

## Clinical-Radiological-Pathological Correlation

### Lymphomatoid Granulomatosis

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#### Case

A 21 year old right handed male was brought to the hospital by his family with complaints of confusion. His family found that he had difficulty dressing himself, was talking repetitively and unable to answer simple questions. These symptoms gradually improved over several hours. He had been suffering from headaches and vomiting intermittently for the preceding 12 days. He was admitted to the hospital for further testing. His past medical history was significant for renal transplant at age 7 for focal sclerosing glomerulonephritis. He was chronically immune suppressed with mycophenolate mofetil and prednisone. He had previously been treated with cyclosporine, which was discontinued 2 years prior to presentation due to nephrotoxicity. Neurological examination was significant for inattention, papilledema, homonymous left upper quadrantanopsia and mild slowing of left foot tapping.

Magnetic resonance imaging (MRI) of the brain showed multiple bilateral lesions which were hypointense on T1 and T2 weighted imaging with surrounding T2 hyperintensity suggestive of edema (Figure 1). The larger lesions showed ring-enhancement, while smaller ones had more homogenous enhancement (Figure 2).

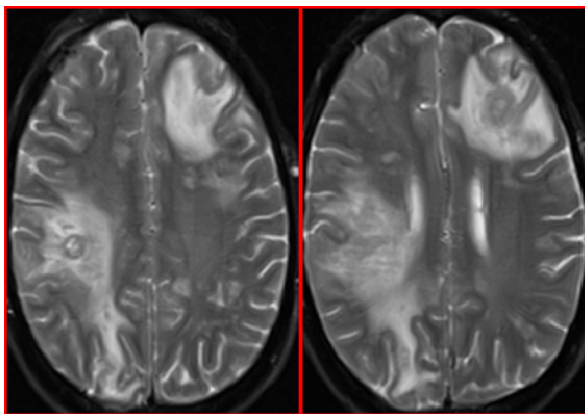


Figure 1: T2axial images showing hypointense lesions with surrounding hyperintensity suggestive of vasogenic edema

