

# Clinical, imaging and histopathological features of isolated CNS lymphomatoid granulomatosis

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## Abstract

Lymphomatoid granulomatosis is a rare systemic angiocentric/angiodestructive, B cell lymphoproliferative disorder. Central nervous system involvement occurs as part of systemic disease. Isolated central nervous system disease is rare with only few case reports. A 53-year-old male presented with progressive cognitive decline, extrapyramidal features, and altered sensorium with seizures over the last 4 years. His magnetic resonance imaging (MRI) of brain showed multiple small enhancing nodules in subependymal/ependymal regions and along the vessels. Brain biopsy showed atypical lymphohistiocytic infiltrate suggestive of lymphomatoid granulomatosis. There was no evidence of systemic disease; thus, isolated central nervous system lymphomatoid granulomatosis was diagnosed.

**Key words:** Lymphomatoid granulomatosis; lympho proliferative disorder; nodular enhancing lesions

## Introduction

Lymphomatoid granulomatosis (LG) is a systemic, Epstein Barr virus (EBV) associated, B cell lymphoproliferative disorder with angiocentric/angiodestructive pattern.<sup>[1]</sup> LG occurs more frequently in patients with immunosuppressive conditions (acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome, and post-transplantation) and autoimmune conditions (Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, and Crohn's disease). It is common in fourth to sixth decade of life. Most cases have lung involvement. Skin, central nervous system (CNS), kidney, and liver can also be involved. Lymph node, spleen, and bone marrow involvement is rare and occurs in late stages of the disease.<sup>[1-3]</sup> Histopathologic triad consists of nodular polymorphic

lymphoid infiltrate (lymphocytes, atypical mononuclear and plasma cells), angiitis (transmural lymphocytic infiltration of vessels), and granulomatosis (lymphoid nodules with central necrosis).<sup>[3]</sup> Steroids and chemotherapeutic agents are effective, with more than 50% response rate.<sup>[1,4]</sup> Thirty percent of the cases can have CNS involvement.<sup>[1-3]</sup> In rare cases, isolated CNS disease can occur, with about 25 cases being described in literature till now. Here we report a case of isolated CNS LG, its clinical, imaging, and histopathologic features, and response to therapy.

## Case Report

A 53-year-old male presented with progressive neuropsychiatric symptoms of 4 years duration, with decreasing social interaction, apathy, altered sleep, poor appetite, emotional disturbances, slowness during routine activities, and intermittent involuntary movements involving both the upper limbs. Since the last 1 year, he had been having progressive decline in memory, with recurrent seizures. At presentation, he had Glasgow Coma Scale (GCS) 10/15 (E2, M 4, V4), generalized rigidity, and sphincter incontinence. MRI (Siemens 1.5 Tesla Avanto Germany 2005) of brain [Figure 1A-D] showed multiple small enhancing nodules in subependymal and ependymal

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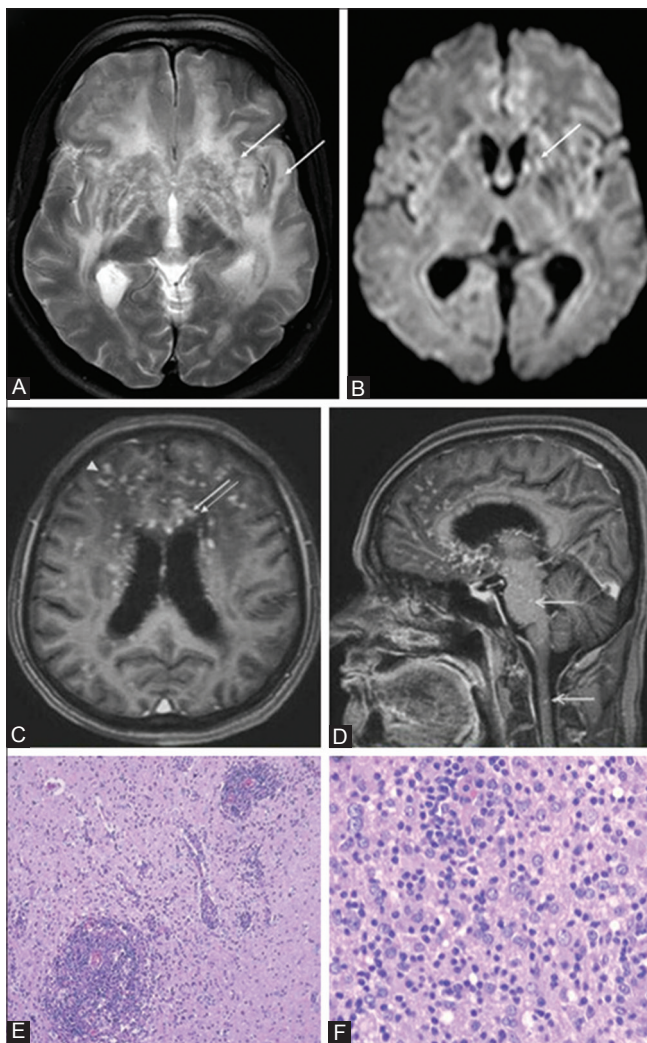
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regions, along the vessels, and gray-white junction. Nodules were numerous in the anterior/basal regions, and were also seen in the brain stem and spinal cord. Nodules were T2 isointense, and showed restricted diffusion and perilesional edema. Cerebrospinal fluid (CSF) analysis showed 190 cells/mm<sup>3</sup> (polymorphs 1%, lymphocytes 99%), 221 mg% proteins, and 56 mg% glucose, without atypical cells. CSF polymerase chain reaction for herpes, EBV, cytomegalovirus, varicella, and adenovirus was negative. CSF cultures (bacterial, fungal, and tubercular) were negative. Blood counts were normal. Screening for hepatitis (B and C) and human immunodeficiency virus (HIV) was negative. Angiotensin converting enzyme level was normal (28 U/l). Bone marrow and computed tomography (CT) (Philips Brilliance 6 Cleveland USA 2005) thorax-abdomen were unremarkable.

