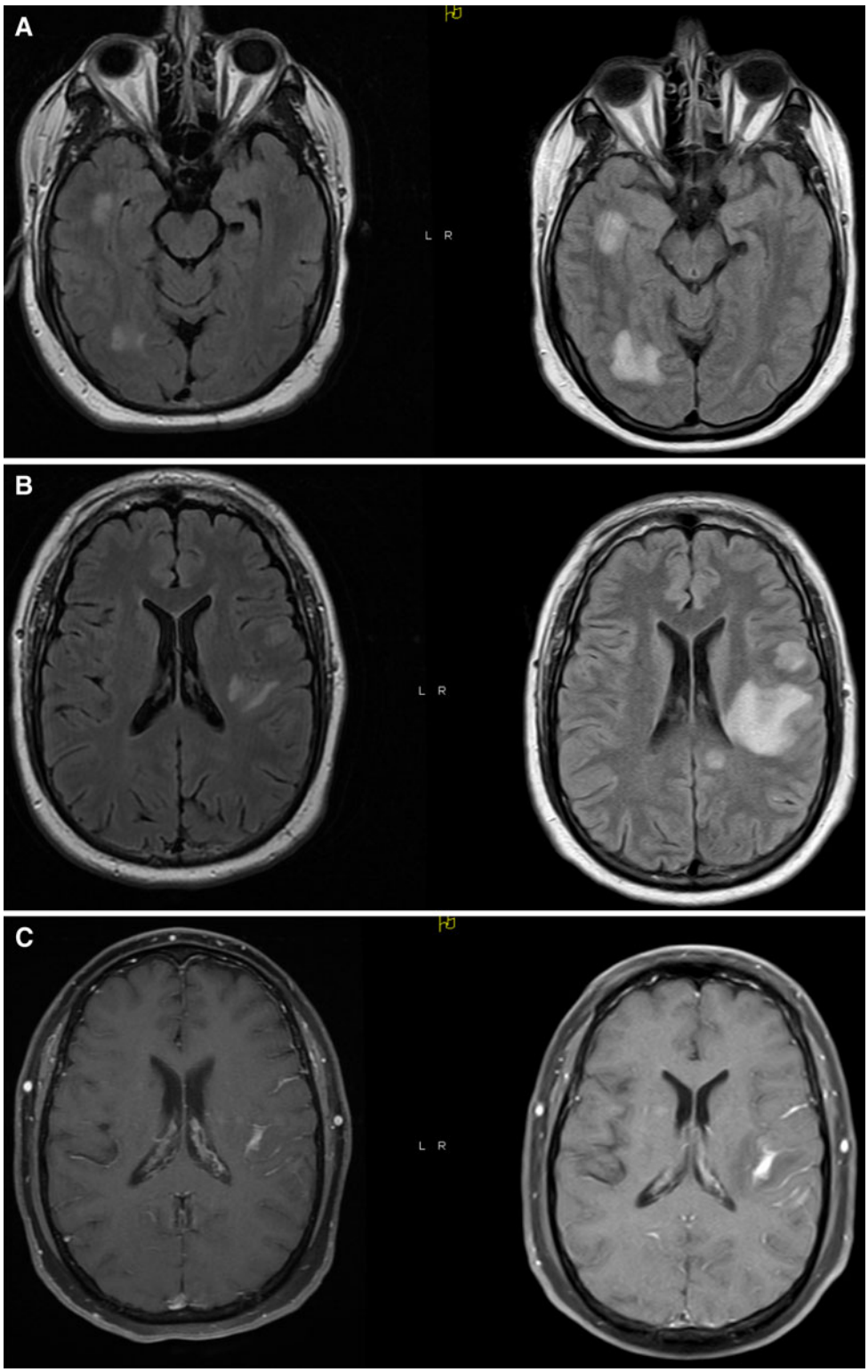

Fig. 1 MRI of the brain shows increased leptomeningeal thickening and enhancement with mild adjacent cortical increased T2 signal and adjacent underlying vasogenic edema in the right temporal, right occipital, left parietal, and left frontal lobes as well as in the left insula, the largest area of which is in the left insula. There were interval increased in size and associated vasogenic edema when compared the two sets of studies. There is also a new small area of leptomeningeal enhancement with adjacent edema in the left medial parietal lobe along the superior aspect of the left posterior corpus callosum. There is no restricted diffusion. Flow-voids are grossly preserved in the major vessels. **a** Axial T2 FLAIR shows vasogenic edema involving the subcortical white matter of the right temporal and occipital lobes. *Left* 3/17/10. *Right* 4/15/2010. **b** Axial T2 FLAIR shows extension of vasogenic edema involving the left corona radiate. *Left* 3/17/10. *Right* 4/15/2010. **c** Axial T1 post-contrast shows patchy leptomeningeal thickening and abnormal enhancement in sulci of the left frontal, right temporal, and right parietal lobes with abnormal increased signal in subcortical white matter adjacent to the abnormal leptomeningeal enhancement, consistent with vasogenic edema. *Left* 3/17/10. *Right* 4/15/2010

