Review

Anti-TNF-α therapy in the management of severe neurosarcoidosis: a report of five cases from a single centre and literature review

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ABSTRACT

Neurologic manifestations are found in 5–15 % of patients with sarcoidosis. This granulomatous disease may affect any part of the peripheral or the central nervous system, being potentially severe and difficult to treat. Corticosteroids are the cornerstone of therapy in sarcoidosis. However, some patients become resistant or experience side effects to corticosteroids. In these patients, second line therapies including immunosuppressive drugs such as methotrexate, azathioprine, mycophenolate, cyclophosphamide and leflunomide have been used. Anti-TNF-α drugs have been proposed as a therapeutic option for those who are refractory to immunosuppressive drugs or initially in cases of severe sarcoidosis. We report on 5 patients with neurosarcoidosis treated with anti-TNF-α drugs in our center. A literature review of patients with neurosarcoidosis treated with anti-TNF-α drugs was conducted. In our series successful response to anti-TNF-α therapy was achieved. However, the high frequency of relapses following anti-TNF-α discontinuation makes necessary a close follow-up of these patients when the biologic agent is stopped.

Introduction

Sarcoidosis is a multisystemic inflammatory disease of unknown etiology with a worldwide distribution. It is characterised by noncaseating granulomas in the affected organs. The most commonly involved organs are lungs and lymph nodes, followed by skin, liver, eyes and nervous system. Neurologic manifestations occur in 5–15% of the cases and both the central and the peripheral nervous systems can be affected. The most frequently affected structures are cranial nerves, but others such as brain parenchyma, meninges, spinal cord or peripheral nerves may also be involved (1-3).

The pathogenesis of sarcoidosis remains unclear. The current hypothesis suggests that it may occur in a genetically predisposed host when it is exposed to a so far unidentified antigen (4). Several antigens, infectious and non-infectious agents, have been proposed to play a role in the pathogenesis of this disorder. Antigen presentation leads to activation of CD4 cells and differentiation to Th1 cells that secrete interleukin 2 (IL-2) and interferon gamma (IFN-γ), and increase macrophage tumour necrosis factor alpha (TNF-α) production. This inflammatory response is the driver of granuloma formation. As the disease progresses, either granuloma may resolve or fibrosis may appear (1, 5).

Corticosteroids are the cornerstone of therapy in sarcoidosis. However, in corticosteroid-refractory patients or when severe side effects appear, immunosuppressive agents are usually prescribed. The most commonly used immunosuppressive agents are methotrexate (MTX), azathioprine, and cyclophosphamide (6). Based on pathogenic mechanisms, animal data and some observational reports (7), anti-TNF-α drugs have been used for refractory sarcoidosis, including neurosarcoidosis (8). TNF-α is released by sarcoid macrophages and it is considered to be involved in granuloma formation. Furthermore, in refractory cases higher levels of TNF-α have been described in bronchoalveolar fluids (9).

The main marketed anti-TNF-α drugs

are the soluble fusion protein of TNF-α type II receptor (etanercept), and the monoclonal antibodies against TNF-α (infliximab [IFX], adalimumab, certolizumab and golimumab). Several studies have been published supporting the use of monoclonal antibodies against TNF-α, specially IFX, in the treatment of pulmonary sarcoidosis, uveitis, cutaneous sarcoidosis including lupus pernio, or neurosarcoidosis (7-18). Infliximab is a chimeric monoclonal antibody that inactivates the pro-inflammatory cytokine TNF-α. *In vitro* data suggest that it can induce the lysis of TNF-α producing cells, suppress cytokine release and induce apoptosis (15, 19).

In this article we present our series of 5 patients with refractory or severe neurosarcoidosis treated with anti-TNF-α drugs in our center. A literature review was also performed.

Patients and methods

Patient population

We reviewed all the patients with refractory and/or severe neurosarcoidosis treated with anti- TNF-α drugs at Hospital Universitario Marqués de Valdecilla (Santander, Spain) from January, 2009 until March, 2013.

Four patients met the criteria of probable neurosarcoidosis:

a) clinical and radiological presentation suggestive of neurosarcoidosis and, *b)* histological evidence of systemic sarcoidosis (20). Histological findings consistent with sarcoidosis granulomas were clusters of epitheliod histiocytes and multinucleated giant cells surrounded by T lymphocytes and collagen and fibroblasts (2, 21) (Fig. 1).

One patient met criteria of possible neurosarcoidosis:

a) clinical presentation suggestive of neurosarcoidosis without histological confirmation and,

b) exclusion of other diagnoses (20).

Patients were followed-up by both a rheumatologist and a neurologist.

Data collection and literature review

Data were extracted from the clinical records according to a standardised protocol and reviewed for confirmation of the diagnosis.

We conducted a review of the literature. For this purpose, the PubMed database (National Library of Medicine, Bethesda, MD) was searched.

We selected studies using terms neurosarcoidosis OR (sarcoidosis AND [brain OR nervous OR nerve OR CNS]) AND (infliximab OR TNF OR tumor OR tumour OR adalimumab OR etanercept) published in English between 1990 and 2013.

