Intractable Neurosarcoidosis Effectively Treated with Infliximab

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Abstract

We herein describe the case of an 18-year-old girl who presented with dizziness and headache in 2012. In 2013, brain magnetic resonance imaging revealed multiple intracerebral small lesions and intracerebral hydrocephalus. She was diagnosed with neurosarcoidosis following a brain biopsy. Although prednisolone, methotrexate, and azathioprine were administered, her hydrocephalus worsened and her granulomatous lesions were observed to increase in number on MRI. The patient’s hydrocephalus showed no improvement despite her undergoing one ventriculoperitoneal shunt procedure, one septum pellucidum fenestration, and three ventriculoatrial shunt procedures. Infliximab therapy was then initiated, which resulted in a reduction in the size of the granulomatous lesions and the improvement of the patient’s clinical symptoms. Infliximab may be a viable therapeutic option for treating intractable neurosarcoidosis.

Key words: infliximab, hydrocephalus, monoclonal antibody, neurosarcoidosis


Introduction

Sarcoidosis is a systemic disorder that is characterized pathologically by the presence of non-caseating granulomas (1). When the pathological alterations associated with sarcoidosis affect both the central and peripheral nervous systems, the disorder is termed neurosarcoidosis. Neurosarcoidosis is estimated to occur in 5-13% of sarcoidosis cases (2). The non-caseating granulomas of patients with neurosarcoidosis may manifest in the cranial nerves, brain, spinal cord parenchyma, or arachnoid membrane (3). Although several medications have proven useful in the treatment of neurosarcoidosis, corticosteroids remain the first-line treatment (4). We herein describe the case of a patient with neurosarcoidosis that persisted despite extensive treatment with a range of surgical procedures, corticosteroids, and immunosuppressive agents. Infliximab, an inhibitor of tumor necrosis factor alpha (TNF-α), was successfully used to control the patient’s clinical symptoms. Although infliximab is typically reserved as a third-line therapy for patients with neurosarcoidosis, when the conditions are severe, infliximab may be useful in the early clinical course to ensure recovery from advanced neurological complications (1-4).

Case Report

An 18-year-old girl presented with headache and dizziness in 2012. Her symptoms gradually worsened over the subsequent 12 months and she was admitted to our hospital when she experienced generalized seizures in 2013. On admission, her body temperature was 36.8°C, her pulse rate was 96 beats/min with a regular rhythm, and her blood pressure was 140/78 mmHg. During admission, she experienced generalized convulsions but remained conscious. Her initial neurological examination was unremarkable and her motor function was normal. No nuchal rigidity was observed. A cerebrospinal fluid analysis showed increases in
Brain magnetic resonance imaging (MRI) showed the enlargement of the third, fourth, and bilateral lateral ventricles, which was consistent with communicating hydrocephalus. Gadolinium-enhanced brain MRI revealed enhanced lesions at the level of the basal cistern, ambient cistern, cerebellomedullary cistern, and leptomeninges (Fig. 1). An Ommaya reservoir was placed on the day of admission because of the severe hydrocephalus. This was followed, one week later, by the placement of a ventriculoperitoneal shunt. Chest computed tomography revealed diffuse nodular shadows in both lung fields and hyperplasia associated with the bronchovascular bundle. With the exception of an aortic ascending aneurysm, there were no abnormal lesions in other anatomical areas. However, the cause of the aneurysm could not be determined. A neuroendoscopic biopsy was performed on a gadolinium-enhanced lesion at the bottom of the third ventricle, which revealed a non-caseating epithelioid granuloma with Langhans-type giant cells (Fig. 2). The biopsy specimen was negative for bacteria and fungi. Based on these results, the patient was diagnosed with neurosarcoidosis.

The patient’s treatment course is shown in Fig. 3. Oral prednisolone (30 mg/day) was started as the initial therapy; however, the hydrocephalus was exacerbated and her clinical symptoms deteriorated. In addition to prednisolone, methotrexate (5 mg/week) was started in May 2013, after her admission; the dose was subsequently increased to up to 10 mg/week. Methotrexate was terminated and azathioprine (100 mg/day) was administered due to the progressive worsening of her hydrocephalus. Septum pellucidum fenestration
Figure 2. Photomicrographs of biopsy specimens obtained from the base of the third ventricle. (A) Discrete, non-caseating epithelioid granulomas were attached to the choroid plexus. Multinucleated giant cells were present. Hematoxylin and Eosin (H&E) staining; scale bar=10 μm. (B) Langhans-type giant cells were present, and the infiltration of inflammatory cells was also observed. H&E staining; scale bar=100 μm.

Figure 3. The clinical course. Although the patient’s hydrocephalus was extensively treated with surgical procedures, steroid therapy, and immunosuppressants, her clinical condition progressively worsened. After the initiation of regular infliximab therapy, her clinical symptoms gradually improved. AZP: azathioprine, MTX: methotrexate, PSL: prednisolone, V-A: ventriculoatrial, V-P: ventriculoperitoneal. Arrows indicate steroid pulse therapies.
and three ventriculoatrial shunt procedures were performed to reduce the hydrocephalus; but did not improve her clinical symptoms and the granulomatous lesions remained visible on brain MRI. After obtaining the patient’s consent, intravenous infliximab (200 mg) therapy was initiated in June 2014. Brain MRI in September 2014 showed a significant reduction in the number and gadolinium signal intensity of the granulomatous lesions (Fig. 1C), and no exacerbation of her hydrocephalus.

**Discussion**

We herein presented the case of a patient with neurosarcoidosis who was effectively treated with infliximab. In cases of neurosarcoidosis associated with encephalopathy, hydrocephalus, convulsions, and myelopathy, a combination of steroid and immunosuppressive drugs is the recommended treatment (5). The pathological mechanism of sarcoidosis is complicated and involves T and B lymphocytes, as well as mononuclear phagocytes, fibroblasts, and dendritic cells (6). Cytokines, such as interleukin 1 and TNF-α, are also involved. The latter are considered to be important in the formation of sarcoid granulomas (6). Infliximab is a TNF-α inhibitor that neutralizes the biological effects of the cytokine by preventing it from binding to its receptors (7-9). Recent case reports have indicated that infliximab may be effective for the treatment of severe neurosarcoidosis (7-9). However, the only case reports describing the administration of infliximab to a patient with neurosarcoidosis in Japan are in regional meeting abstracts (10-12).

Because sarcoidosis is a severe, chronic disorder, it is important to select the most effective treatment on an individual basis to minimize the likelihood of adverse effects. In general, corticosteroids and immunosuppressants are the recommended first- and second-line therapies, respectively, for sarcoidosis (13, 14). Although infliximab is not approved by the Pharmaceuticals and Medical Devices Agency of Japan for the treatment of sarcoidosis, it is recommended as a second-line therapy for the treatment of severe neurosarcoidosis (15). Maneiro performed a review of the sarcoidosis literature and mentioned that there are many reports indicating that infliximab is more effective than other immunosuppressants for the treatment of neurosarcoidosis (16); however, stronger clinical evidence demonstrating the efficacy of infliximab for the treatment of neurosarcoidosis is required.

The authors state that they have no Conflict of Interest (COI).

**References**