Treatment of refractory neurosarcoidosis with Infliximab

Ernestina Santos,[1] Sandip Shaunak,[2] Shelley Renowden,[3] Neil J Scolding[4]

[1]Neurology Department, Hospital Geral Santo António, Porto, Portugal [2]Royal Preston Hospital, Sharoe Green Lane, Fulwood, Preston, UK [3]Neuroradiology Department, Frenchay Hospital, Bristol, UK [4]Neurology Department, Institute of Clinical Neurosciences, Frenchay Hospital, Bristol, UK

Correspondence to
Professor N J Scolding, Neurology Department, Institute of Clinical Neurosciences, Frenchay Hospital, Bristol BS16 1LE, UK;
n.j.scolding@bristol.ac.uk

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ABSTRACT

Background Neurological involvement in sarcoidosis is serious and often aggressive. Many patients respond to steroids but some show a progressive course despite treatment with steroids and even more potent immunosuppressive drugs.

Objective The aim of this study was to describe our experience in the treatment of refractory neurosarcoidosis with Infliximab—its effect on the course of the disease and side effects.

Methods A series of four patients are reported with neurosarcoidosis refractory to treatment with steroids combined with various immunosuppressive drugs in whom Infliximab was used.

Results A good response, with improvement or stabilisation of the neurological condition, was seen in all cases, without significant side effects. Infliximab is a chimeric monoclonal antibody that neutralises the biological activity of tumour necrosis factor α, a cytokine thought to play an important role in the pathophysiology of sarcoidosis.

Conclusion Our experience using Infliximab adds to the growing evidence that it may fulfil a useful role in cases of refractory neurosarcoidosis.

INTRODUCTION

Sarcoidosis is an inflammatory systemic disorder of unknown cause, characterised pathologically by non-caseating epithelioid granulomas which help emphasise its inflammatory nature. The lungs are usually affected (up to 90% of patients) but practically any organ can be involved.[1] The prevalence is about 1–40/100 000, varying among ethnic groups.[2]

The nervous system is involved in 5–15% of patients.[3] Neurosarcoidosis commonly causes facial, optic or other cranial neuropathies[4] but any part of the nervous system can be affected: meninges, hemispheres, hypothalamus, brainstem, ventricular subependyma, choroid plexuses, peripheral nerves and/or the nervous system vasculature.[5] The diagnosis of neurosarcoidosis requires a compatible clinical, laboratory or radiological picture of sarcoidosis and histological confirmation of non-caseating granulomas.[6]

Corticosteroids remain the mainstay of therapy. Increasingly, adjunctive therapy with immunosuppressive agents is used, including azathioprine, methotrexate, ciclosporin, cyclophosphamide and mycophenolate, if steroids prove inefficacious or intolerable. As with steroids, however, such treatments are based only on anecdotal experience and observational case studies. In one recent long term follow-up study of 48 neurosarcoidosis patients, 26 were treated with steroids plus immunosuppressive therapies: 18 improved (69%), four remained stable (15%) and four worsened (15%),[7] emphasising the treatment resistant nature of a significant minority of patients, even with contemporary immunosuppressants.

Immunomodulatory agents have also been used,[2] including pentoxyfilin, hydroxychloroquine and thalidomide, and 'biologicals' such as adalimumab, etanercept and Infliximab, especially in refractory situations.[8 9] Here we describe our experience in the treatment of refractory neurosarcoidosis with Infliximab.

METHODS

All patients met the criteria of *definite* (CNS biopsy proven) or *probable* neurosarcoidosis[6] (compatible clinical presentation; laboratory support of CNS inflammation; exclusion of other possible causes; and evidence of systemic sarcoidosis in the form of histology or at least two indirect indicators—gallium scan, chest imaging and serum angiotensin converting enzyme (ACE)). One investigator evaluated all patients; all had proved refractory to 'conventional' treatments with steroids and immunosuppressive drugs.

We retrospectively studied those case reports and describe the clinical data: demographics, signs and symptoms, laboratory studies, neuroimaging, biopsy results and treatments before Infliximab. We report the effect of Infliximab on the progress of neurological and/or systemic features, and complications during follow-up. One case has been reported previously in a review journal.[10]

The dose used in all four cases was 3–5 m/kg body weight, administered intravenously, at 0, 2 and 6 weeks and then every 8 weeks.