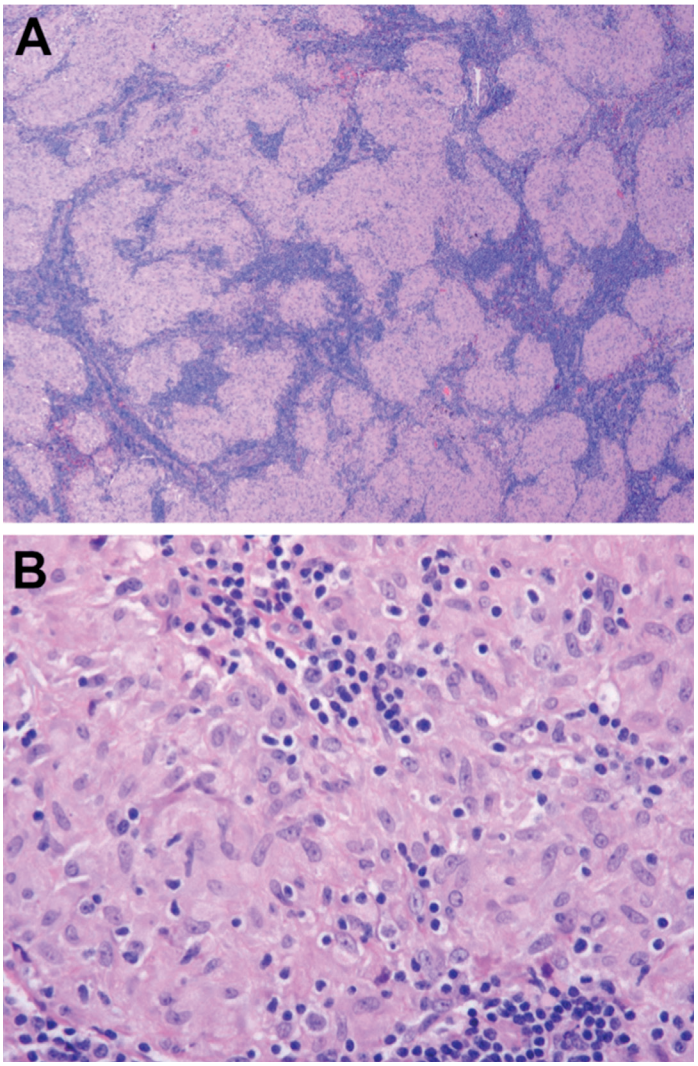

Fig. 1. **A**: Microscopic lower power view of lymph node biopsy showing multiple non-necrotising granulomas (H&E, original magnification x6). **B**: Higher power view showing non-caseating epithelioid cell granuloma (H&E, original magnification x100).

Results

We identified 5 (3 female, 2 male) patients diagnosed as having neurosarcoidosis requiring anti-TNF-α therapy in our hospital. The median age of the entire series was 54.6 years (range: 29–65 years).

The main clinical features of the five patients are summarised in Table I.

a) Two of them showed meningeal involvement that was confirmed with cerebrospinal fluid (CSF) analysis, and also in one case by magnetic resonance imaging (MRI).

b) Another two patients showed intramedullary spinal cord involvement presenting with lower limb paresis and lumbar pain. This was confirmed by MRI showing intramedullary lesions.

c) The remaining patient of this series showed central nervous system (CNS) vasculitis presenting with multiple transient ischaemic attacks; MRI disclosed an ischaemic lesion in the right thalamus.

They were treated with infliximab and/or with adalimumab. Infliximab was used initially in all 5 cases, at a dose of 5 mg/kg administered intravenously using an induction regimen at 0, 2 and 6 weeks and then every 6 to 8 weeks depending on the clinical response. Infliximab was switched to adalimumab

Table I. Literature review and present series showing the main features of patients with neurosarcoidosis treated with anti-TNF-α drugs.

