

Intra-abdominal T-cell Lymphoma Presenting with Seizures and MRI Changes

Florence Morriello, G. Bryan Young

Can J Neurol Sci. 2013; 40: 426-428

T-cell lymphoma is rarely associated with direct or indirect neurological complications. We present a unique case with features of both a paraneoplastic syndrome, with early encephalopathy and new onset refractory status epilepticus (NORSE)¹ and later multifocal brain infarctions that were likely related to more direct complications of lymphoma. Though infectious encephalitis is likely to underlie many, if not the majority of cases of adult onset NORSE, others have suggested that adult NORSE is likely to be more heterogenous and includes para-infectious, immune-mediated as non-infectious.¹

CASE PRESENTATION

A 20-year-old right-handed Asian man was admitted to the intensive care unit with status epilepticus. He had previously been in good health and was on no medications when he and his girlfriend contracted an upper respiratory tract infection one month prior. Two weeks later he presented to the emergency room with headaches, fever, and ocular pain associated with eye movements. He was diagnosed with sinusitis, given oral antibiotics and sent home. A week later he developed episodes of slurred speech and confusion. On the day of presentation to a local hospital, his mother had found him unconscious. His initial blood pressure was 105/35 mm Hg, heart rate 58 beats per minute and regular. Oral temperature was 38.3 degrees Celsius; his Glasgow Coma score (GCS) was 5. After admission he developed generalized convulsive seizures and was intubated and mechanically ventilated. Pupils were equal and reactive to light. The eyes showed nystagmoid jerks to the right once every minute.

His status epilepticus required multiple maintenance antiepileptic drugs, midazolam and propofol infusions and intermittent doses of lorazepam. Magnetic resonance imaging (MRI) showed bilateral medial temporal signal change. Spinal fluid results were unremarkable. Two days later, he was transferred to our centre for further workup of his refractory seizures for which he received phenytoin 500 mg every 12 hours, phenobarbital 100 mg every 8 hours, levetiracetam 500 mg every 12 hours, a propofol infusion at 80-120 µg/kg/min and midazolam 2-4 mg IV q 10 min as needed. Continuous electroencephalogram (EEG) monitoring captured multifocal electrographic seizures. In addition, there were multiple independent interictal epileptiform discharges in the left occipital and both central regions. Given the presence of ongoing seizure activity, pregabalin 275 mg every 8 hours was added to the antiepileptic drug regimen.

His blood work showed normocytic anemia with a hemoglobin concentrations in the low 80s (g/L) and elevated

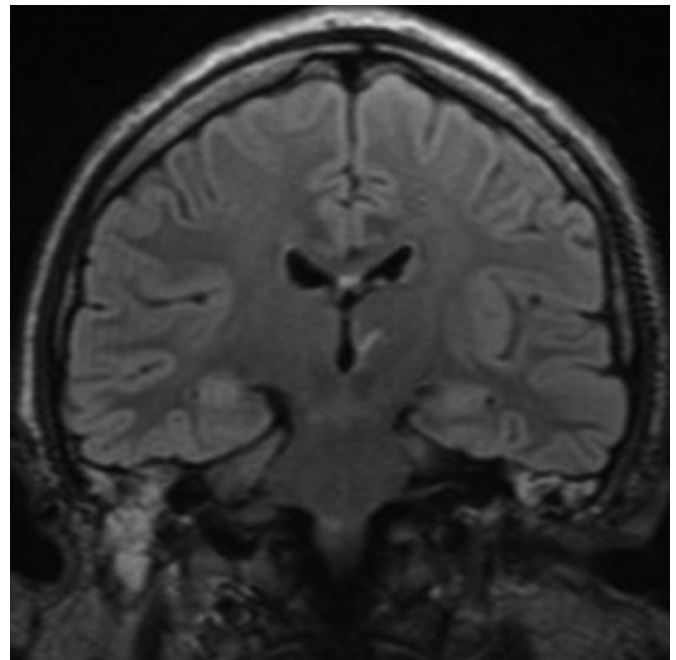


Figure 1: Magnetic resonance imaging showing signal change in the hippocampi suggestive of T2 signal change.

eosinophils at 2.040 and monocytes at $1.122 \times 10^9/L$. Serum electrolytes, calcium, magnesium and thyroid hormones were normal. A repeat lumbar puncture revealed an elevated protein of 59 g/L, no cells and a normal glucose. Autoimmune encephalitis testing was not performed. Electrocardiogram (ECG) showed normal sinus rhythm with normal QT and no ST changes. His chest x-ray on admission was unremarkable.