RESULTS

Case No 1

A 34-year-old man developed cough and night sweats. Following chest x-ray and mediastinal lymph node biopsy, the diagnosis of pulmonary sarcoidosis was made. He was treated with oral steroids starting at 30 mg/day.

A year later he developed spots in his vision, and suffered two seizures. Carbamazepine was introduced to good effect. An MRI scan showed focal white matter lesions throughout the neuraxis and neurosarcoidosis was presumed; azathioprine 150 mg/day was commenced and his steroids were stopped. In the following months, his walking gradually deteriorated, with sensory symptoms in his feet, urinary frequency, impaired rectal sensation, impaired sexual function and mood deterioration. Neurologically, he had visual acuities of 6/6 (right) and 6/3 (left), normal visual fields and pale optic discs; bilateral upper limb spasticity, brisk

deep tendon reflexes but normal strength, ankle clonus, bilateral extensor plantar responses and spastic weakness (4/5) in the lower limbs. Sensory testing revealed a T9 level to pinprick and light touch bilaterally. Joint position sense was normal but vibration was decreased to the left knee and right anterior iliac spine. His gait was spastic.

Blood count, autoantibody screen, rheumatoid factor, C reactive protein level, liver function and urea were all normal or negative. His sodium level was consistently low (123–131 mmol/l). Brain and whole spine MRI showed multifocal white matter lesions throughout the neuraxis. His CSF contained no cells, 1.05 g/l protein, normal glucose and no oligoclonal bands.

He was treated with 5 days of intravenous methylprednisone (500 mg/day) and then oral steroids 40 mg, tapering to 20 mg/day, and methotrexate 15 mg/week (with folate). He was stable for 12 months but then his gait progressively deteriorated. Repeat MRI suggested reactivated inflammatory disease—basal meningitis with thickening and contrast enhancement around the cavernous sinus and the apex of the tentorium cerebelli, T2 weighted brainstem high signal change (particularly right medulla) and extensive signal change virtually throughout the spinal cord especially in the cervical and mid-thoracic regions, with foci of intense enhancement at multiple areas in the cervical cord, at T4, lower thoracic cord and conus (figure 1A–E). Lumbar puncture showed an opening pressure of 21 cm H_2O, 2 wbc/μl, protein 0.78 g/l, normal glucose and no oligoclonal bands.

Treatment with Infliximab was started in April 2007. His clinical condition stabilised. MRI in August 2007 showed substantial improvement, with no intracranial signal change and no gadolinium enhancement. Within the spinal cord there were only subtle signal changes at C2/3 and C3/4, C6, T7/8 and at the border of T12 associated with gadolinium enhancement (figure 2A–F). No untoward effects of therapy were reported.

Case No 2

A 35-year-old Asian man developed headaches and severe left visual impairment, progressing over 1 week. He had a left afferent pupillary defect, swollen optic disc with restricted elevation of that eye. MRI showed swelling and peripheral gadolinium enhancement of the left optic nerve but no brain lesions. Endoscopic biopsy of the left optic nerve showed a patchy perivascular infiltrate of small mature appearing B and T

