


Pulmonary lymphomatoid granulomatosis: An uncommon disease but not to be forgotten—a single centre experience

Pradeep Balakrishnan¹ , Matthew Ing¹, Zaid Househ² & Ajantha Raguparan¹

¹Department of Respiratory & Sleep Medicine, St George Hospital, Kogarah, NSW, Australia.

²Department of Anatomical Pathology, St George Hospital, Kogarah, NSW, Australia.

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Correspondence

Pradeep Balakrishnan, Department of Medicine, SJOG Midland Public & Private Hospital, 1 Clayton St, Midland, WA 6056, Australia. E-mail: pradeep23b@gmail.com

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Abstract

Pulmonary lymphomatoid granulomatosis (PLG) is a rare multisystem Epstein–Barr virus (EBV)-associated lymphoproliferative disorder. Exact incidence is unknown and, with its variable clinical presentation, making an accurate diagnosis of PLG can be difficult. We present two distinct cases at our tertiary centre that underline PLG's non-specific clinical presentations. This resulted in the failure of recognizing PLG early with consequently progressive fatal outcomes. The rationale is to enlighten us concisely the knowledge surrounding PLG and consider it as a potential differential diagnosis, particularly in those immunosuppressed patients with radiological evidence of worsening pulmonary infiltrates not responding to customary treatment for common diagnoses. Having a high degree of suspicion for PLG in the right setting and pursuing lung biopsy early if appropriate for histopathology examination would be justified. This is essential to correctly diagnose PLG up-front and subsequently utilize best management approach for a better survival and mortality risk outlook.

Introduction

Lymphomatoid granulomatosis is an uncommon distinct entity of systemic angi-destructive B-cell lymphoproliferative disorder associated with Epstein–Barr virus (EBV). The World Health Organization (WHO) has categorized lymphomatoid granulomatosis to be under “mature B-cell neoplasms” classification in its revised 2016 version [1]. Characteristically, on chest imaging, multiple pulmonary nodular lesions would be appreciated with lymphocytic invasion of the vascular walls on histopathology. Whilst lung is the most commonly involved organ, giving rise to pulmonary lymphomatoid granulomatosis (PLG) terminology, multiple other organ systems can also be affected. Deciding on treatment plan should be based on the severity of symptoms, presence of any inciting immunosuppressive drugs, degree of extrapulmonary involvement, and astute histopathological grading of biopsied lesion [2,3].

Case Report

Case 1

A 76-year-old Sudanese female initially presented with a non-productive cough and progressive dyspnoea at our clinic.

A computed tomography (CT) chest done showed significant bilateral pulmonary ground-glass opacities (GGO). Other remarkable pathology findings included elevated rheumatoid factor (98 IU), low-titre antinuclear antibody (1:80), and positive Quantiferon Gold (interferon gamma release assay). Sputum microbiology showed a light growth of *Candida albicans* with a negative acid-fast bacilli smear and culture. The first bronchoscopy performed showed positive rhinovirus polymerase chain reaction (PCR).

Subsequently, the patient deteriorated necessitating admission into hospital. Inpatient main treatment comprised of broad-spectrum antibiotics and hydrocortisone. However, our patient continued to worsen with ongoing oxygen requirements.

At this juncture, a second bronchoscopy was performed that yielded cultures felt to be of contaminants; *Streptococcus sanguinis* group and a positive cytomegalovirus PCR. Cell count analysis from bronchoalveolar lavage showed a predominance of neutrophils (59%) and lymphocytes

(19%). Repeat serology showed elevation in rheumatoid factor again (59 IU) and borderline anti-cyclic citrullinated peptide antibody value (22 U/mL). Immunoglobulin (Ig) tests showed mild deficiency in both IgA (0.69 g/L) and IgM (0.33 g/L). HIV test was negative.

