CASE REPORT

Lymphomatoid granulomatosis associated with azathioprine use for immune-mediated neuropathy

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SUMMARY

Lymphomatoid granulomatosis (LG) is a rare Epstein-Barr virus-driven lymphoproliferative disorder that generally arises in immunosuppressed patients and which can be life-threatening. Here we describe the development of pulmonary LG in a patient on long-term azathioprine for immune-mediated neuropathy. Although azathioprine carries a boxed warning for malignancy, its association specifically with LG, an otherwise rare entity, is poorly recognised. Early recognition of drug-induced LG is critical, since discontinuation of the offending agent, and implementation of effective therapy can provide rapid clinical benefit in some patients. In this case, rituximab was used as an effective treatment for LG, which also provided an additional benefit of controlling the patient's underlying neuropathy. Further research is needed to identify vulnerable patients who are at high risk of developing drug-induced LG.

BACKGROUND

Azathioprine is an immunosuppressive drug indicated for the management of rheumatoid arthritis and for the prevention of rejection following renal transplantation. It has additional off-label uses, particularly for immune-mediated disorders such as inflammatory bowel disease (IBD). Lymphocytes are particularly sensitive to purine antimetabolites like azathioprine due to their reliance on the de novo pathway of purine synthesis. A metabolite of azathioprine, 6-thioguanine triphosphate, has been found to block CD28 signalling via Rac1, an important co-stimulatory signal for T-lymphocyte activation.¹ Azathioprine is well known for its potential haematological toxicities, but it also carries a boxed warning for malignancy, including post-transplant lymphoproliferative disorders and hepatosplenic T-cell lymphoma. Here we report a case of lymphomatoid granulomatosis (LG), a rare Epstein-Barr virus (EBV)-driven lymphoproliferative disorder, arising in a patient on azathioprine for immune-mediated neuropathy.

It is important for clinicians to recognise LG as a rare but potentially life-threatening disease entity, and to be aware of its emerging association with azathioprine use. Early recognition of LG requires careful clinical and histopathological evaluation. Timely clinical decision-making can result in positive patient outcomes.

CASE PRESENTATION

The patient is a 64-year-old woman with a long history of type 2-diabetes and a 6-year history of polyneuropathy. She initially presented with diffuse

weakness and sensory loss in her lower extremities. Nerve conduction studies demonstrated length-dependent primarily axonal polyneuropathy without electrodiagnostic evidence for acquired segmental demyelinating polyneuropathy. Imaging studies of the spine were unrevealing and laboratory evaluation including vitamin B₁₂, folic acid, serum protein electrophoresis, quantitative immunoglobulins and antineuronal antibody panel were negative. Cerebral spinal fluid sampling demonstrated an elevated protein of 69 mg/dL (normal 15–45) but no oligoclonal banding was identified. Glycated haemoglobin around this time was 6.2%.

She was treated with intravenous immunoglobulin (IVIG) for a suspected autoimmune neuropathy, with improvement in her neuropathic pain and motor strength. Monthly infusions were continued. She continued to have sensory loss in the bilateral lower extremities and sustained bilateral foot drop requiring braces. Azathioprine was added and ultimately increased to 250 mg daily in divided doses. Attempts at weaning off IVIG were unsuccessful due to recrudescence symptoms.

She remained on a maintenance regimen of IVIG and azathioprine, when about 6 years later, she developed new onset of persistent non-productive cough, unintentional weight loss, fevers, malaise and night sweats. She had no new neurological symptoms and no associated cutaneous or gastrointestinal manifestations. On examination, no palpable lymphadenopathy or organomegaly was appreciated. She does not drink alcohol and is a lifetime non-smoker. She has no family history of neurological disorders or malignancy. Except as described above, she had not received additional immunosuppressive or immunomodulatory agents.

Initial labs demonstrated a normocytic anaemia with a haemoglobin of 10.7 g/dL, white cell count of 2.6 K/ μ L and platelets of 255 K/ μ L. Albumin was 2.7 g/dL. Aspartate aminotransferase was elevated at 96 units/L (0–37) with normal alanine transaminase and total bilirubin. Creatinine was normal at 0.73 mg/dL. Lactate dehydrogenase was elevated at 327 units/L (0–249).