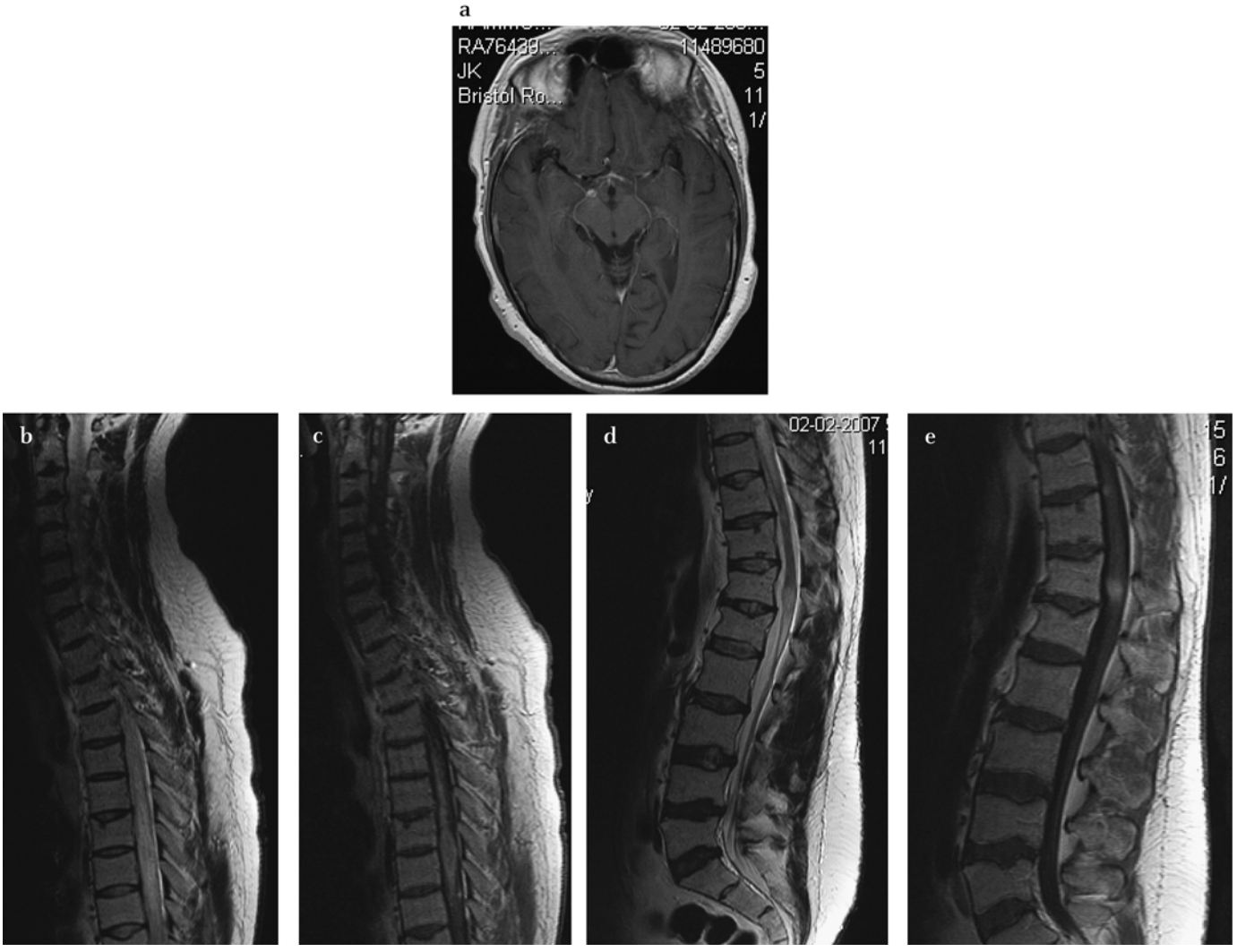

Figure 1 Cranial axial T1 weighted gadolinium enhanced MR image (A) demonstrates a basal meningitis with nodular enhancement of the optic chiasm and hypothalamus. T2 weighted sagittal MR images of the cervicothoracic (B) and thoracolumbar spine (D) demonstrate high T2 signal—that of oedema in the mid-thoracic cord. Gadolinium enhanced T1 weighted sagittal images of the cervicothoracic (C) and thoracolumbar spines (E) confirm an extensive spinal meningitic process with irregular thickening and nodular enhancement of the spinal leptomeninges in the cervical and thoracic regions and at the conus (E).

lymphocytes. Staining for glial fibrillar astrocytic protein was negative, excluding an intrinsic neoplasm, and an inflammatory cause was considered. His visual symptoms were stable although he had no perception of light in the left eye. One year later, repeat MRI showed left optic nerve expansion extending to the chiasm, with bilateral optic nerve enhancement. Repeat optic nerve biopsy showed a focal dense inflammatory infiltrate with surrounding giant cell response, and some mural thickening. There was scant glial fibrillar astrocytic protein positivity, and the appearance was compatible with a granulomatous process. Chest x-ray, serum autoantibodies and ACE levels were all normal.

A year later he developed exercise intolerance, numbness and parasthesiae in his feet, progressing proximally, erectile dysfunction and severe constipation with occasional faecal incontinence, together with oscillopsia and deafness. On examination, he was obese and had gait ataxia, a left exotropia with failure of elevation and abduction, and no perception of light in the left eye with an atrophic disc. He had bilateral sensorineural deafness. The upper limbs were normal but there was grade 4/5 symmetrical paraparesis, with absent ankle reflexes and bilateral extensor plantar responses. There was a sensory level at T12 to all modalities.

