A case report of neurosarcoidosis successfully treated with an infliximab biosimilar after a relapse while on dual therapy

Sirs,

Sarcoidosis is a rare granulomatous systemic disease with a prevalence of approximately 20 per 100,000 population (1). Typically presents in patients between 20 and 60 years of age. Involvement of the central or peripheral nervous system (neurosarcoidosis) occurs in 5–10% of patients with sarcoidosis. The histological hallmark of sarcoidosis is non-necrotising granulomata, but they are not pathognomonic. There is a consensus that glucocorticoids (GC) are the first line treatment (1). Methotrexate and azathioprine are second line steroid sparing agents. Treatment with infliximab is reserved for refractory disease (2).

A 48-year-old Caucasian man was admitted with a 2-week history of memory problems, confusion and seizures. He was reviewed by neurology and was commenced on Levetiracetam. His EEG was normal while his MRI head (Fig. 1) revealed widespread, nodular enhancement scattered throughout both cerebral hemispheres and the brainstem with extensive oedema on T2 sequences. He was further investigated with blood tests, which showed pituitatry hypofunction; a lumbar puncture, which, showed markedly elevated protein, low glucose, high lactate dehydrogenase (LDH), high ACE, negative Gram stain and cultures and a CT chest abdomen pelvis, which showed multiple lymph nodes above and below the diaphragm raising a differential diagnosis of inflammatory (sarcoid), infectious (tuberculosis) or malignant (lymphoma) process. A left inguinal lymph node biopsy showed extensive non-caseating granulomatous inflammation containing numerous epithelial-type granular matter scattered throughout the lymph node parenchyma, consistent with sarcoidosis. He was then commenced on intravenous methylprednisolone followed by tapering oral prednisolone and testosterone and levothyroxine for his panhypopituitarism. At 5 months, while on prednisolone 25 mg daily, he was commenced on oral methotrexate 10 mg weekly as long-term disease-modifying steroid sparing therapy. At 9 months, while on prednisolone 5 mg daily, he developed general fatigue, arthralgia, impaired concentration and deterioration of gait. A repeat MRI head revealed bitemporal signal changes with associated vasogenic oedema and patchy white matter changes in the frontal and occipital lobes. He was started on oral methylprednisolone 500 mg daily for 3 days, followed by prednisolone 40 mg daily. At 12 months, he was commenced on Infliximab biosimilar Remsima 3 mg/kg infusions 2 monthly. He has received 6 infusions to date, he is on methotrexate 10 mg weekly, tapering prednisolone, and is asymptomatic. A repeat MRI showed significant improvement (Fig. 2).

Neurosarcoidosis can present with non-specific symptoms such as fatigue, headache, cognitive dysfunction with progressive decline, fever, nausea, vomiting, and mood disorders, making its diagnosis a challenging process. The clinical picture depends on the site of the granulomatous infiltration, including involvement of cranial nerves, most commonly the optic (II) and facial nerve (VII), seizures or focal neurological deficits such as haemiparesis mimicking stroke (3). It can also cause dysfunction of the endocrine system, when it most commonly presents with diabetes insipidus, gonadotropin and TSH deficiency, or panhypopituitarism (12). MRI is the preferred and most sensitive diagnostic imaging technique, revealing cranial nerve involvement in 50%, leptomeningeal involvement in 40%, parenchymal mass lesions or granulomas in 35%, and pituitary gland, infundibulum or hypothalamus infiltration in 18% of patients (3). Although the base of the brain is characteristically involved in neurosarcoidosis, the above MRI findings are not sufficiently specific and therefore the diagnosis of sarcoidosis should be based on suggestive clinical picture, biochemical profile, histopathological demonstration of non-caseating granulomas, and exclusion of other diseases able to produce similar findings. The differential diagnosis includes infectious disorders, most importantly tuberculosis, vasculitis and neoplastic disorders.

There is general consensus that GC are the first-line treatment for neurosarcoidosis. If a prednisone maintenance dose of more than 10 mg/day is required for symptom control, clinical response is insufficient, intolerable side effects develop or immediate relapse occurs, immunosuppressants can be used as steroid sparing agents. Methotrexate or azathioprine can be used either as monotherapy or in combination with corticosteroids allowing a faster corticosteroid tapering, however relapses are not uncommon (4). Leflunomide at 20 mg/d may be similarly effective to MTX with fewer side effects (5). Tumour necrosis factor (TNF) has been identified as a pivotal mediator in refractory sarcoidosis (5). As third-line therapy, biological agents targeting tumour necrosis factor-alpha (TNF-alpha) such as infliximab and adalimumab can be used in patients with refractory neurosarcoidosis (6). This is the first case report where infliximab biosimilar has been used successfully in neurosarcoidosis. Cyclophosphamide is generally avoided in neurosarcoidosis due to its high toxicity and significant side effects (7). There is a single case report about successful treatment of neurosarcoidosis with the monoclonal anti-CD20 rituximab (8).