A chest X-ray was performed which demonstrated a new left lower lobe opacity. Follow-up CT scan confirmed an 8.8 cm mass in the left lower lobe of the lung along with additional smaller pulmonary nodules noted bilaterally. Subcentimetre mediastinal lymphadenopathy was appreciated. An abdominal CT scan demonstrated mild enlargement of the spleen without enlarged abdominal lymphadenopathy and mild fatty liver without hepatic lesions.

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She underwent bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies. BAL culture results were negative for bacterial or fungal infection, with negative mycobacterial acid-fast stain. Tissue pathology was non-diagnostic.

She subsequently underwent CT-guided biopsy of the dominant lung mass. Pathology revealed extensive histiocytic infiltrates with associated fibrin deposition, necrosis, with thrombotic occlusion of an isolated blood vessel. There was no evidence of neoplasia or fungal micro-organisms on special stain. The possibility of a necrotising vasculitic process was raised, and testing for circulating antineutrophil cytoplasmic autoantibodies (ANCA) was recommended. However, testing for C-ANCA (PR3) and P-ANCA (MPO) were negative. A positron emission tomography CT scan was performed, which demonstrated that the dominant mass had an standard uptake value (SUV) of 12.2. Additional lesions in the left lower lobe and right lower lobe had maximum SUV of 5.4. No significant fluorodeoxyglucose uptake was noted outside of the lungs. Since the diagnosis remained unclear, the consulting physicians requested further review of the biopsy specimen by haematopathologist.

INVESTIGATIONS

Internal haematopathology review found that in one area with prominent necrosis, there were multifocal sheets of large atypical lymphoid cells expressing CD20 and PAX-5. Atypical B cells were also present in the background of small CD3+CD4+ T cells and CD163+ histiocytes. The large atypical B cells were positive for BCL-2, BCL-6 (subset), MUM-1 and negative for CD30, CD15, CD23 and CD56. By in-situ hybridisation, the majority of B cells were found to contain EBV encoded small RNA (figure 1). In some areas, EBV+ cells were of high density (>50/high-power field) while in other areas they were less abundant (20–50/high-power field). As a result of these new observations, the diagnosis of LG was made. LG can be further divided into three grades based on the level of EBV+ B cells and necrosis present. Grade 1 lesions have a low frequency of EBV+ cells and little necrosis. Grade 2 lesions have occasional large atypical cells and EBV+ cells number 5–20/high-power field. In grade 3 lesions, there is extensive necrosis and an abundant population

of large atypical cells. In our case, the lesion demonstrated grade 3 features.

DIFFERENTIAL DIAGNOSIS

Infectious or malignant aetiologies were high on the initial differential and these possibilities were quickly investigated using bronchoscopy with BAL and transbronchial biopsies. These tests may have helped to identify a number of potential alternative aetiologies (including typical bacterial infections, mycobacterial or fungal infections, or a lung neoplasm) but unfortunately did not provide any particular clues to the diagnosis of LG. Although malignancy remained a concern, CT-guided biopsy did not identify an obvious neoplasm and a vasculitic process was favoured. This prompted additional work-up for such an entity. Indeed, LG can be confused with a polyangiitis (such as Wegener's granulomatosis), due to the presence of angiodestructive infiltrates in LG lesions, and a propensity to involve the lungs. In contrast to LG, Wegener's granulomatosis is associated with positive ANCA serology and often involves the nasal and oral cavities, resulting in oral ulcers and purulent or bloody nasal discharge. The kidneys are also often affected. In this case, the absence of these features raised doubt about the diagnosis. Ultimately, it took a high index of suspicion by one of the consulting physicians to have the tissue re-reviewed by a haematopathologist at our institution who subsequently identified features of LG as described above.

TREATMENT

Given the diagnosis of LG, immunosuppressive therapy with azathioprine was held. She was treated with rituximab at 375 mg/m² intravenously weekly ×4 weeks, followed by observation.