Working on the presumptive diagnosis of viral encephalitis and from his laboratory and clinical presentation he was started on dexamethasone 10 mg IV daily and acyclovir 10 mg/kg IV Q8h.

From the Department of Critical Care Medicine (FM), University of Toronto, St. Michael's Hospital, Toronto; Department of Critical Care Medicine & Clinical Neurological Sciences (GBY), The University of Western Ontario, London, Ontario, Canada.

RECEIVED SEPTEMBER 4, 2012. FINAL REVISIONS SUBMITTED NOVEMBER 2, 2012.
Correspondence to: Florence Morriello, Department of Critical Care Medicine, University of Toronto, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, M5B 1W9, Canada. Email: florence.morriello@utoronto.ca, morriellof@smh.ca.



Figure 2: MRI T2 image demonstrating a focal signal abnormality in the medulla.

During his hospital stay, the patient remained comatose with refractory status epilepticus. A repeat contrast enhanced MRI head/magnetic resonance angiography (MRA) a week after admission, showed new findings including new T2/FLAIR hyperintensities in the medulla. These lesions were seen inferiorly on the dorsal aspect of the medulla and more superiorly on the right side.

Given the new MRI/MRA findings and the ongoing seizures, extensive workup was done including CSF polymerase chain reaction for herpes simplex virus, serum antibody testing for Human Immunodeficiency Virus, (HIV), Human T-lymphotropic virus Type I (HTLV-1), Epstein-Barr virus (EBV), quantitative Cytomegalovirus (CMV), mycoplasma, *Chlamydia* and *Neisseria gonorrhoeae* autoimmune encephalitis, hepatitis screen (including Hepatitis B, C, D screen), syphilis testing and a bone marrow which were all negative except positive serology for IgG EBV, of questionable significance. Rheumatologic testing (included anti-nuclear antibody (ANA), double stranded DNA (dsDNA), rheumatoid factor, complements C3 and C4, cyclic citrullinated peptide antibody (CCP), extractable nuclear antigen antibodies (ENA), anti myeloperoxidase antibodies (MPO), anti proteinase-3 antibodies (PR3), c-reactive peptide (CRP) and erythrocyte sedimentation rate (ESR) was all negative. His serum bilirubin concentration was initially normal but later rose to 164.8, direct bilirubin peaked at 134.8 mmol/L and elevated lactic acid dehydrogenase (LDH) at 2325 U/L. Ammonia was elevated at 183 mmol/L.

