Intravenous Cyclophosphamide: a Safe and Reliable Treatment for Neurosarcoidosis

Howiada H. Salim MBBS  
*University of Tennessee College of Medicine, howiada.salim@erlanger.org*

Michael L. Brit MD, PhD  
*University of Tennessee College of Medicine, michael.brit@erlanger.org*

Abdelazim Sirelkhatim  
*University of Tennessee College of Medicine, Chattanooga, ASirelkhatim@gmail.com*

Victor O. Kolade MD, FACP  
*The Guthrie Clinic, vkolade@gmail.com*

Follow this and additional works at: [http://ejournal.tnmed.org/home](http://ejournal.tnmed.org/home)

Part of the [Neurology Commons](http://ejournal.tnmed.org/home), [Other Medical Specialties Commons](http://ejournal.tnmed.org/home), and the [Primary Care Commons](http://ejournal.tnmed.org/home)

**Recommended Citation**


This Article is brought to you for free and open access by Tennessee Medicine e-Journal. It has been accepted for inclusion in Tennessee Medicine E-Journal by an authorized administrator of Tennessee Medicine e-Journal.
Intravenous Cyclophosphamide: a Safe and Reliable Treatment for Neurosarcoidosis
Howiada H. Salim, MBBS; Michael L. Brit, MD, PhD; Abdelazim Sirelkhatim, MD; Victor O. Kolade MD, FACP

Email: Howiada.Salim@erlanger.org

ABSTRACT
The standard treatment of neurosarcoidosis involves a high dose of methylprednisolone followed by a prolonged course of prednisone; thus, the majority of patients must endure treatment that invariably generates numerous complications. Recurrence of neurological symptoms and/or persistence of magnetic resonance imaging (MRI) findings are not uncommon. Intravenous cyclophosphamide is a known mode of treatment that is usually reserved for either steroid-resistant cases or patients who cannot tolerate steroids. We describe a 49 year-old male who presented with progressive gait imbalance, decreased hearing and tinnitus associated with headache, weight loss and fever. By assessment of clinical features, imaging and histopathology, a diagnosis of neurosarcoidosis with multi-organ involvement was established. The patient was treated with two one-gram doses of methylprednisolone, followed by rapidly-tapered prednisone. Azathioprine was added in follow-up; however, MRI of the brain showed disease progression. Seven infusions of cyclophosphamide were given for treatment, resulting in complete symptomatic improvement and resolution of radiographic signs of active central nervous system sarcoidosis. We conclude that cyclophosphamide is a safe and reliable treatment option for neurosarcoidosis.

A previously healthy 49 year-old African American male had been evaluated by his primary care physician for lower back pain, low-grade fever, night sweats, and a ten-pound weight loss over eight to ten weeks. A basic work-up to confirm suspicions of connective tissue disorders, Lyme disease and viral infection was negative. The patient was given a trial of 50 mg of prednisone tapered over two weeks, resulting in substantial improvement. Two weeks later, the patient noticed progressive gait imbalance; four days prior to admission, he experienced tinnitus and decreased hearing, especially in his left ear, associated with severe headache. No vertigo, diplopia, facial asymmetry or slurred speech were noted. The patient is a school teacher, married and monogamous; he had been in the military much of his life, and traveled abroad extensively. He did not smoke, drink alcohol, or use illicit drugs. Family history was significant for multiple sclerosis in his mother and lung cancer in his father.

Physical examination was remarkable for left-gaze horizontal nystagmus, with the following specifics:
- Normal symmetrical bilateral facial muscles
- Sensorineural deafness in the left ear, later confirmed by audiometry
- Mild weakness in upper and lower extremities - power 4/5 - with normal tone and reflexes
- No sensory level, but decreased position and vibration sense in both feet
- Positive Romberg’s sign
- Gait was unsteady and slightly wide-based
- No lymphadenopathy or skin rash.