OUTCOME AND FOLLOW-UP

Following treatment, she had significant clinical improvement of her symptoms and dramatic improvement in her lung lesions on CT scan (figure 2). One month following completion of treatment she also reported abrupt resolution of her bilateral lower extremity sensory neuropathy. Bilateral foot drop has persisted, but she did not develop any new progressive motor symptoms. Currently, the patient remains off both IVIG and azathioprine for the first time in over 6 years.

DISCUSSION

LG is a rare lymphoproliferative disorder associated with EBV infection, particularly in patients who are immunosuppressed. It was first described by Liebow and colleagues in 1972 and is characterised by multiple nodular lesions with polymorphic lymphoid cells and a necrotising angiocentric infiltrate.² The lungs are most often involved, though cutaneous and neurological involvement are also described. Typical presenting symptoms include fever, cough, malaise and weight loss.³ Prior case reports have suggested an association of LG with azathioprine therapy. A patient with rheumatoid arthritis on methotrexate and azathioprine developed pulmonary LG responsive to steroids and rituximab.⁴ In another case report, a patient with Crohn's disease was on azathioprine maintenance therapy when she developed LG involving the lungs, liver and central nervous system (CNS). She was treated with interferon- α and four weekly doses of rituximab with good response.⁵ A patient with autoimmune hepatitis was on 50 mg/day azathioprine for 10 months when she developed fatal LG involving the CNS.⁶ Prior reports have also described LG associated with 6-MP in a paediatric patient with Crohn's disease.⁷ A study at the Mayo

Figure 1 Histopathological features of lymphomatoid granulomatosis. Lung biopsy with H&E stained sections: (A) Angiodestruction associated with tissue necrosis. (B) Polymorphous lymphoid infiltrates. (C) Immunohistochemical stains for PAX-5. (D) EBER in situ hybridisation. Images (A–D) were taken using an Olympus microscope at ×40 original magnification. EBER, EBV encoded small RNA.

Figure 2 Radiographical improvement following treatment for LG. Representative CT scan sections of the chest showing the dominant pulmonary mass at baseline (A), after 1 month of treatment (B) and 6 months post-treatment (C). LG, lymphomatoid granulomatosis.

Clinic demonstrated a significant association between EBV-positive lymphoma and prior treatment with azathioprine/6-MP in patients with IBD, and estimated an incidence of 0.5%.⁸

Low grade LG may be managed by the withdrawal of immunosuppression, while high-grade LG often requires systemic treatment, including interferon, rituximab, steroids or combination chemotherapy.⁹ In this case, rituximab was used as a treatment for LG, which also provided additional benefit for controlling the patient's underlying neuropathy.

To the best of our knowledge, this is the first reported case of LG occurring in a patient on azathioprine for immune-mediated neuropathy. It appears increasingly likely that azathioprine use is associated with the development of LG in a small percentage of patients, independent of the specific underlying diagnosis. While it is unclear precisely how azathioprine promotes EBV-driven LG, EBV-specific cytotoxic T cells are important for restricting the expansion of latently infected B cells and maintaining a long-term carrier state.¹⁰ Since azathioprine

suppresses CD28 signalling, it will be important to identify whether novel agents that block this pathway also associate with the development of LG. Further research is needed to identify patients at high risk of LG, including the utility of EBV monitoring strategies outside of the post-transplant setting.¹¹

Contributors NB wrote the paper. NB and ZMD prepared the figures. SAB, ZMD and RER critically reviewed the paper.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- Lymphomatoid granulomatosis (LG) is a rare Epstein-Barr virus-driven lymphoproliferative disorder often arising in the setting of immunosuppression. It typically involves the lungs, and is characterised histopathologically by angiodestruction and a polymorphic lymphoid infiltrate.
- Here we describe the development of LG arising in a patient on long-term azathioprine for immune-mediated neuropathy. In this case, the use of rituximab helped successfully treat the patient's LG with the added benefit of controlling the underlying immune-mediated neuropathy.
- Early recognition of drug-induced LG is critical, since cessation of the offending agent and initiation of effective therapy can result in rapid clinical improvement in some patients.

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