Clinical Reasoning:

An unusual case of papilledema after orthotopic liver transplantation

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Figure Photographs of the optic disc of the right and left eyes, showing bilateral pale swollen discs with flame-shaped hemorrhages and venous engorgement of the vessels

SECTION 1

A 59-year-old, right-handed woman presented with a 7-day history of insidious onset of progressive blurring of vision of the right eye. She had undergone orthotopic liver transplantation 15 months previously due to non-A non-B fulminant hepatic failure. Her postoperative period was complicated by 2 episodes of acute rejection which responded to methylprednisolone, dalcizumab, and change of immunosuppressive therapy from tacrolimus to cyclosporine. Three months prior she had developed nonspecific symptoms of weight loss, malaise, and anorexia.

On examination she was alert and oriented. Visual acuity was 6/60 on the right and 6/36 on the

left. Color vision was impaired bilaterally as tested with the Ishihara pseudoisochromatic plates. There was enlargement of both blind spots and severe constriction of fields with relative preservation of inferior nasal fields only. Ophthalmoscopic examination and fluorescein angiography showed bilateral pale swollen optic discs with peripapillary hemorrhages and venous engorgement (figure). The remaining neurologic examination was normal.

Questions for consideration:

1. What are the possible differential diagnoses?
2. Which initial investigations would you recommend?

GO TO SECTION 2

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SECTION 2

The initial differential diagnosis for optic neuropathies with disc swelling included raised intracranial pressure, malignant hypertension, bilateral compressive thyroid ophthalmopathy, bilateral optic nerve tumors, bilateral simultaneous anterior ischemic optic neuropathy, idiopathic intracranial hypertension, and infective and inflammatory conditions.

Twenty-four-hour ambulatory blood pressure monitoring was normal. Free thyroxin and thyroid stimulating hormone levels were normal. Thyroid antibodies were negative. Inflammatory markers were normal. Gadolinium-enhanced MRI of

brain, orbits, pituitary, and optic nerves revealed increased signal uptake in the left optic nerve only, excluding intracranial and optic nerve tumors, demyelination, hematomas, vascular malformations, and hydrocephalus. MR venography and angiography were normal, reducing the likelihood of cerebral sinus thrombosis and subarachnoid hemorrhage.

Questions for consideration:

1. What additional diagnostic tests would you consider at this time?
2. What is your differential diagnosis at this point?

GO TO SECTION 3

SECTION 3

Lumbar puncture showed an opening CSF pressure >31 cm H₂O, raised protein of 2.6 g/L, glucose of 3.2 mmol/L (serum glucose 5.1 mmol/L), and raised white cell count of 45 cells/mm³ (100% lymphocytic).

The differential diagnosis for a lymphocytic pleocytosis includes parameningeal infections (partially treated bacterial meningitis), non-viral infectious meningitides (fungi, mycobacteria, parasites, syphilis, listeria, brucella, Coxiella, mycoplasma), neoplastic meningitis, non-infectious inflammatory disease (Behcet disease, sarcoid), HIV, herpes simplex virus (HSV), cytomegalovirus (CMV), human herpes virus 6 (HHV6), varicella zoster virus (VZV) (Artus), polyomavirus, Epstein-Barr virus (EBV), and demyelinating and neoplastic conditions.

CSF culture, Gram stain, acid-fast staining, Indian ink preparation, and cryptococcal antigen were negative. CSF cytology suggested reactive lymphocytes only. CSF PCR testing and serum titers for HIV were negative. Serum toxoplasma antibodies were negative. CSF Venereal Disease Research Laboratory was negative. CT of the thorax, abdomen, and

pelvis was normal. The absence of enhancement of the pia mater or white matter lesions on gadolinium-enhanced MRI made the diagnosis of sarcoid less probable but did not definitively exclude it as a possible diagnosis at this stage. Normal brain imaging and no history of mucocutaneous disease or pathergy made Behcet disease unlikely.

CSF lymphocyte immunophenotyping showed proliferation of both helper and cytotoxic T cells demonstrating activation markers, a minor population of natural killer cells (6%), and non-clonal proliferation of B cells (4%), consistent with a reactive response to an established viral infection.

PCR for HSV, CMV, HHV6, VZV (Artus), and polyomavirus DNA were negative. A total of 108 copies/mL of EBV DNA were detected in CSF. Whole blood EBV IgM viral load was 41,090 copies/mL, consistent with active EBV infection.

Questions for consideration:

1. What additional diagnosis must you consider now?
2. How would you manage this patient?

GO TO SECTION 4

SECTION 4

Repeated lumbar punctures confirmed active EBV disease but no malignant lymphoid cells. CSF opening pressure returned to normal (16 cm H₂O) but CSF protein remained elevated (2.1 g/L). The differential diagnosis at this point included isolated EBV meningitis and posttransplant lymphoproliferative disease (PTLD). Due to her clinical presentation, history of organ transplantation, use of high-dose immunosuppression with cyclosporine, persistence of EBV DNA on serial CSF analysis, and circulating levels of EBV DNA between 20,000 and 200,000 copies/ μ g (41,090 copies/mL), even in the absence of lymphoid cells, the assumed diagnosis was PTLD.

Her immunosuppressive therapy was reduced and she was commenced empirically on dexamethasone to preserve residual vision. Her vision improved to 6/24 on the left and 6/36 on the right with persistence of initial disc changes. She was treated with valacyclovir and discharged well with close follow-up surveillance of vision and CSF EBV DNA levels.