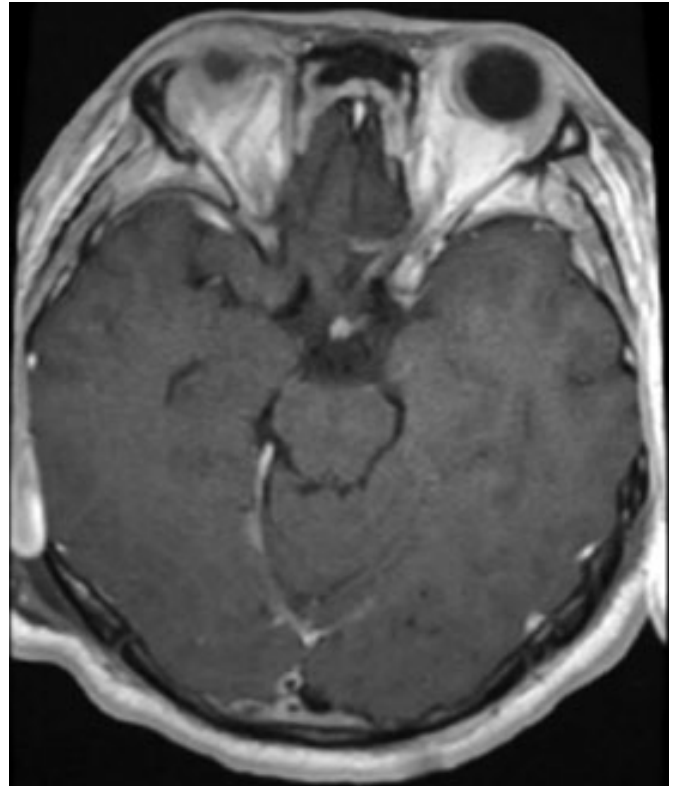


Figure 3: MRI with gadolinium contrast showing enhancement around the optic nerves.

While in hospital, he continued to have recurrent fevers but multiple blood, urine and stool cultures were negative. He grew *Staphylococcus aureus* in his respiratory culture on several occasions initially Methicillin-sensitive and later Methicillin-resistant strains, requiring cloxacillin initially and later treated with vancomycin. Despite treatment, he continued to be febrile. At the same time his transaminases, amylase and lipase were extremely elevated: alanine aminotransferase (ALT) rose from 47 U/L to 1272 U/L, aspartate aminotransferase (AST) from 57 U/L to 626 U/L, alkaline phosphatase (ALP) from 43 U/L to 152 U/L; gamma glutamyl transpeptidase (GT) was 1158 U/L, in keeping with an intrahepatic cholestasis. The possibility of intra-abdominal septic focus was eliminated with computed tomogram (CT) abdomen/pelvis. About one week later he developed bloody diarrhea. A repeat CT abdomen/pelvis showed an increase in a number and size of lymph nodes, predominantly in the mesentery of the small bowel, and a thickened gallbladder. A tentative diagnosis was acalculous cholecystitis for which a cholecystostomy tube was inserted.

His neurological status remained compromised; he remained deeply comatose and required multiple antiepileptic medications to control his seizures. We therefore repeated an MRI two weeks later which in comparison to the previous MRI, now showed new, small focal signal abnormalities in the left globus pallidus and anterior thalamus. A small amount of hemosiderin was associated with both lesions.

With no improvement in neurological status, he underwent MR with MRA a week later which showed evolution of the previously noted infarcts. But the contrast-enhanced MRI of the brain was suggestive of optic nerve enhancement around the left optic nerve particularly with extensive sinus inflammatory changes seen. The MRA showed patency of the major intracranial vessels and their major branches. The major dural sinuses were also patent and there was no aneurysm or vascular malformation.

Repeat MRI two days later showed increased T2 and FLAIR signal as well as diffusion restriction in the medial temporal lobes bilaterally. There was symmetric involvement of the amygdala and hippocampus. There was involvement of the inferior frontal lobes and caudate heads as well as possibly the cingulate gyri. This showed mild mass effect.

He developed profuse watery diarrhea. Stool culture results were negative. A colonoscopy showed mild ileitis; a biopsy of the small bowel mucosa revealed a marked decrease in goblet cells and increased mitotic activity in both the surface and crypt epithelium. There was also a nodular infiltrate of small lymphocytes, eosinophils, and a few highly atypical large cells that involved the mucosal lymphoid follicles. The lymphoid infiltrate was positive for CD3, CD4 and CD5. Many of the neoplastic cells were also positive for CD30; some were positive for bcl-2, and possibly rare cells were positive for bcl-6. The biopsy was negative for EBV-encoded RNA by (EBER) *in situ* hybridization. No viral inclusions, parasites, or granulomas were identified. The crypt architecture in the large bowel mucosa and submucosa was normal but there was increased apoptosis and focally damaged crypts, one with a small crypt abscess. A nodular atypical infiltrate similar to that in the small bowel was noted. A diagnosis of T-cell lymphoma, CD30+ with large anaplastic cells was made.