Reference	Cases	Age/Sex	Neuroanatomic location	Extraneurological affection	Biopsy proven	Previous therapies (in addition to oral corticosteroids)
Pettersen (16)	1	48/M	Intracerebral	Skin, liver, knees, and lungs	Yes	Radiation, AZA, MTX, cloroquine, OHCQ, CyA
Katz (53)	1	35/F	Meningeal	Hiliar, mediastinal lymph nodes	Yes (lymph nodes)	Acetazolamide, IVMP, CYM
Carter (18)	1	41/F	Intracerebral (pituitary gland), optic nerve	No	Yes (pituitary gland)	IVMP, MTX, CYM
Solberger (54)	1	45/M	Meningeal, intracerebral, peripheral nervous system	Hiliar, mediastinal lymph nodes	Yes (lymph nodes)	IVMP, AZA
Salama (55)	1	41/M	Meningeal, optic nerve,	Mediastinal lymph nodes	Yes (lymph nodes)	IVMP, acetazolamide, AZA, MTX
Kumar (17)	1	74/M	Meningeal, Intracerebral (cerebellar),	Retroperitoneal lymph nodes	Yes (cerebellar mass)	Immunossuppressants (not specified)
Doty (11)	1		Intracerebral	Skin	ND	ND
Toth (10)	1	37/F	Leptomeningeal	ND	Yes (leptomeningeal)	
Dolhun (56)	1	25/M	Meningeal, intramedullary spinal cord	Pulmonary	Yes (pulmonary)	IVMP, plasmapheresis
Kobylecki (13)	1	35/M	Optic nerve, cauda equina syndrome?	Hiliar and mediastinal lymph nodes and lung	Yes (optic nerve and lung)	IVMP, AZA, MM
Santos (14)	4	34/M	Meningeal, intracerebral, intramedullary spinal cord,	Pulmonary	Yes (lung)	IVMP, AZA, MTX
		35/M	Optic nerve, cauda equina syndrome	Pulmonary, lymph nodes	Yes (optic nerve, pulmonary)	IVMP, AZA, MM
		28/F	Meningeal, Intracerebral	Uveitis, pericarditis, lachrymal glands, colon, lymph nodes	Yes (brain, lymph node)	IVMP, CYM, AZA, MTX, OHCQ
		36/M	Meningeal	Hiliar and mediastinal lymph nodes	Yes (lymph node)	AZA, MTX
Sodhi (15)	4	50/F	Intramedullary spinal cord, meningeal, intracerebral	Subcarinal lymphadenopathy	Yes (spinal cord, transbronchial biopsy)	IVMP, CYM
		36/F	Intracerebral, meningeal	ND	Yes (cerebral)	Dexamethasone, MTX, CYM
		49/F	Optic nerve	Lung	Yes (optic nerve, nonspecific)	MTX, CYM
		49/F	Orbital mass	Lymph nodes	Yes (orbital mass, lymph node)	MTX, CYM
Moravan (12)	7	53/F	Extradural	Ophthalmologic, sinuses, pulmonary, rheumatologic	Yes (extradural mass)	IVMP, AZA
		42/F	Meningeal	Rheumatologic, sinuses	Yes (lymph node)	IVMP
		40/F	Intracerebral	Pulmonary	Yes (intracerebral lesion)	IVMP
		52/F	Meningeal	Pulmonary, ophthalmologic	Yes (lymph node)	IVMP, AZA
		35/M	Intramedullary spinal cord	Pulmonary	Yes (lymph node)	IVMP
		54/F	Intramedullary spinal cord	Pulmonary	Yes (lymph node)	IVMP, CYM, etanercept, OHCQ
		52/F	Meningeal, intramedullary spinal cord	No	Yes (leptomeningeal)	IVMP, ventriculoperitoneal shunt
Pereira (7)	3	36/M	Meningeal, intracerebral, intramedullary spinal cord, optic nerve	No	No	IVMP, AZA, CYM, IVIG, CyA, MTX, plasma exchange
		29/M	Intracerebral,	No	Yes (nerve root)	IVMP
		33/F	Meningeal, Intracerebral,	No	Yes (leptomeningeal)	IVMP, MTX, AZA, ventriculoperitoneal shunt
Marnane (40)	1	22/F	Meningeal	Uveitis, lymph nodes, lungs	No	IVMP, MTX, OHCQ
Chintamaneni (57)	1	50/M	Meningeal, intracerebral, intramedullary spinal cord	No	Yes (cerebellar, non-diagnostic)	Pentoxyfilline
Hostettler (23)	6	ND	CNS	ND	Yes	Inmunomodulatory drugs
Croft (38)	1	36/M	Meningeal, intraparenchymal, and peripheral neuropathy	Lymph nodes, endocrine and cardiac system	Yes	MTX, CYM, ventriculoperitoneal shunt
Russell (22)	8	ND	CNS	No data	Yes	Immunossuppressants (not specified)
Riancho-Zarrabeitia (present series)	5	65/F	Meningeal	Lymph nodes	Yes (mediastinal lymph node)	IVMP, MTX
		58/M	Meningeal	Lungs	No	No
		64/F	Intramedullary spinal cord	Lymph nodes	Yes (inguinal lymph node)	IVMP, MTX
		59/F	Intramedullary spinal cord	Lymph nodes	Yes (lymph node)	IVMP, MTX
		27/M	CNS vasculitis	Lymph nodes, lacrimal glands, nasopharingeal	Yes (lymph node)	MTX

M: male; F: female; AZA: azathioprine; MTX: methotrexate; OHCQ: hidroxichloroquine; IVMP. intravenous methylprednisolone; CYM. cyclophosphamide; Cyclosporine A: CyA; CNS. Central nervous system; MM. Mycophenolate mophetile.

as a second option due to infections in 2 cases or reactivation in another case. Adalimumab was used at a standard dose of 40 mg subcutaneously every other week.

Case 1

A 65-year-old woman with history of peripheral vertigo, transient ischaemic attack and rigid-akinetic syndrome was admitted to the hospital because of headache, worsening of gait disturbances and absence-like episodes. Physical examination showed gait imbalance, rigidity and pyramidal signs. CSF analysis showed low glucose (37 mg/dL), high protein (186 mg/dL) and 49 cells/mm^3 (97% lymphocytes); Angiotensin-converting enzyme (ACE) level was 4 μg/L (normal <1). Microbiology studies were negative. A brain MRI showed diffuse leptomeningeal abnormalities with nodular enhancement, dural thickening and chronic ischaemic lesions. Empiric antituberculous therapy was initially started. However, within a few days after admission the patient developed symptoms suggestive of cauda equine syndrome. A spinal cord MRI revealed diffuse arachnoiditis with predominance in cauda equina. Computed tomography (CT) scan and positron emission tomography (PET) scans showed enlargement of mediastinal lymph nodes. Mediastinoscopy biopsy of a lymph node showed sarcoid granulomas (Fig. 1). Therapy with high dose steroids intravenously was started. The patient experienced clinical improvement and was discharged on prednisone 1 mg/kg/day. During the following months prednisone was slowly tapered and MTX was added (initially at a dose of 7.5 mg/week that was then increased to 10 mg/week). On follow-up the patient remained clinically stable until 12 months after discharge, when the symptoms worsened with gait difficulty. A MRI showed progression of the lesions of diffuse arachnoiditis (Fig. 2A). Treatment with IFX was added (5 mg/kg at 0, 2, 6 week and then every 6 weeks) to oral corticosteroids and methotrexate. There was clinical improvement as well as reduction in the size and enhancement of the spinal cord lesions on MRI (Fig. 2B). The patient remained stable, with symptoms caused by her spastic bladder and muscular spasticity. On MRI, however, supratentorial activity was observed. After 2 years of treatment, IFX was progressively reduced and finally discontinued. The patient continued on MTX 10 mg per week and oral methylprednisonole 2 mg per day during the following three months when she was readmitted to the hospital due to inability to walk. High-dose intravenous methylprednisonole was given and, due to the history of recurrent urinary tract infection episodes when the patient was undergoing IFX therapy, adalimumab was started at a dose of 40 mg subcutaneously every other week. Following this treatment the patient experienced a progressive clinical improvement.