At follow-up 2 years after presentation, she remained well; her visual acuity had improved to 6/36 on the right and 6/18 + 1 on the left. Repeat CSF examination showed normal pressure, protein of 0.73 g/L, and white cell count of <1 cell/mm³, and EBV DNA was not detected. She continued on mycophenolate mofetil 500 mg twice daily, cyclosporine 50 mg twice daily, and valacyclovir 450 mg twice daily.

DISCUSSION The detection of EBV DNA in CSF in the setting of optic nerve involvement, lymphocytic pleocytosis, and raised intracranial pressure in a transplant recipient suggests PTLD. PTLD is a syndrome that encompasses hyperplastic and neoplastic proliferation of lymphocytes with a wide spectrum of disease severity.¹ It is the most common noncutaneous malignancy in organ transplantation recipients with significant morbidity and mortality.² The incidence of PTLD varies between different allografts. It is reported at 1%–2% in renal transplant recipients and 2% in liver transplantation.³ PTLD is a tissue diagnosis and a high index of suspicion is required as its presentation is often nonspecific.

Most PTLD is driven by EBV infection. Acquired CD3 immunodeficiency secondary to immunosuppressant agents reduces the clearance of EBV, promoting primary infection or reactivation of the virus. EBV in turn promotes oncogenic activation and increases the incidence of lymphoma posttransplantation by up to 40 times that of the general population.⁴

The clinical presentation is often subtle, leading to a delay in diagnosis, with the mean time to diagnosis posttransplant of 20 to 35 months.⁵

Nonspecific symptoms may include fever, weight loss, and anorexia, as present 3 months prior in this patient. Ocular PTLD is recognized in the differential diagnosis of uveitis after organ transplantation, with anterior chamber cells and iris nodules being the most common ocular signs. But the posterior segment can be involved without evidence of systemic disease, again, as in this case.

The incidence of PTLD has risen with the introduction of more potent immunosuppressant agents. Different sites may be involved, with the incidence of CNS involvement up to 27%.⁵ CNS involvement in transplant recipients with PTLD carries a poor prognosis; however, isolated CNS involvement without extracranial involvement has a better prognosis.⁶

Risk factors for the development of PTLD include intensity and type of immunosuppressant, EBV status prior to transplantation, and titers of whole blood EBV DNA.⁷ Circulating levels of EBV DNA between 20,000 and 200,000 copies/ μ g are associated with the development of PTLD.⁸

Management of PTLD involves reduction of immunosuppression. The presence or absence of bcl-6 has been associated with favorable response to this therapeutic intervention.⁹ The role of antiviral agents remains controversial. Acyclovir and ganciclovir inhibit viral replication but have little effect on latent virus. However, antiviral therapy is incorporated into treatment schemes to eliminate replicating virus. Other novel treatments have been used with varying success, including IV immunoglobulin, interferon- α , and rituximab. Chemotherapy including the CHOP regimen alone or combined with low-dose cyclophosphamide has been reserved for patients with overt malignancy, with monitoring EBV DNA levels suggested as a measure of response to treatment.¹⁰

The patient we describe has an unusual cause of visual blurring and papilledema that exemplifies the need for vigilance and early detection of PTLD in the setting of unexplained infectious syndrome after solid organ transplantation.

DISCLOSURE

Dr. Gorman reports no disclosures. Dr. Tubridy receives funding for travel to attend meetings by Biogen-Idec and Schering. Dr. Hutchinson serves on a medical advisory board of Biogen-Idec; serves on the editorial boards of *Multiple Sclerosis* and the *International MS Journal*; and receives research support from Dystonia Ireland.

REFERENCES

1. Frizzera G, Hanto DW, Gajl-Peczalska KJ, et al. Polymorphic diffuse B-cell hyperplasias and lymphomas in renal transplant recipients. *Cancer Res* 1981;41:4262–4279.
2. Buell JF, Gross TG, Woodle SE. Malignancy after transplantation. *Transplantation* 2005;80:254–264.
3. Le Meur Y, Potelune N, Jaccard A, et al. Lymphoproliferative syndromes after renal transplantation. *Nephrologie* 1998;19:255–261.

4. Hochberg FH, Miller G, Schooley RT, Hirsch MS, Feorino P, Henle W. Central-nervous-system lymphoma related to Epstein-Barr virus. *N Engl J Med* 1983;309:745–748.
5. Mihalov ML, Gattuso P, Abraham K, et al. Incidence of post-transplant malignancy among 674 solid-organ-transplant recipients at a single center. *Clin Transplant* 1996;10:248–255.
6. Rogers BB, Sommerauer J, Quan A, et al. Epstein-Barr virus polymerase chain reaction and serology in pediatric post-transplant lymphoproliferative disorder: a three-year experience. *Pediatr Dev Pathol* 1998;1:480–486.
7. Shpilberg O, Wilson J, Whiteside TL, et al. Pre-transplant immunological profile and risk factor analysis of post-transplant lymphoproliferative disease development: the results of a nested matched case-control study: The University of Pittsburgh PTLD Study Group. *Leuk Lymphoma* 1999;36:109.
8. Rowe DT, Qu L, Reyes J, et al. Use of quantitative competitive PCR to measure Epstein-Barr virus genome load in the peripheral blood of pediatric transplant patients with lymphoproliferative disorders. *J Clin Microbiol* 1997;35:1612–1615.
9. Cesarman E, Chadburn A, Liu YF, et al. BCL-6 gene mutations in post-transplantation lymphoproliferative disorders predict response to therapy and clinical outcome. *Blood* 1998;92:2294–2302.
10. Elstrom RL, Andreadis C, Aqui NA, et al. Treatment of PTLD with rituximab or chemotherapy. *Am J Transplant* 2006;6:569–576.

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