His brain MRI was unchanged, with no meningeal enhancement, and spinal MRI was normal. Lower limb neurophysiological studies showed denervation from L2 to S2 bilaterally, consistent with a cauda equina syndrome. CSF showed 0 cells, 2.17 g/l protein

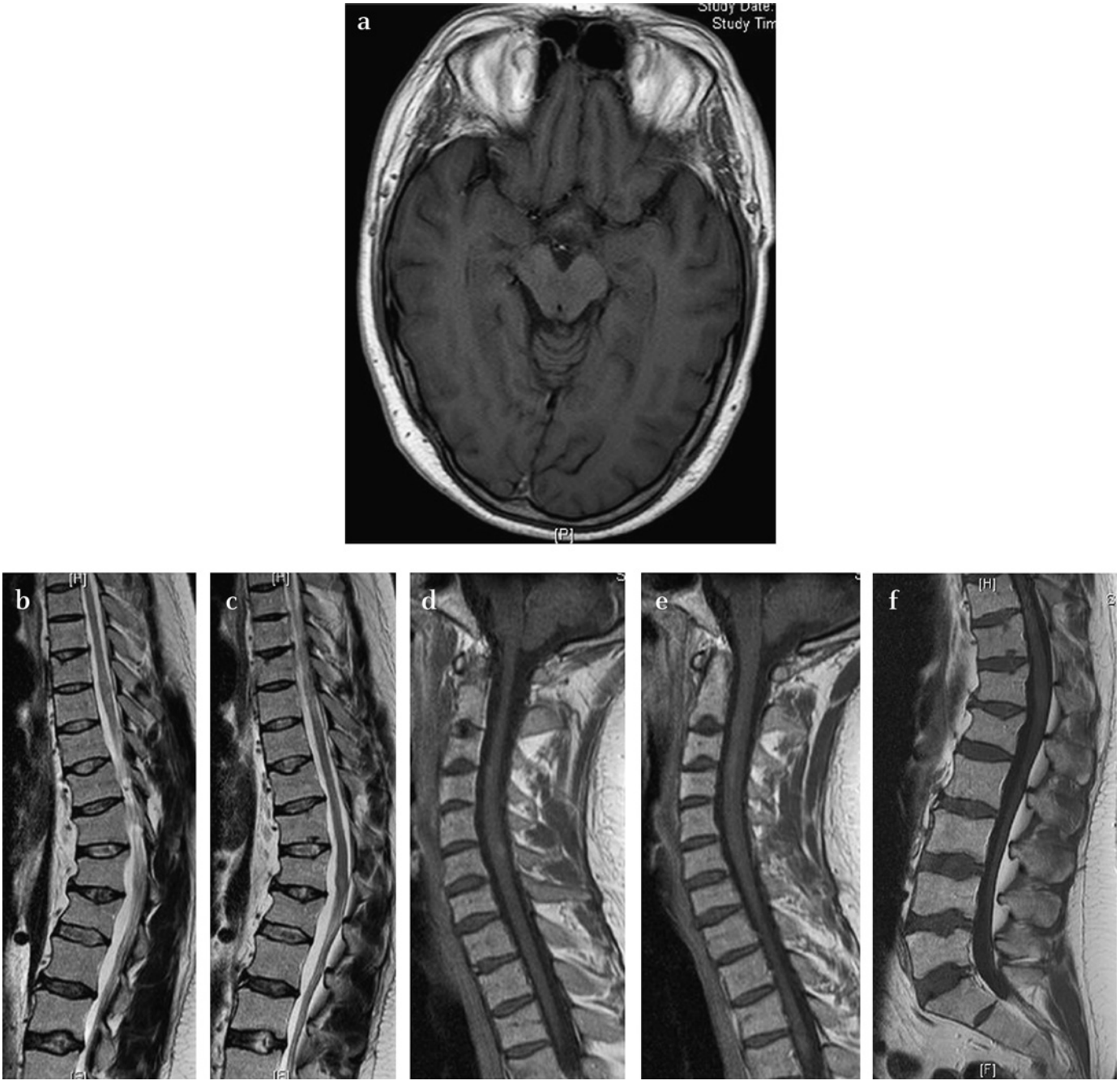

Figure 2 Cranial axial T1 weighted gadolinium enhanced MR image (A) confirms marked improvement following treatment with Infliximab. There is minimal residual meningeal thickening and enhancement at the chiasm. Similarly, spinal MR images (B–F) after Infliximab demonstrate a significant improvement with a marked reduction in cord oedema in the T2 weighted sagittal images of the thoracic spine (B, C) and a reduction in the leptomeningeal thickening, nodularity and enhancement in the T1 weighted gadolinium enhanced sagittal images of the cervical spine (D, E) and conus (F).