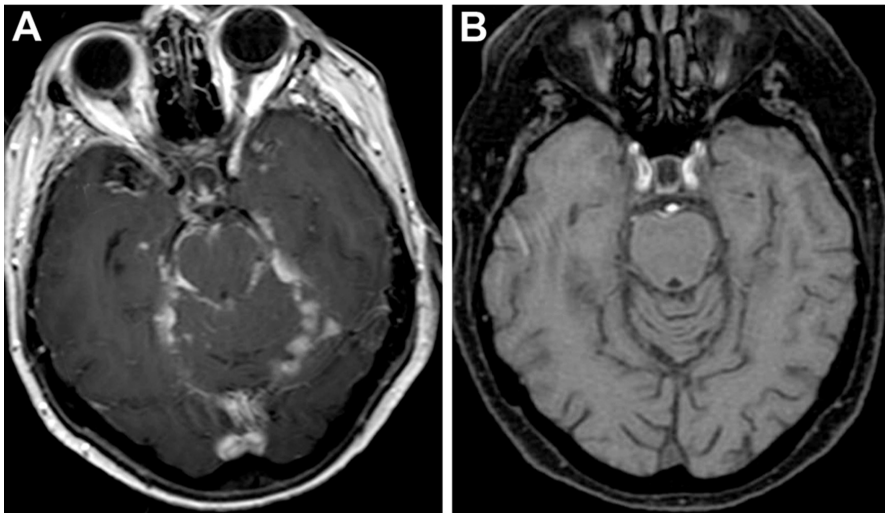

Fig. 2. Axial T1-weighted gadolinium enhanced MR images of the brain passing through mesencephalon. **A**: Note intense nodular leptomeningeal contrast enhancement compatible with basal meningitis. **B**: Such meningeal enhancement is resolved following infliximab treatment.

Case 2

A 58-year-old man, with a previous history of lymphocytic meningitis 11 years before, was admitted to hospital because of intense headache, fever and sore throat. CSF analyses showed 55 cells/mm^3 (65% lymphocytes) and proteins 71 mg/dL and oligoclonal bands. ACE level in CSF was 2 µgr/L (normal <1). Brain CT and MRI were normal. Body CT showed mild infiltrates and non-specific millimetric nodules in the right lung. Gallium scan showed increased pulmonary hilar uptake. Treatment was then started with prednisone 40 mg/day, MTX 10 mg per week and IFX 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks. The patient experienced clinical and scintigraphic improvement but 5 months later he began complaining of headache again. Because of that, IFX was switched to adalimumab 40 mg every 2 weeks. Three months after the onset of adalimumab therapy and due to persisting symptoms and lack of treatment compliance, adalimumab was stopped. The patient abandoned medical follow-up.

Case 3

A 64-year-old woman with unremarkable past medical history was admitted to the hospital with a history of subacute paraparesis and urinary incontinence. Neurological examination showed weakness of both legs, loss of pinprick sensibility, absence of tendon reflexes and bilateral Babinski sign. Laboratory disclosed for high ACE in serum (107 µgr/L). CSF analysis showed 35 cells/mL (100% lymphocytes), proteins 180 mg/dL, high ACE (17µgr/L) and glucose consumption. Microbiology studies were negative. A spinal cord MRI showed an enhancing intramedullary lesion that extended between T3-T9. A CT scan showed enlargement of mediastinal, retroperitoneal and inguinal lymph nodes. A biopsy of inguinal lymph node was consistent with sarcoidosis. High dose steroids (intravenous methylpredniso-