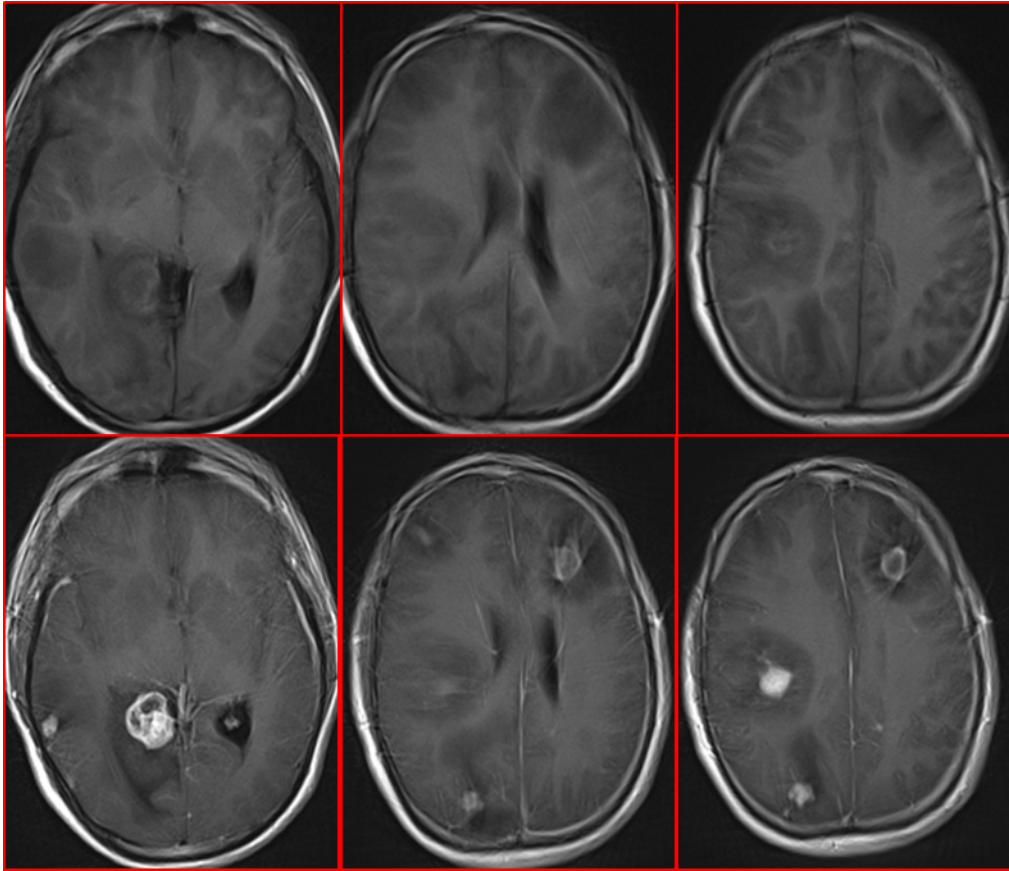


Figure 2: T1 pre- (top row) and T1 post- (bottom row) contrast showing multiple ring enhancing lesions with some enhancement inside the larger lesions

A tuberculin sensitivity test was placed and serology was sent for toxoplasmosis, histoplasmosis, and Cryptococcus. Empiric therapy was started for toxoplasmosis, which was discontinued when the serology was determined to be negative. A biopsy was then performed and showed perivascular infiltrate of small lymphocytes, plasma cells and occasional large lymphocytes (Figure 3). A few clusters of large atypical cells were also seen. These cells featured irregular nuclear contours, clumped chromatin, prominent nucleoli and scant to moderately abundant cytoplasm. Immunohistochemistry was performed. CD3 and CD5 small T lymphocytes were present in similar numbers. These were a mixture of CD4 and CD8-positive cells. CD20 and CD79a stained small B lymphocytes and occasional large B cells. Large CD68 positive histiocytes were also present (Figure 4). In situ hybridization revealed the presence of Epstein-Barr viral (EBV) RNA, along with kappa light chain and lambda light chain message in some large B cells expressing CD20 and CD79a (Figure 5). The presence of

atypical large B-cells with EB-virus in a setting of polyclonal light-chain expression is typical for lymphomatoid granulomatosis (LYG), grade 2.

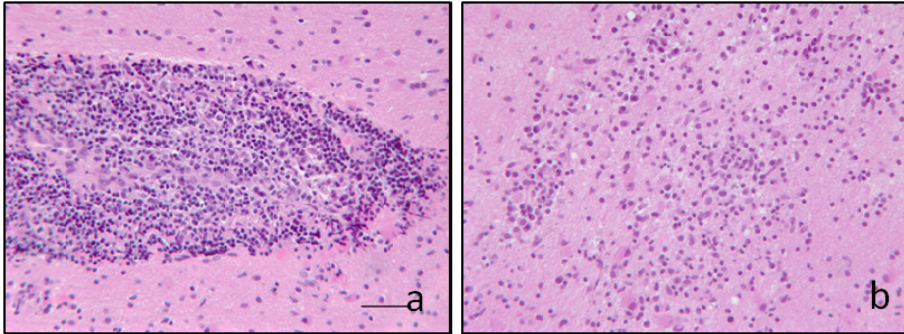


Figure 3: Photomicrographs of the brain biopsy reveal a) perivascular accumulation of lymphocytes and larger cells, and b) with other areas having infiltration of these cells into the brain parenchyma. Hematoxylin and eosin. Scale bar = 50 micrometers.

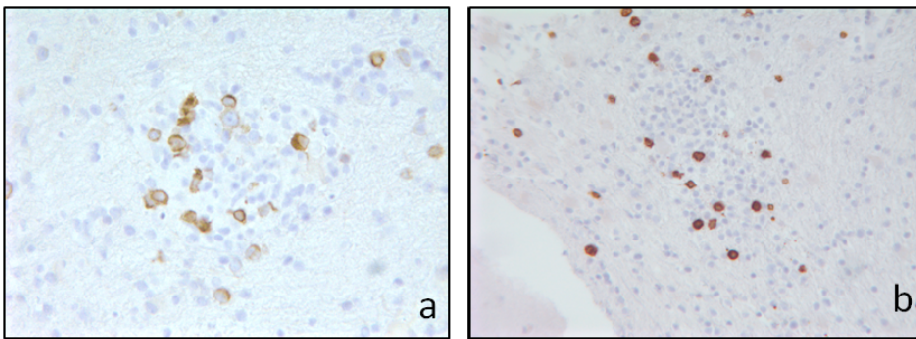


Figure 4: Immunohistochemical staining labels some of the large cells as a) B-lymphocytes (CD79a-antibody), and b) histiocytes (CD68-antibody). DAB-immunoperoxidase. Scale bar = 50 micrometers.