In addition to development of sarcoid with TNFAIs, there have been a wide range of neurological conditions, including multiple sclerosis, polycranial neuritis, and chronic inflammatory axonal polyradiculoneuropathy reported to be associated with TNFAI therapy [13]. It is unclear if these agents increase the risk of developing autoimmune disorders or simply aggravate an indolent autoimmune process already present. The etiology of this paradoxical induction of autoimmune process with TNFAIs in granulomatous disease and other autoimmune condition is unknown. Different

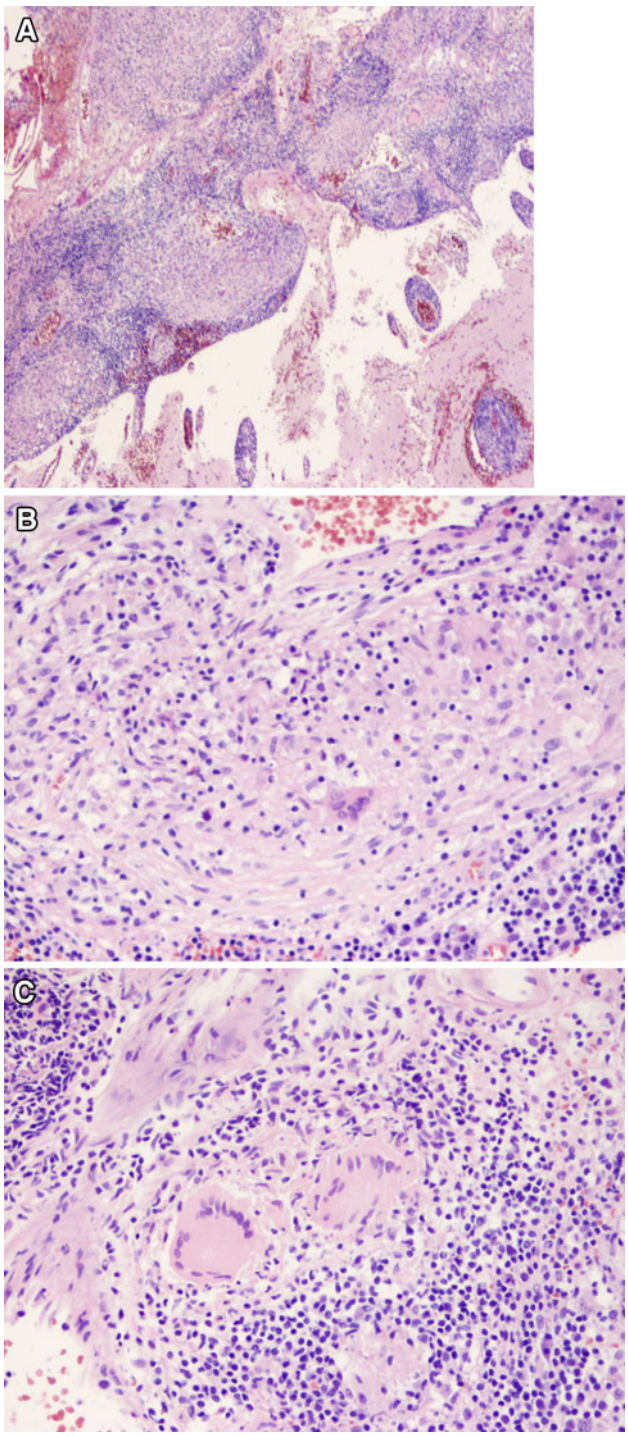

Fig. 2 Brain biopsy shows noncaseating epithelioid granulomas. **a** Low power (×40) shows lymphocytic invasion of the leptomeningeal inflammation consisting of lymphocytes and plasma cells with well-formed epithelioid granulomas (describes histiocytes) with giant cells. **b** High-power (×400) shows lesion diagnostic of sarcoidosis: non-caseating granuloma with lymphocytic rim, plasma cells, and histiocytes along with giant cells. Over time, a fibrotic response develops with a diffuse network of collagen and proteoglycans around the granuloma. **c** Giant cells formed by macrophages

pathogenic mechanism may play a role in different disease scenarios and may vary from patient to patient depends on genetic make-up and other comorbidity.

Conflicts of interest None.

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