Laboratory data included negative rheumatoid factor (RF), antinuclear cytoplasmic antibody, and human immunodeficiency virus (HIV); sedimentation rate was 42 and C-reactive protein (CRP) was 10.7. Albumin was 3.3 g/dL, calcium 9.9 mg/dL; white blood count was 4.3 thousand/microliter, hemoglobin 11 g/dL, and hematocrit 34.7. Purified protein derivative test was negative. Cerebrospinal fluid had 18 white blood cells per microliter, 100% lymphocytes, and protein of 68 mg/dl with normal glucose.
MRI of the brain showed bilateral mild enhancement of the eighth cranial nerve (Figure 1A). MRI of the cervical spine showed a lower cervical cord mass and edema at the level of C5-T1. Post contrast imaging showed intense homogeneous enhancement of the posterior cord (Figure 2A). CT scan of the thorax and abdomen showed diffuse mediastinal, paratracheal and hilar lymphadenopathy with mild bilateral pleural effusion, and a mass in the right upper quadrant of the abdomen. Ultrasound of the abdomen showed a 3 cm solid mass within the right hepatic lobe, suspicious for granuloma. Gallium nuclear scan showed uptake in the salivary glands, mediastinum and left upper quadrant of the abdomen. Transbronchial biopsy of hilar lymph nodes revealed non-caseating granulomatous inflammation with negative acid fast bacilli (AFB) and Gomori methenamine silver (GMS) stains. The diagnosis of sarcoidosis was established. Affected organs included the intrathoracic lymphatic system, liver, cranial nerves, cervical and upper thoracic spinal cord.

The patient was started on 1 gram of methylprednisolone intravenously daily for two days, then switched to prednisone 50 mg daily on discharge with rapid tapering in follow-up. After two weeks of treatment, the patient felt better. Prednisone was tapered to 30 mg/day and azathioprine 100 mg daily was added. MRI of the brain done one month after diagnosis showed mild reduction in the contrast enhancement within the internal auditory artery canal; however, there was greater enhancement in the left eighth cranial nerve distribution, with new enhancement of the cochlea bilaterally and enlarged infundibulum. Seven monthly infusions of cyclophosphamide 750 mg were administered, and prednisone was tapered to 10 mg daily. The patient became asymptomatic with complete enhancement resolution of the brain and cervical MRI (Figures 1B and 2B). Intravenous cyclophosphamide was discontinued. The patient was maintained on azathioprine 50 mg and prednisone 5 mg daily for the next two years and remained asymptomatic.

DISCUSSION

Neural involvement is sometimes the presenting feature of sarcoidosis.1 Standard treatment of extrapulmonary sarcoidosis relies on extensive use of corticosteroids. In cases of central nervous system (CNS) involvement, “stress” doses of intravenous methylprednisolone are usually followed by a prolonged course of high-dose prednisone. 1,2 The majority of affected patients have to endure treatment that invariably generates numerous complications, including hypothalamic-pituitary-adrenal insufficiency. Azathioprine, methotrexate, mycophenolate and hydroxychloroquine have often been used to lessen steroid-induced toxicity.2,3

Symptomatic response to glucocorticoids typically is quick. However, recurrence of neurological symptoms and residual MRI-detectable CNS lesions are not uncommon after initial treatment.1 Intravenous cyclophosphamide is a known but infrequently used alternative.1 It has typically been reserved for either steroid-resistant cases or cases in which the patient is unable to tolerate treatment with glucocorticoids.4,5 The main concern is toxicity of cyclophosphamide, based primarily on cumulative experience of prolonged use of oral or intravenous cyclophosphamide for treatment of systemic vasculitis or connective tissue diseases.4 Adverse effects of short-course therapy have included opportunistic infection, however, steroid dose reductions of up to 66% can be achieved.5

In this case, our experience demonstrates that intravenous cyclophosphamide is a safe and reliable treatment option for extra-pulmonary sarcoidosis involving the CNS. It allows avoidance of prolonged courses of high-dose prednisone following high initial doses of methylprednisolone with no recurrence of neurological symptoms or residual CNS lesions. Perhaps in selected patients this treatment modality will prove safer in the long term.
References:

Figure 1A: MRI of the brain with contrast, showing bilateral mild enhancement of the eighth cranial nerve (arrowed).
Figure 1B: shows a follow-up MRI after finishing treatment with cyclophosphamide, with complete resolution of cranial nerve VIII enhancement.
**Figure 2A:** MRI of cervical spine with contrast, showing an intense homogeneous enhancement of posterior cord at the cervicothoracic junction (arrowed).

**Figure 2B:** shows a follow-up MRI with contrast after seven monthly infusions of cyclophosphamide, with complete resolution of posterior cord enhancement.