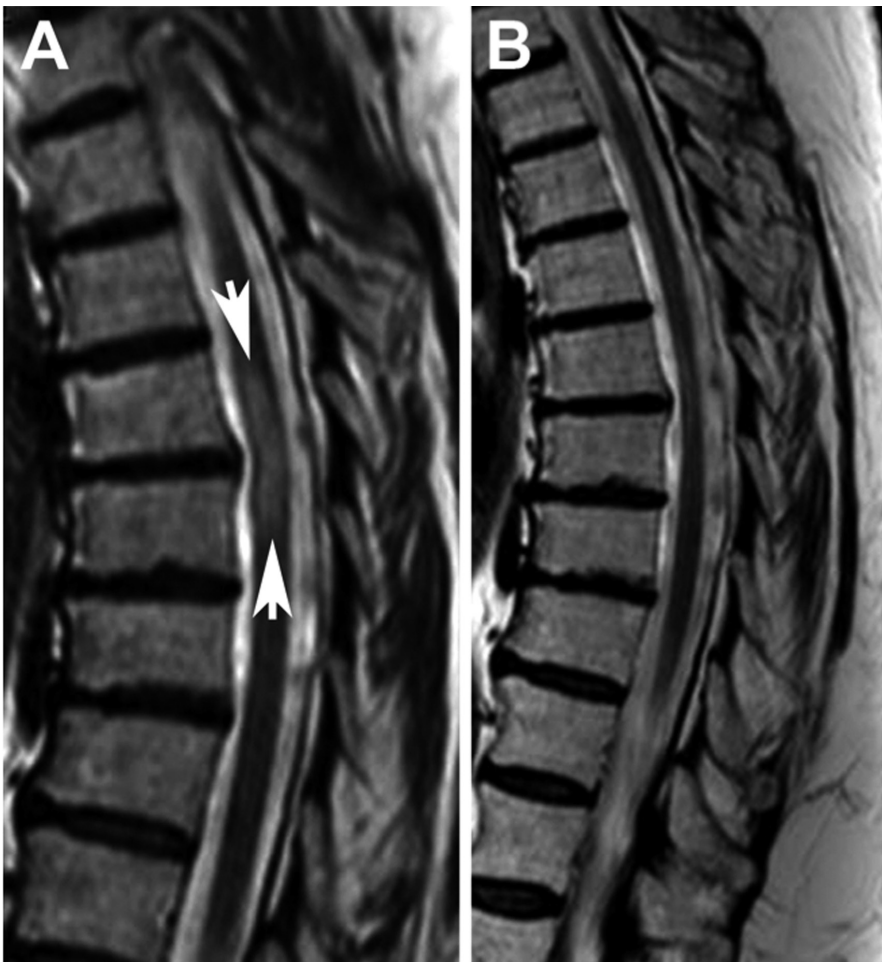

Fig. 3. Magnetic resonance imaging of neurosarcoidosis affecting the spinal cord. T2-weighted sagittal MRI of the thoracic spine image (**A**) demonstrates high T2 signal in the mid thoracic cord extending form T6 to T7 (arrows), resolved following infliximab treatment (**B**).

lone 1g) were started for 5 consecutive days followed by 60 mg prednisone per day and methotrexate 15 mg per week. As there was only partial clinical improvement, IFX 5 mg/kg was added to MTX using an induction regimen of 0, 2, 6 weeks and then every 8 weeks, and steroids were slowly tapered. A spinal cord MRI showed improvement of the lesion, which at that time affected the T6 segment. Regrettably, after 3 doses of IFX the patient suffered a *P. Jirovecii* pneumonia and, because of that, IFX and MTX were discontinued. Two months later adalimumab 40 mg subcutaneous every other week was started and prednisone progressively tapered. MTX was not added at this time due to the patient's history of upper respiratory tract infections. The patient remains stable, with no MRI evidence of intramedullary lesions after 18 months of follow-up.

Case 4

A 59-year-old woman presented with lumbosciatic pain and gait disturbances. Neurological exam revealed paresis of right leg, hypoactive lower-limb tendon reflexes, and right Babinski. Spinal cord MRI showed hyperintensity in T2-weighted images with gadolinium enhancement at T6-T7 (Fig. 3A). CSF analysis showed 11 cells/mm^3 (95% lymphocytes), proteins 37 mg/dL and oligoclonal bands. Treatment with dexamethasone was started with clinical improvement. Chest CT showed enlarged lymph nodes, with increased activity in a Gallium-67 scan. Biopsy of a mediastinal lymph node showed non-necrotising granuloma. Treatment was initiated with prednisone 60 mg/day. After 1 month prednisone dosage was progressively tapered. However, 2 years after diagnosis, symptoms worsened, with lower limb motor and sensory deficits. High corticosteroid dose, MTX 10 mg per week and IFX 5 mg/kg at 0, 2 and 6 weeks and then every 8 weeks were started with subsequent clinical and MRI improvement (Fig. 3B). After 1 year of MTX and IFX therapy, IFX administration was switched from an infusion every 8 weeks to an infusion every 12 weeks. After 18 months of follow-up the patient has remained stable on IFX every 12 weeks and MTX 15 mg per week.

Case 5

A 27-year-old man was admitted because of several recent transient neurological deficit episodes consisting of aphasia, dysarthria and right side hemiparesis lasting up to five minutes. Complete blood count, serum chemistries, and serum ACE were normal. A brain MRI showed an acute ischaemic lesion affecting the right thalamus and internal capsule (Fig. 4). Body CT and PET scans showed enlarged paratracheal lymph nodes. A gallium-67 scintigraphy demonstrated increased uptake in hilar lymph nodes, nasopharyngeal region and lacrimal glands. Lymph node's biopsy showed non-caseating granulomas consistent with sarcoidosis. Treatment with 60 mg/day prednisone was begun. During follow-up, prednisone was progressively tapered. However, 18 months after diagnosis the patient suffered vertical diplopia. At that time a brain MRI did not show any changes and prednisone was increased to the initial dose. Treatment with IFX 5 mg/kg with an induction regimen of 0, 2, 6 weeks and then every 8 weeks and MTX 10 mg per week were then started, leading to clinical improvement. After 11 months, IFX dose was discontinued maintaining treatment with MTX at a dosage of 20 mg per week. Due to hepatic toxicity MTX had to be reduced to 10 mg per week. However, one month later, the patient was readmitted with vertical diplopia: he was treated with high dose corticosteroids and MTX dose was increased. Six months later he was admitted again because of transient sensory, motor and verbal deficits. A brain MRI was consistent with active neurosarcoidosis. Three boluses of 1g

intravenous methylprednisonole were given and IFX was again restarted at a dose of 5 g/kg at weeks 0, 2 and 6 and then every 8 weeks. The patient remains asymptomatic after four months of follow-up.

Anti-TNF-α therapy in neurosarcoidosis: literature review

Several case reports and some small case series have been reported involving IFX in refractory neurosarcoidosis treatment (Tables I-II). Both sexes were affected, with an age ranging from 25 to 74 years. Some patients presented isolated neurosarcoidosis, while most of them had systemic involvement being lymph nodes, and lungs the most commonly affected organs. All reported patients had received treatment with corticosteroids prior to the initiation of the biologic therapy. Most of them had been treated with one ore more immunosuppressive drugs, MTX and AZA being the most commonly used. IFX dose regimen varied from 3–5 mg/kg, generally induction regimen was at 0, 2 and 6 weeks, and then it ranged according to each patient. All reported patients responded to biological therapy (being IFX the agent of election except for a case report in which adalimumab was tried). Only the series reported by Russell *et al*. (22) and Hostettler et al (23) found resolution or improvement in 62.5% and 83% of patients treated with infliximab, respectively. Adverse effects were relatively uncommon these being as follows: herpes zoster, transient leukopenia and infusion reaction with liver enzymes alteration.