It was judged that this type of lymphoma would be poorly responsive to chemotherapy. The patient's general condition precluded starting chemotherapy while acutely ill and he died several weeks later of multiorgan failure. No paraneoplastic workup was carried out. No autopsy was carried out as the family declined.

DISCUSSION

We propose that the early features of this case, with findings attributable only to the seizures and negative spinal fluid were due to a remote effect of lymphoma. There was never any radiological or spinal fluid evidence of lymphoma affecting the central nervous system or meninges. Central nervous system (almost always B-cell) lymphoma has characteristic radiographic features: the lesions primarily involve the deep white matter, are well demarcated, but with "fuzzy" margins and uniformly enhance with contrast.²

Lymphoma has been associated with paraneoplastic syndromes affecting both peripheral and central nervous systems (CNS), with the former predominating.³ All the cases have been associated with B-cell lymphomas.¹ Cerebellar degeneration is the most common central nervous system complication.³ There has only been one case of limbic encephalitis with seizures.³

The strokes or brain infarcts that occurred later may have, however, been due to more direct involvement by lymphoma, either with infiltration in the perivascular spaces of the brain,

compromising vascular lumina or, less likely, intravascular lymphoma with infarction or marantic (nonbacterial, thrombotic) endocarditis with cerebral emboli. Stroke in a young patient with T-cell lymphoma was associated with small perivascular lymphomatous deposits in the brain, however the larger middle cerebral artery territory infarction could not be explained.⁴ EBV-associated T/NK cell lymphoproliferative disorder of children and young adults is generally referred to as severe chronic active EBV infection. This can later result in transformation into a lymphoma. We speculate that the upper respiratory infection that the patient and his girlfriend had before he became so ill was caused by EBV.

The factor that triggered the growth of this tumour in the bowel remains unclear. In the literature there are references correlating the incidence of T-cell lymphoma to ileitis due to inflammatory bowel disease and/or celiac disease. Moreover, in a hamster model of non-Hodgkin's lymphoma which closely parallels the disease in man, and which is induced by an unusual agent(s), a diarrheal bowel disease was a major cause of mortality. Since necrosis in the gut-associated lymphoid tissue can lead to perforation and sepsis, ulcerative bowel lesions can be lethal.^{3,5} Our patient had neither celiac disease nor chronic inflammatory bowel disease in the usual sense. A full-body autopsy would have been useful to determine whether or not the patient had disseminated lymphoma, not restricted to his small bowel.

This is the first reported case of NORSE in the presence of bowel lymphoma. His ongoing refractory status epilepticus could have been due to an immunological process against brain antigens. The unfavourable outcome observed in our patient may have been partly because of the delay in diagnosis, but mainly due to the aggressive course and unresponsiveness of this type of lymphoma.

REFERENCES

1. Wilder-Smith EP, Lim EC, Teoh HL, et al. The NORSE (new-onset refractory status epilepticus) syndrome: defining a disease entity. *Ann Acad Med Singapore*. 2005;34:417-20.
2. Slone HW, Blake JJ, Shah R, et al. T and MRI findings of intracranial lymphoma. *AJR Am J Roentgenol*. 2005 May;184(5):1679-85.
3. Briani C, Vitaliani R, Grisold W, et al. Spectrum of paraneoplastic disease associated with lymphoma. *Neurology*. 2011;76:705-10.
4. Fragou M, Karakitsos A, Kalogeromitros A, et al. Peripheral T-cell lymphoma presenting as an ischemic stroke in a 23-year-old woman: a case report and review of the literature. *J Med Case Reports*. 2009;3:83.
5. Manci EA, Heath LS, Leinbach SS, et al. Lymphoma-associated ulcerative bowel disease in the hamster (*Mesocricetus auratus*) induced by an unusual agent. *Am J Pathol*. 1984;116:1-8.