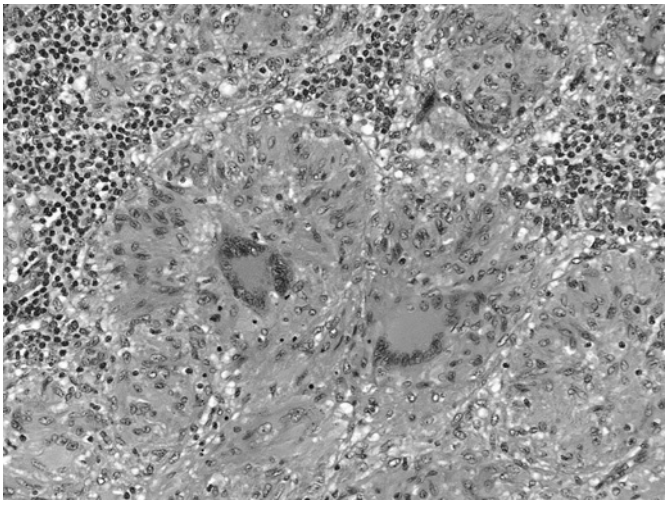

Figure 3 Lymph node biopsy showing non-caseating epithelioid cell granulomas (haematoxylin and eosin staining, ×20 magnification).

and the presence of oligoclonal bands. Serum ACE and calcium were normal. Thorax CT showed bilateral hilar and mediastinal lymphadenopathy and a gallium scan showed increased mediastinal uptake. A transbronchial lung biopsy showed lymphocytic aggregates with one granuloma, consistent with sarcoidosis.

Treatment was started with intravenous methylprednisone, followed by oral prednisone 1 mg/kg/day and azathioprine. His mobility and lower limb weakness improved but azathioprine caused a rash and severe fatigue, and was changed to mycophenolate. Some months later, on reducing prednisone to 20 mg/day, he developed worsening oscillopsia, vomiting and disequilibrium. He received further intravenous methylprednisone and higher doses of oral prednisone. At this point, diabetes mellitus was diagnosed, and glimepiride and metformin started. Over the next 5 months he had two further exacerbations requiring intravenous methylprednisone and he complained of worsening mobility, headache, oscillopsia and increasing weight.

There was no suggestion of tuberculosis, and Infliximab was started. His mobility improved and proximal lower limb power has also improved to 4+/5. Lower limb sensation improved, with resolution of his urinary and bowel symptoms. He successfully reduced his prednisolone to 10 mg/day, leading to significant weight loss and improved diabetic control and has been stable since then with no adverse effects.

Case No 3

A woman of African origin presented, aged 28 years, with a lump in the neck, following which a chest x-ray showed hilar lymphadenopathy, and a subsequent neck node biopsy showed evidence of Hodgkin's lymphoma. Further investigation apparently revealed no other lymph node or organ involvement and she was treated with local radiotherapy alone. Five years of follow-up yielded no evidence of recurrence although she later developed diabetes mellitus and had a previous anterior uveitis. She had a family history of sickle cell disease.

At 38 years, she developed right foot cramps then progressive bilateral leg stiffness and incoordination. She also developed numbness of the left thorax. Spine and brain MRI were normal. An acute admission 1 month later was precipitated by 2 days of diplopia on left gaze and right facial numbness and weakness. Her mobility had deteriorated such that she needed assistance from two people to transfer. She also had urinary urgency and frequency, and slurred speech. A previous anterior uveitis was elicited. She had right lower motor neuron facial weakness, a spastic paraparesis, ataxia in all four limbs and a broad based gait. She had reduced vibration to the hip on the left. (General examination was unremarkable.)