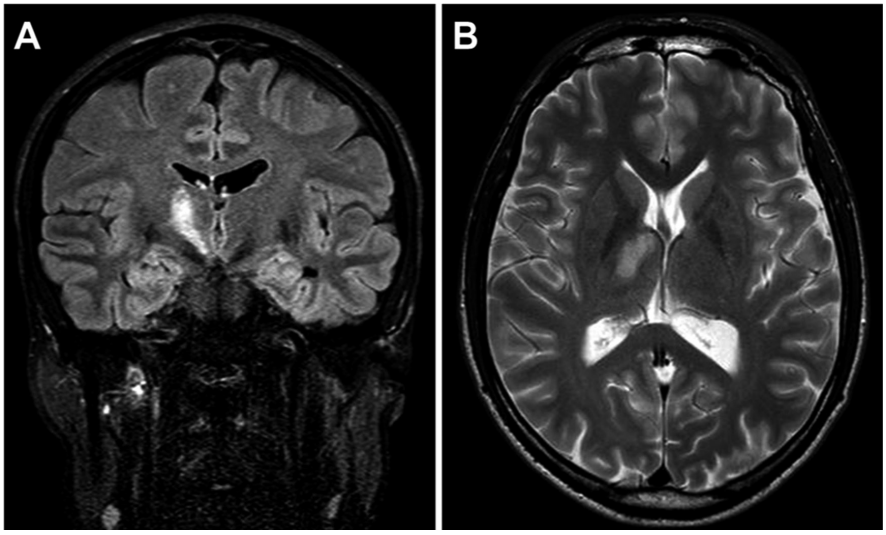

Fig. 4. A: Coronal postcontrast T1-weighted MR image of the brain showing a subacute ischaemic lesion involving the right thalamus. **B**: Such thalamic lesion is also observed in this T2 axial image.

Discussion

Neurosarcoidosis is a relatively uncommon but potentially severe disease. Corticosteroids are the first line of treatment. In refractory cases or in those with intolerable side effects, immunosuppressive drugs are those of choice, biologic agents being an adequate option for non-responders. Anti-TNF-α drugs, possibly due to TNF-α implication in the pathogenic mechanism, have been reported as valuable agents for refractory and disabling neurosarcoidosis. In this study we have described a successful response in 5 patients with refractory neurosarcoidosis treated with anti-TNF-α drugs.

Sarcoidosis is a systemic granulomatous disease that affects nervous system in 5–15% of the cases (3). Most patients with neurosarcoidosis have a systemic disease, and less than 5% of patients have isolated neurosarcoidosis (24). Four of the five patients described in our report, although asymptomatic, presented intrathoracic lymph node enlargement. Neurosarcoidosis usually affects people in the fourth decade of life (3), with female predominance. Intracranial structures as well as spinal cord or peripheral nerves can be affected. Cranial nerve palsies are the most common manifestation, the VII nerve being the most frequently affected. However, none of our cases showed cranial neuropathy. Meningeal infiltration is described in around 10 to 20% of patients with neurosarcoidosis, although in some series this finding was described in up to 40% of the cases (3, 25, 26). Patients may present with headache, nuchal rigidity and fever, usually with a subacute or chronic time course. Basal meningitis is common and when it occurs, cranial nerve palsies and hypothalamus dysfunction have also been described. Cerebrospinal fluid studies typically show mononuclear inflammatory cells with high levels of proteins and occasionally low glucose. Oligoclonal bands are found in about 30 to 50% of patients (3, 5, 25, 27). Negative cultures and cytology may help to distinguish sarcoidosis from other causes of meningitis. High ACE levels are insensitive but suggestive for CNS neurosarcoidosis (25, 28), although they may also be increased in infections and malignancies. In this regard, although its use as a diagnostic tool is controversial, it seems to be useful as a marker of activity and treatment response (29). MRI typically shows leptomeningeal enhancement at the skull base. Neurosarcoidosis may cause parenchymal CNS lesions. Hypothalamic and pituitary dysfunction, usually presenting as diabetes insipidus and hyperprolactinemia, are common (30). Seizures and behavioural changes have also been described. Ischaemic cerebrovascular events have been occasionally reported. These events may be secondary to blood vessels involvement by sarcoid granulomas (31). One of the patients in our series presented with multiple transient ischaemic attacks secondary to sarcoid vasculitis (25). The spinal cord is typically less frequently affected. Patients may present with paraplegia or quadriplegia, urinary incontinence, and other manifestations of mielopathy. Neurosarcoidosis can cause arachnoiditis, cauda equina dysfunction and extradural, intradural or intramedullary lesions (32). Intramedullary sarcoidosis may manifest enlargement of the cord with focal or diffuse gadolinium enhancement; being spinal cord atrophy

Table II. Anti-TNF-α therapy in patients with neurosarcoidosis: literature review and present series.