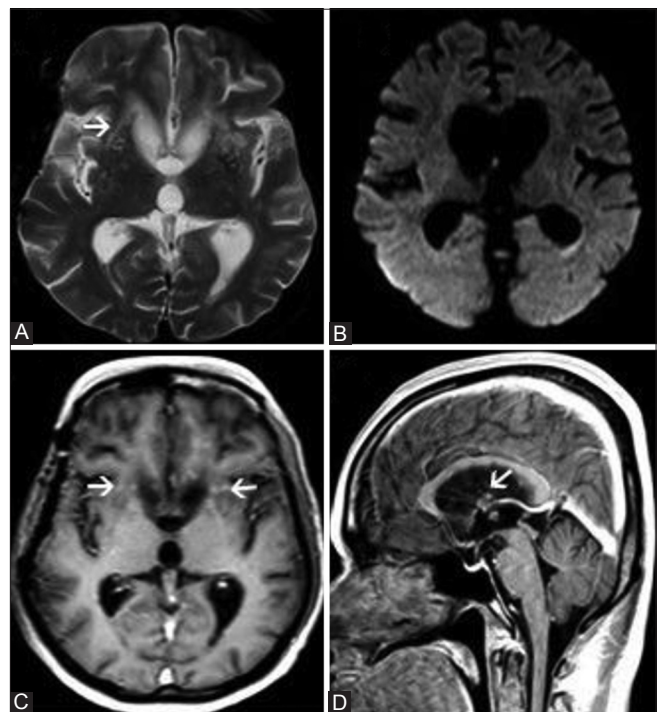


**Figure 1 (A-F):** MRI brain and histopathology images. (A) T2 axial image shows multiple small T2-isointense lesions (arrows) with perilesional edema (B) Diffusion-weighted image (DWI) shows restricted diffusion of the lesions (arrow) (C) Post-contrast axial image shows enhancing lesions in the subependymal (double arrows) and gray-white junction (arrowhead) distribution. Also note the brainstem and cervical cord lesions in the post-contrast sagittal (D) image (arrows) (E and F) Photomicrographs illustrating lymphohistiocytic infiltrate in an angiocentric pattern (H and E, x90)

Histopathology [Figure 1E and F] from right temporal lobe biopsy showed cerebral gray and white matter with reactive astrocytosis, densely infiltrated by sheets of small and medium-sized CD3+ T cells with coarse clumped chromatin and scant cytoplasm. Also seen were CD20+ B cells, with vesicular nuclei, prominent nucleoli, and moderate cytoplasm. The T cell population consisted of CD4+ and CD8+ cells. The tumor showed an angiocentric pattern of distribution. There were several CD68+ histiocytes and few plasma cells. Immunostaining for CD56, CD30, and EBV latent membrane protein 1 (LMP-1) was negative. Overall features were of atypical lymphohistiocytic infiltrate, and immunomorphologic features were in favour of LG. Based on the investigations, a diagnosis of LG, isolated to the CNS, without any evidence of systemic involvement was made. He was treated with pulse cyclophosphamide and methylprednisolone. At 3 months follow-up, he was seizure free, had deficits in recent memory, bilateral rigidity, and exaggerated reflexes. He was ambulant without support, but required minimal assistance for activities of daily living. His repeat MRI brain showed atrophy, with reduction in the number and size of the enhancing nodular lesions and perilesional edema [Figure 2].