Full blood count and serum ACE were normal. Autoantibodies and rheumatoid factor were negative. Repeated lumbar puncture showed elevated white cell (lymphocytes) count 40–80/μl and 1.5 g/l protein. Cytological examination showed no evidence of malignancy, and CSF serology, virology and microbiological examination were negative. Chest x-ray and CT scans of the thorax, abdomen and pelvis were all normal. Spinal cord MRI was normal. Brain MRI showed gadolinium enhancement of the left pons, and areas of high signal in the left amygdala, floor of the anterior fossa and left ventrolateral thalamus. A further small non-enhancing lesion was seen in the right medulla. Echocardiography showed a small pericardial effusion. Two brain biopsies were performed—the first, frontal, showed a coincidental meningioma. The second biopsy, of a temporal lesion, showed focal grey matter necrosis with perivascular inflammation. Gallium scan showed raised uptake in the lachrymal glands and transverse colon. It was concluded that she had an inflammatory disorder affecting the nervous system, possibly vasculitis or sarcoidosis. There was no evidence of recurrent lymphoma.

There was a slow but steady improvement following treatment with intravenous steroids and oral cyclophosphamide. She became continent, could walk with her frame and climb stairs. Her steroids were slowly reduced and azathioprine (150 mg/day) substituted for cyclophosphamide. She developed a cardiac conduction defect and a pacemaker was implanted (preventing further MR imaging). In 2005 she worsened, needing a wheelchair to move. Repeat gallium scanning showed right axillary focus and ACE was elevated (91 U/l; normal <70). CT scanning of the pelvis and full blood count were normal. Neurosarcoidosis was assumed and she restarted steroids; methotrexate was used instead of azathioprine. In June 2005 she developed a left side burning sensation, and her methotrexate dose was slightly increased to 7.5 mg weekly. Fluorodeoxyglucose–positron emission tomography and abdomen ultrasound disclosed significant inguinal lymphadenopathy, and lymph node biopsy was performed. Histology confirmed inflammatory granulomatous reaction, suggesting sarcoid and excluding malignancy (figure 3).

The following year her visual acuity and mobility both deteriorated further. The former was attributed to diabetic retinopathy (no retinal vasculitis was found). Methotrexate treatment was stopped, and hydroxychloroquine started. In April 2006 she worsened again, becoming completely unable to walk, with generalised pain, dry cough and metacarpophalangeal joint swelling and inflammation. Lung function tests showed a mild reduction in diffusion capacity. Serum ACE was 104 U/l.

Infliximab was initiated. She felt immediately much better in terms of systemic symptoms. She reported that 5–6 days after each infusion she became able to walk for short distances with crutches and to manage stairs, the improvement wearing off 6–7 weeks later. Regular infusions with Infliximab continue every 8 weeks with no side effects.

Case No 4

A 36-year-old man developed right facial tingling with deafness and drooping of one side of his mouth, which lasted a few hours. A few weeks later he had an episode of numbness in his arm, with deafness for 1 h, and headaches. However, 3 months later he developed vomiting, more severe headaches and diplopia in all

directions. His wife noted some 'personality change' and within weeks he suffered a tonic/clonic seizure, precipitating admission. He reported occasional sweating attacks but no skin or joint problems or ear or nose discharge. Repeated examinations revealed no focal neurological signs but impaired higher function, with Mini-Mental scores of 25/30 (altered memory, calculation and visuo-spatial abilities, confirmed by more detailed neuropsychological evaluation) and mood disturbances. During admission he developed papilloedema. MRI brain imaging showed patchy meningeal enhancement but no parenchymal change. Repeated spinal fluid examination showed variable lymphocytosis, white cell counts up to 125/μl and elevated protein levels of up to 2.6 g/l, with low glucose levels. Mycobacteria spinal fluid cultures were negative; oligoclonal bands were positive in CSF and negative in serum. Vasculitic and thrombophilia screens were negative. CT scanning of the chest and abdomen showed prominent bilateral hilar and mediastinal lymphadenopathy, and a mediastinal lymph node biopsy showed multiple granulomata, some of which had central necrosis, with multinucleated giant cells, helping to confirm the diagnosis of sarcoidosis and neurosarcoidosis.