Reference	cases	Anti-TNF-α drug and dose	Concomitant immunossuppresant	Response	Adverse events	Follow-up (months)
Pettersen (16)	1	IFX 5 mg/kg 0, 2, 6 w and every 8 w for 6 months	No	Yes	No	7.5
Katz (53)	1	IFX 3 mg/kg 0 and 10 months and then every month	CYM	Yes	Herpes zoster dermatitis	13
Carter (18)	1	IFX 5 mg/kg 0, 2, 6 w and every 8 w for 5 months	MTX	Yes	No	5
Solberger (54)	1	IFX 5 mg/kg 0, 2, 8, 14, 20 and 26 w	AZA	Yes	No	7
Salama (55)	1	IFX 450 mg, 5 doses in total	No	Yes	No	12
Kumar (17)	1	IFX / ND	No	Yes	ND	6
Doty (11)	1	IFX 5 mg/kg 0, 2, 8 w and every 8 w	No	Yes	ND	ND
Toth (10)	1	IFX 3 mg/kg 0, 2, 6 w and every 8 w	No	Yes	Infusion reaction, elevation of liver enzymes, low titer ANA	12
Dolhum (56)	1	IFX 5 mg/kg 0, 2, 4 w	No	Yes	ND	1
Kobylecki (13)	1	IFX 5 mg/kg 0, 2 w and every 6 w	MM	Yes	ND	8
Santos (14)	4	IFX / ND	No	Yes	No	4
		IFX / ND	No	Yes	No	ND
		IFX every 8 w	No	Yes	No	ND
		IFX every 8 w	No	Yes	No	ND
Sodhi (15)	4	IFX 5 mg/kg / ND	MTX	Yes	No	ND
		IFX 5 mg/kg every 4-6 w	MTX	Yes	No	ND
		IFX / ND	MTX	Yes	No	ND
		IFX 3 mg/kg / ND	MM	Yes	No	ND
Moravan (12)	7	IFX5 mg/kg 0, 2, 6 w and every 6-8 w	MM in 6 cases	Yes		24-39
Pereira (7)	3	IFX 5 mg/kg 0, 2, 4 w and then 3mg/kg every 6 w	No	Yes	Transient leukopenia	20
		IFX 5 mg/kg 0, 2, 6 w and then every 8 w	No	Yes	No	9
		IFX 5 mg/kg 0, 4, 8 w and every 8 w	MTX	Yes	No	26
Marnane (40)	1	Adalimumab 40 mg EOW	MTX	Yes	ND	24
Chintamaneni (57)	1	IFX / ND	No	Yes	ND	7
Hostettler (23)	6	IFX 3 mg/kg 4, 6, 8 w	Immunossuppresant (not specified)	Yes	ND	13-59
Croft (38)	1	IFX 3 mg/kg 0, 2, 6 w	CYM	Yes	ND	ND
Russell (22)	8	IFX / ND	ND	Yes	ND	ND
Riancho-Zarrabeitia (present series)	5	IFX 5 mg/kg 0, 2, 6 w and every 6 w for 24 months	MTX	Yes	Recurrent urinary infections	24
		Adalimumab 40 mg EOW				4
		IFX 5 mg/kg 0, 2, 6 and then every 8 w	MTX	Yes	No	9+1
		Adalimumab 40 mg EOW				
		IFX 5 mg/kg	No	Yes	P. jirovecci pneumonia	2
		Adalimumab 40 mg sc EOW				18
		IFX 5 mg/kg 0, 2, 6 and every 8 w for 1 year and then every 12 w	MTX	Yes	No	18
		IFX 5 mg/kg 0, 2, 6 and every 8 w for 11 months	MTX	Yes	No	12
		Again IFX 0, 2 and every 8 w				

IFX: infliximab; ADA: adalimumab; w: week; EOW: every other week; MTX: methotrexate; AZA: azathioprine; IVMP: intravenous methylprednisolone; CYM: cyclophosphamide; ND: not described; MM: Mycophenolate mofetil.

a late finding of spinal cord sarcoidosis (3). Two patients of our series presented with lumbar pain and lower limb paresis. In both cases MRI showed cases focal enhancement consistent with intramedullary lesion at the dorsal region. Peripheral neuropathy may be seen as manifestation of neurosarcoidosis. Multiple mononeuropathies, chronic sensorimotor axonal polyneuropathy and acute or chronic demyelinating polyneuropathies have been described. Anti TNF therapy has been suggested for small fiber neuropathy (33). Muscle involvement due to sarcoidosis is not usually symptomatic, although presentation as either acute or chronic myopathy has been previously described (34). Isolated cranial nerve abnormalities and aseptic meningitis are generally monophasic with good response to short corticosteroid course (35). Nevertheless, patients with other manifestations usually have a remitting-relapsing course.

Corticosteroids are the mainstay of the treatment for neurosarcoidosis. For severe clinical manifestations intravenous corticosteroids may be administered. Oral prednisone 40 to 60 mg per day for 4 to 6 weeks followed by a slow rate of tapering is recommended for mild symptoms such as myopathy, facial palsy or neuropathy (35). Second line treatment options include immunosuppressive drugs such as MTX, AZA, MM or even hydroxichloroquine. Cyclophosphamide has been indicated in severe refractory patients. Immunosuppressive drugs have reported to

be useful in treating sarcoidosis. The largest experience has been reported with MTX (6), with a response rate of around 60% used in combination with corticosteroids (25).

Biologic therapy has been suggested to be a rescue option for refractory cases. Several case reports, some case series and a randomised trial (5) have been published evaluating the effectiveness of TNF-α antagonists in refractory sarcoidosis.