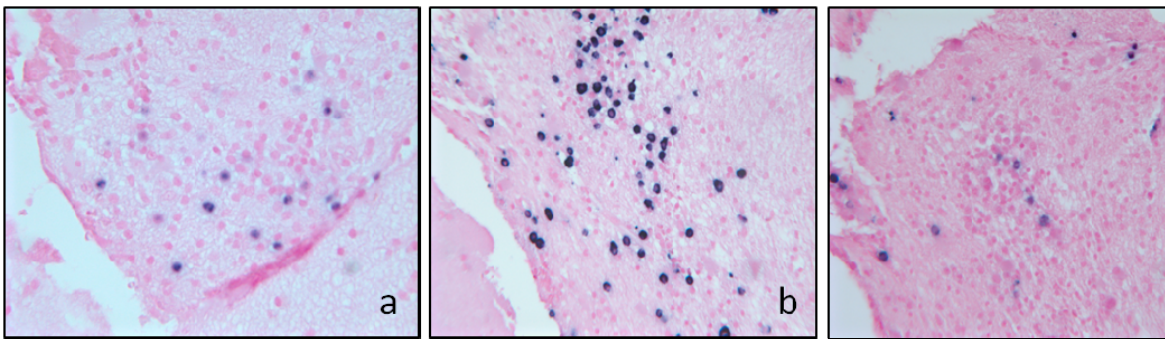


Figure 5: In situ hybridization studies label some of the cells with a) Epstein-Barr viral message, and message for both b) kappa-light chain, and c) lambda light chain. Scale bar = 50 micrometers.

The patient was initially treated with dexamethasone, rituximab and cyclophosphamide. His mycophenolate was discontinued. He had worsening of his mental status and was readmitted one month later. Imaging was repeated and found to have an increased number of lesions. Given worsening of his illness, he was started on a course of whole brain radiation. He soon developed left lower extremity sensory changes which lead to imaging of the spine. He was found to have a 1cm T2 hyperintense lesion with contrast enhancement at T10 with cord edema from T6-T12 (Figure 6) which was thought to represent further lymphomatoid granulomatosis. His radiation therapy was therefore modified to include the thoracic cord. Gradually, his cognition and behavior appear back to normal. In the last follow up appointment, 5 months after initial presentation, he reported no further progression.

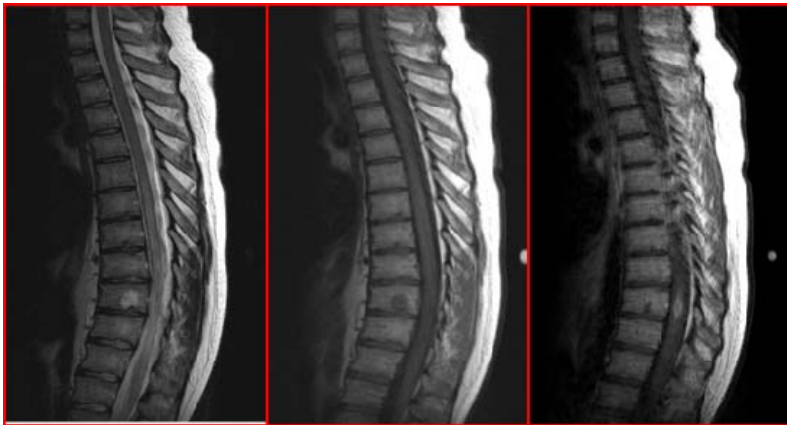


Figure 6: T2 Sagittal of thoracic spine shows cord edema from about T6-T12 with a lesion at T10 that is enhanced post contrast.