## Discussion

Isolated CNS disease is a rare manifestation of LG. Common symptoms described in the previous reports



**Figure 2 (A-D):** MRI brain images at 3 months follow-up (A) T2 axial image shows decrease in the number of T2-isointense lesions and perilesional edema (arrow) (B) DWI does not show any restriction (C and D) Post-contrast images show fewer enhancing nodular lesions in the subependymal regions and deep gray nuclei (arrows)

include headache, disorientation, memory loss, spastic gait, hemiparesis, visual blurring, involuntary movements, incontinence, and seizures.<sup>[1]</sup> Our case had presented with behavioral changes, chorea, and later had decline in memory, rigidity, bradykinesia, seizures, and incontinence, similar to those in previous reports.<sup>[1]</sup>

Radiological features previously reported include multifocal enhancing intraparenchymal lesions or masses with perilesional edema, enhancement of leptomeninges, cranial nerves, and choroid plexus. Punctuate/linear enhancement can be seen in LG, as it mainly affects the perivascular tissue and vessel walls.<sup>[1,5,6]</sup> Isolated CNS disease presents usually as mass lesions which are uncommon in systemic LG with CNS involvement.<sup>[1,5]</sup> However, these imaging features are non-specific and can be seen in vasculitis, encephalomyelitis, lymphoma, malignant glioma, metastasis, neurosaroidosis, leptomeningeal carcinomatosis, and infections, especially tuberculosis in cases with associated pulmonary involvement.<sup>[1,7]</sup> In a case report by Nishihara *et al.*, magnetic resonance spectroscopy of the lesions showed increased peak of choline and lactate and a decreased peak of N-acetylaspartate (NAA), suggesting the presence of abnormally proliferating cells, loss of nervous tissue, and necrosis, respectively.<sup>[8]</sup> MRI in our case showed multiple enhancing nodules, mainly subependymal, ependymal, and perivascular. Lesions were also seen in the brainstem and spinal cord. No mass lesions were seen in our case, but were common in isolated CNS cases in previous reports.<sup>[1]</sup> Spinal lesions were not mentioned in the previous reports, but were seen in our case.<sup>[1]</sup>

In a case report by Nishihara *et al.*, 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan showed low uptake in the lesion suggestive of necrotizing lesion and methionine (MET) PET scan exhibited a high uptake in the lesion suggestive of highly cellular proliferative lesion. They proposed that the mismatch in accumulation of FDG- and MET PET could be characteristic of LG.<sup>[8]</sup> Kawai *et al.* have suggested that PET imaging with kinetic analysis is effective in LG of the CNS, which would show increased hexokinase activity in the lesions due to accelerated glycolytic metabolism.<sup>[9]</sup>

Histopathologic findings reported consist of infiltration of the meninges, blood vessels, and brain by atypical cells with plasmocytoid characteristics. The differentials to be considered on histopathology include vasculitis and lymphoma. The angiocentric pattern and polymorphic nature of the infiltrate favor the diagnosis of LG over lymphoma. Compared to vasculitis, angiocentric pattern of infiltrates and absence of eosinophils and giant cells are suggestive of LG.<sup>[1-3]</sup> Our case showed atypical lymphohistiocytic infiltrate with angiocentric pattern of distribution and negative immunostaining for EBV

LMP-1. These features were similar to those described in earlier reports, including negative EBV status in isolated CNS cases compared to cases with systemic involvement where it is positive.<sup>[1,3]</sup> Response to steroids and cyclophosphamide was seen in our case, similar to that in previous reports. There was improvement in functional status, with MRI brain showing decrease in size and enhancement of the lesions, and cerebral atrophy. Resolution of the lesions after treatment has been reported, but the cerebral atrophy seen in our patients has not been well described in literature.<sup>[6]</sup> Other modalities of therapy used in LG include, cisplatin, cytarabine, methotrexate, rituximab, combination of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP regimen), radiotherapy, and surgical excision of lesions.<sup>[1,4]</sup>

## Conclusion

Isolated CNS LG, though rare, is an important differential diagnosis in patients presenting with enhancing cerebral mass, diffuse punctuate lesions, and with disease isolated to the CNS. Brain biopsy for the characteristic histopathologic findings and EBV status will aid in diagnosis. In view of the protracted course and response to treatment, steroids with immunotherapy can result in good outcome in isolated CNS LG.

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