TNF is a mediator of sarcoidosis, and it is thought to be necessary for granuloma formation. TNF-α antagonists have been reported to be useful for the treatment of pulmonary and extrapulmonary sarcoidosis (9). There are five different TNF antagonists, three of them have been proposed as potential treatment of refractory sarcoidosis: etanercept, IFX and adalimumab. Etanercept, a TNF-α p75 soluble receptor fusion protein, failed to show benefit in patients with progressive pulmonary disease or refractory ocular sarcoidosis (36, 37). IFX is a chimeric monoclonal antibody that blocks TNF-α bioactivity (15); it has potential benefits binding both free and cellular bound TNF-α, suppression of TNF-α mediated expression of intercellular adhesion molecule 1, inhibition of macrophage aggregation and suppression of T lymphocyte activation and proliferation (10). Observational studies have suggested that IFX may be a useful treatment of corticosteroid-refractory neurosarcoidosis as well as a corticosteroid sparing agent (17, 25, 38). All five patients described in the present study had a favorable response to IFX. Potential factors that may predict good response to IFX are unknown. Considering the neurological involvement in our series, it is possible that anti-TNF-α therapy may be more effective in patients with sarcoidosis who present meningeal or intramedullary spinal cord involvement. However, larger series are needed to establish the response rate to anti-TNF-α agents in patients with neurosarcoidosis. Nevertheless, our results are in line with the high response rate reported by other authors. As shown in Table I, all cases described in the literature have been reported to respond to infliximab. In all of our five patients who responded to IFX, prednisone dose was tapered and even stopped in one case. This fact confirms previous reports that suggested the role of IFX as a corticosteroid-sparing agent. In 2 of our 5 patients after IFX was discontinued after 24 and 11 months on remission continuing on MTX and low dose of prednisone. However, 4 and 18 months later, respectively, both patients suffered a relapse control of disease progression being not possible with just immunosuppressive drugs. In the first patient adalimumab was initiated and in the second IFX therapy was restarted with the same dose regime achieving clinical and radiological response. These results are in keeping with a previous study that reported an 86% relapse rate after discontinuation of IFX in patients with recalcitrant sarcoidosis (39). In contrast, another 2 cases reported by Russell et al remained in clinical remission after IFX withdrawal (22). To our knowledge, there are no controlled trials assessing the optimal dose, and the dose regime of infliximab in refractory sarcoidosis. Therefore, further studies are needed to determine the optimal biological therapy duration, and doses.

Adalimumab is a humanised monoclonal anti TNF-α antibody. It has been used successfully in cutaneous sarcoidosis as well as in some cases of multisystemic sarcoidosis (40-42). A small randomised trial has showed its efficacy in refractory cutaneous sarcoidosis (43). However, there are very few reports of refractory neurosarcoidosis responsive to adalimumab (40, 41). Although these results are promising, clinical trials will determine the efficacy of adalimumab in neurosarcoidosis patients. In our series three patients were switched from infliximab to adalimumab. Clinical and radiological response was obtained in two of the patients, third the patient being that who abandoned the treatment. Further studies are also needed to determine the effectiveness of switching to a different TNF-α antagonist in refractory cases or in those with intolerable adverse effects.

When analysing the lack of response to etanercept unlike to other anti-TNF-α drugs, some hypotheses have been suggested. IFX is highly specific for TNF-α whereas etanercept also bind another molecule, TNF-β also called lymphotoxin (11, 44). Both IFX and adalimumab structures are an IgG1 antibody, capable of crossing blood-brain barrier and initiating complement pathway causing cell lysis (35). Furthermore, IFX but not etanercept induces T cell apoptosis (45).

Potential adverse effects of anti TNF-α agents include reactivation of tuberculosis, opportunistic infection (46) as shown in one of our patients, central demyelination (17), malignancies or increase incidence of autoantibodies. Infusion reactions and development of antibodies to IFX have also been reported (16). The combination of IFX with low-dose MTX may be used to limit the risk of antibody formation (8). In all our cases latent tuberculosis was excluded before starting biological therapy. No infusion reactions were reported. However, one of our patients developed opportunistic P jirovecci pneumonia and, because of that, IFX was stopped. However, therapy with adalimumab was well tolerated in this patient being recurrent urinary tract infections the only serious adverse effect reported in the 18 months of follow-up. Anti-TNF-α drugs have recently been described to have a paradoxical effect. Some cases of sarcoid-like granuloma development have been reported after TNF-α inhibitors including etanercept, adalimumab and IFX (47-50). Lungs, lymph nodes and skin were the most commonly affected organs whereas only two cases of CNS affection have been reported (48, 51). The mechanism is still unknown, but it is thought to be a "class effect" rather than being drug specific, as cases have been reported with all three anti-TNF-α drugs. However, etanercept has been the agent most commonly implicated (47, 49), suggesting that the use of a TNF-α receptor antagonist has higher risk of developing sarcoidosis than the anti TNF-α monoclonal antibodies. This fact could be partially explained by the different mechanism of action of the TNF antagonists. Etanercept increases production of IFN-γ and blocks incompletely TNF-α bioactivity (49), preserving partially the mecha-

nisms required to granuloma formation. In summary, anti-TNF-α drugs are effective in refractory sarcoidosis. They have been successfully used in pulmonary sarcoidosis as well as in certain extrapulmonary manifestations. Although controlled trials are not available, case reports and short case series suggest that IFX is an adequate option for patients with neurosarcoidosis not responding to corticosteroids or other second line immunosuppressive drugs. IFX has shown efficacy in controlling disease manifestations as well as in reducing corticosteroids requirements. Although there are few data supporting the efficacy of adalimumab in refractory sarcoidosis, some cases have showed promising results (52). Finally, discontinuation of anti-TNF-α is frequently associated with a relapse of the neurological manifestations in patients with neurosarcoidosis. Therefore, clinicians should be very cautious at the time of considering anti-TNF-α withdrawal in these patients.

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