### **Discussion**

LYG is a rare angiocentric, angiodestructive lymphoproliferative disorder. While LYG rarely involves the central nervous system (CNS) in isolation, there are cases reported of primary CNS LYG.<sup>1-5</sup> It more commonly affects the lungs, and may also involve the skin, kidneys, and liver. The exact pathology remains uncertain. When it effects the CNS it is more commonly due to spread of systemic LYG to the CNS. Based on imaging and pathological examination it can be divided into space occupying or infiltrative lesions. The most common finding in a

series of 25 patients with LYG affecting the CNS (primary or secondary) was multifocal T2 hyperintensities with linear or punctuate contrast enhancement. This finding is felt to be due to the angiocentric and angiodestructive nature of the disease. These lesions typically involve the white matter and the deep grey nuclei. Leptomeningeal and cranial nerve enhancement is also commonly seen in LYG affecting the CNS.<sup>6</sup> Systemic LYG which spreads to the CNS is associated with EBV and has B-cell predominance.<sup>4</sup> Cases of primary CNS-LYG have not been associated with EBV and seem to have T-cell predominance.<sup>3, 4</sup> Our patient thus far has not been found to have disease outside the CNS, despite having atypical B-cells with EBV RNA.

In a case series of 152 patients diagnosed with pulmonary LYG, 21% presented with neurologic complaints.<sup>7</sup> A more recent study has found radiographic involvement of the central nervous system in 52% of patients diagnosed with LYG, of which 77% were symptomatic for CNS effects.<sup>6</sup> While it may develop in the immunocompetent, LYG is more common in the immune suppressed including human immunodeficiency virus patients.<sup>5</sup> It has rarely been reported in pharmacologically immune suppressed patients including post-transplant patients, patients treated with methotrexate for rheumatoid arthritis,<sup>1</sup> and patients treated with azathioprine for autoimmune hepatitis.<sup>8</sup> The course of the illness is highly variable, ranging from self-limited or steroid responsive disease to malignant transformation.<sup>2</sup> The 5 year mortality rate is 60-90% with a median survival of 14 months.<sup>7</sup> At present, the optimal therapy remains unclear. Prospective trials and multicenter studies are lacking.<sup>8</sup>

### **References**

1. Agarwal V, Agarwal A, Pal L, Misra R. Arthritis in lymphomatoid granulomatosis: report of a case and review of literature. *Indian journal of medical sciences*. Feb 2004;58(2):67-71.
2. Gitelson E, Al-Saleem T, Smith MR. Review: lymphomatoid granulomatosis: challenges in diagnosis and treatment. *Clin Adv Hematol Oncol*. Jan 2009;7(1):68-70.
3. Lucantoni C, De Bonis P, Doglietto F, Esposito G, Larocca LM, Mangiola A, Martini M, Papacci F, Teofili L, Pompucci A. Primary cerebral lymphomatoid granulomatosis:

- report of four cases and literature review. *Journal of neuro-oncology*. Sep 2009; 94(2): 235-242.
4. Nishihara H, Tateishi U, Itoh T, Nagashima K, Tanaka S. Immunohistochemical and gene rearrangement studies of central nervous system lymphomatoid granulomatosis. *Neuropathology*. Oct 2007; 27(5): 413-418.
  5. Wyen C, Stenzel W, Hoffmann C, Lehmann C, Deckert M, Fatkenheuer G. Fatal cerebral lymphomatoid granulomatosis in an HIV-1-infected patient. *The Journal of infection*. Mar 2007; 54(3): e175-178.
  6. Patsalides AD, Atac G, Hedge U, Janik J, Grant N, Jaffe ES, Dwyer A, Patronas NJ, Wilson WH. Lymphomatoid granulomatosis: abnormalities of the brain at MR imaging. *Radiology*. Oct 2005; 237(1): 265-273.
  7. Katzenstein AL, Carrington CB, Liebow AA. Lymphomatoid granulomatosis: a clinicopathologic study of 152 cases. *Cancer*. Jan 1979; 43(1): 360-373.
  8. Katherine Martin L, Porcu P, Baiocchi RA, Erter JW, Chaudhury AR. Primary central nervous system lymphomatoid granulomatosis in a patient receiving azathioprine therapy. *Clin Adv Hematol Oncol*. Jan 2009; 7(1): 65-68.

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