He was treated with prednisolone 60 mg and phenytoin 300 mg. He was also found to have pulmonary emboli and was treated with warfarin. Over the next few months, some symptoms improved but he remained breathless and became cushingoid. Three months later, attempts to reduce steroids led to the emergence of double vision and slurred speech, general malaise, irritability and forgetfulness. Azathioprine was started but proved intolerable. A reduced dose of 7.5 mg methotrexate weekly was tolerated but his headaches, double vision and facial tingling persisted, and a repeat CSF showed 40 lymphocytes/μl. His steroids were increased to 40 mg/day but his symptoms persisted.

Treatment with Infliximab was started and his neurological symptoms improved considerably (headache, facial tingling and cognitive complaints). CSF also improved, showing 12 cells/μl. He is still receiving Infliximab infusions every 8 weeks without side effects and with steroids at 10 mg/day.

DISCUSSION

While the cause of sarcoidosis is unknown, increasing evidence implicates tumour necrosis factor α (TNF-α). Excessive TNF-α expression is found in sarcoid affected lymph nodes.[11] Elevated TNF-α levels are found in bronchoalveolar lavage fluid from sarcoid patients, and their alveolar macrophages produce exaggerated amounts of TNF-α spontaneously and after lipopolysaccharide stimulation.[12] TNF-α induces proinflammatory cytokines such as interleukin (IL)1 and IL6, which enhance leucocyte migration by increasing endothelial permeability and the expression of adhesion molecules by endothelial cells and leucocytes, activating neutrophil and eosinophil functions, and inducing acute phase and other liver proteins. TNF-α is therefore a crucial cytokine in the establishment and maintenance of inflammation in various autoimmune disorders.

Infliximab is a chimeric monoclonal antibody that neutralises the biological activity of TNF-α by binding to its soluble and transmembrane forms and inhibiting receptor binding.[13] The TNF-α blocking effect of Infliximab has been found to be beneficial in several diseases that involve aberrantly behaving lymphocytes, macrophages and neutrophils.[12] Placebo controlled trials have shown that Infliximab is effective in refractory Crohn's disease[13] for which it is now widely used. It is also approved for rheumatoid arthritis and ankylosing spondylitis. Several reports suggest systemic sarcoidosis responds to Infliximab,[14–17] and isolated case studies show promising effects in patients with refractory neurosarcoidosis.[18–21]

Infliximab may, however, be associated with reactivation of infection, particularly tuberculosis, and also may precipitate oncological and autoimmune complications. Other potential adverse effects include infusion reactions and the development of antibodies.[18] Considerable caution in its use is therefore required; histological confirmation of the diagnosis is important, as is screening for tuberculosis. All of our patients had undergone a recent chest x-ray, and CSF microscopy and culture for α-fetoprotein was performed when lumbar punctures were required for diagnostic purposes or monitoring neurosarcoid.

The four patients we report had severe, progressive, disabling neurological disease despite receiving high dose steroids and various immunosuppressive drugs, the latter either proving ineffective or intolerable. The first patient has been clinically stable with significant improvement in MRI scans; the second had significant neurological improvement allowing steroid reduction; the third after the long course of steroids and different immunosuppressive drugs is now stabilised with periods of functional improvement and is systemically better; and the fourth also had a good response, with improvement of his neurological symptoms. All four patients reported symptomatic improvements (including sense of well being), and in none of these four cases has any new sarcoid related problems emerged since commencing Infliximab over a mean of more than 20 months of follow-up. Treatment was well tolerated (especially compared with previous immunosuppressive drugs)—no adverse events from treatment have been seen to date in any of these patients. All continue to receive Infliximab and to be screened for infection and malignancy. The optimal dose, duration of therapy, long term effect and toxicity are yet to be determined in prospective trials[22]; as with these four patients, multiple sequential infusions are often required.

In summary, our experience of four consecutive patients suggests that Infliximab may be useful in cases of progressive neurosarcoidosis refractory to more common immunosuppressive drugs. In such a condition—uncommon, difficult to diagnose, and with no firm evidence base for using even steroids, let alone more conventional immune suppressive agents—acquiring level I–II evidence for a new therapeutic approach is extremely difficult, so that individual open studies may yet inform clinical practice. While the known side effects of Infliximab suggest caution should always be exercised in its use, our findings may help to justify future randomised controlled studies of Infliximab in refractory neurosarcoidosis.

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Competing interests None.

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