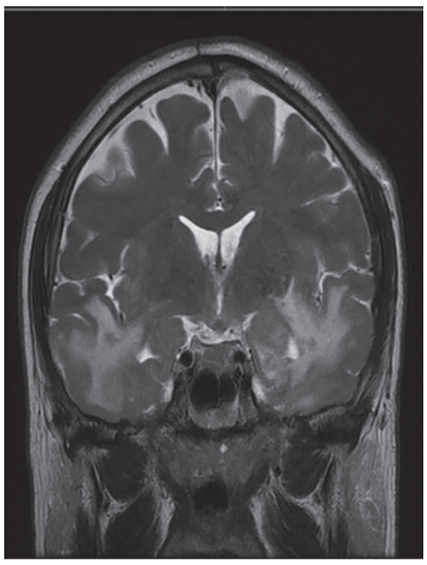

Fig. 1. Corrona / T2 MRI sequence showing extensive vasogenic oedema.

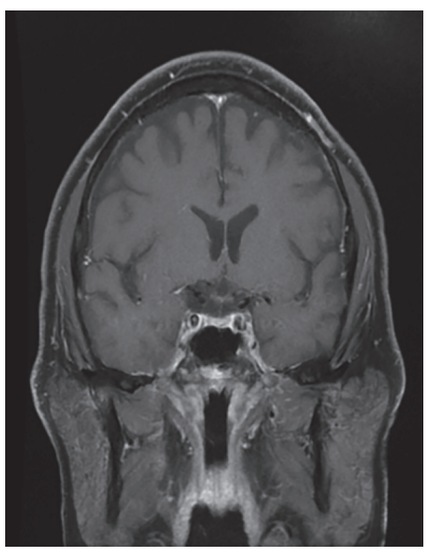

Fig. 2. Repeat MRI showing significant improvement; after 6 remsima infusions and while on tapering regime of prednisolone and methotrexate 10 mg.

Our patient presented with a probable seizure and cognitive impairment. He was diagnosed with neurosarcoidosis and he was initially treated with high dose steroids and subsequently with the addition of methotrexate as a second agent. While on dual therapy he relapsed; his steroids were increased and a third line agent, infliximab biosimilar, was added with clinical and imaging response. This case documents the first reported instance of successful treatment of refractory neurosarcoidosis on dual therapy, with an infliximab biosimilar.

Key message

This case documents the first reported instance of successful treatment of refractory neurosarcoidosis on dual therapy, with an infliximab biosimilar.

D. MERINOPOULOS[1]
F. HAYES[1]
D.A. GALLAGHER[1]
B. DASGUPTA[1,2]

[1]Southend University Hospital, Essex, UK;
[2]Anglia Ruskin University, Cambridge, UK.

Address correspondence to:
Dr Dimos Merinopoulos,
Southend University Hospital Foundation
NHS Trust, Prittlewell Chase, Westcliffe on Sea,
SS0 0RY Essex, United Kingdom.
E-mail: dmerinopoulos@yahoo.com

Competing interests: none declared.

References

1. STERN B, CORBETT J: Neuro-ophthalmologic Manifestations of Sarcoidosis. *Curr Treat Options Neurol* 2007; 9: 63.
2. STJEPANOVIĆ M, VUCINIĆ V, JOVANOVIĆ D, MIJAJLOVIĆ M, TRIFUNOVIĆ V, STJEPANOVIĆ M: Treatment of neurosarcoidosis innovations and challenges. *Med Pregl* 2014; 67: 161-6.
3. NOWAK D, WIDENKA D: Neurosarcoidosis: A review of its intracranial manifestation. *J Neurol* 2001; 248: 363-72.
4. NOZAKI K, JUDSON M: Neurosarcoidosis. *Curr Treat Options Neurol* 2013; 15: 492-504.
5. SAHOO D, BANDYOPADHYAY D, XU M *et al*.: Effectiveness and safety of leflunomide for pulmonary and extrapulmonary sarcoidosis. *Eur Respir J* 2011; 38: 1145-50.
6. CHAPELON-ABRIC C *et al*.: Long-term outcome of infliximab in severe chronic and refractory systemic sarcoidosis: a report of 16 cases. *Clin Exp Rheumatol* 2015; 33: 509-15.
7. HEBEL R, DUBANIEWICZ-WYBIERALSKA M, DUBANIEWICZ A: Overview of neurosarcoidosis: recent advances. *J Neurol* 2015; 262: 258-67.
8. BOMPREZZI R, PATI S, CHANSAKUL C, VOLLMER T: A case of neurosarcoidosis successfully treated with rituximab. *Neurology* 2010; 75: 568-70.