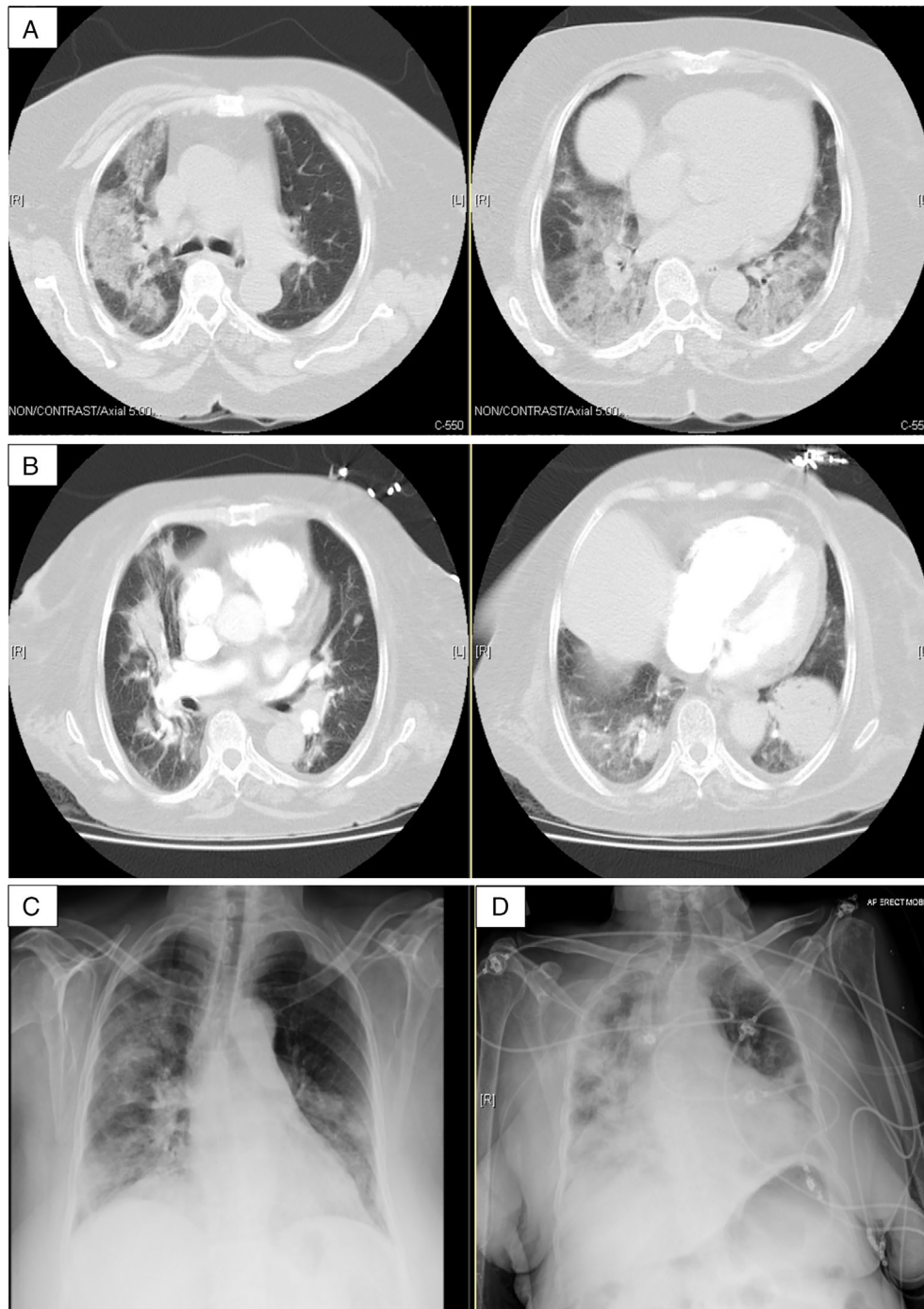


Figure 1. Case 1: radiological images showing progression of infiltrates over time (computed tomography (CT) chest and chest X-ray (CXR)). (A) CT chest in May 2018. (B) CT chest in February 2019. (C) CXR in May 2018. (D) CXR in May 2019.

Repeat CT chest demonstrated persistent bilateral GGO suggestive of a non-specific interstitial pneumonitis rather than an infective process (Fig. 1). Positron emission tomography (PET) scan confirmed significant gallium uptake within the corresponding pulmonary infiltrates. CT-guided fine-needle aspiration (FNA) of the left lower lobe of lung showed non-specific mild interstitial inflammation with no evidence of infection. Here, results were felt to be likely of rheumatoid lung disease without articular manifestations.

Subsequently, the patient was treated with methylprednisolone resulting in clinical improvement. Following this, she was transitioned to prednisone and mycophenolate and began chemoprophylaxis for the treatment of latent tuberculosis. She was discharged with a tentative plan for surgical lung biopsy to confirm the diagnosis.

But as the above immunosuppression was weaned off, the patient deteriorated again. She presented to hospital two further times over the subsequent months with worsening dyspnoea, hypoxic respiratory failure, and progressive infiltrates radiologically. The surgical lung biopsy plan had to be abandoned.

A further third bronchoscopy was performed but unremarkable. Nonetheless, the repeat histopathology of the CT-guided biopsy of the left lower lobe on this occasion (Fig. 2) showed extensive areas of necrosis with diffuse interstitial and angiotropic large atypical B-cells with associated background T-cells infiltrate. Immunohistochemical stains were positive for CD20, CD79a, BCL-2, BCL-6, and CD30 alongside positive staining for EBV-encoded RNA in situ hybridization (EBER ISH) in less than 50 cells/HPF (high-power field).

As described above, accurate diagnosis of PLG grade II–III was made. Subsequently, intrathecal methotrexate and R-MiniCHOP (rituximab and reduced dose of CHOP) were used to treat her PLG. Despite intensive treatment over three months, her disease progressed and the patient died eventually from respiratory failure.

Case 2

A 74-year-old Indian female presented with dyspnoea alongside abnormal vital signs of tachycardia, hypoxia, and fevers. Her past medical history was notable for rheumatoid arthritis (on immunosuppressant of methotrexate and hydroxychloroquine).

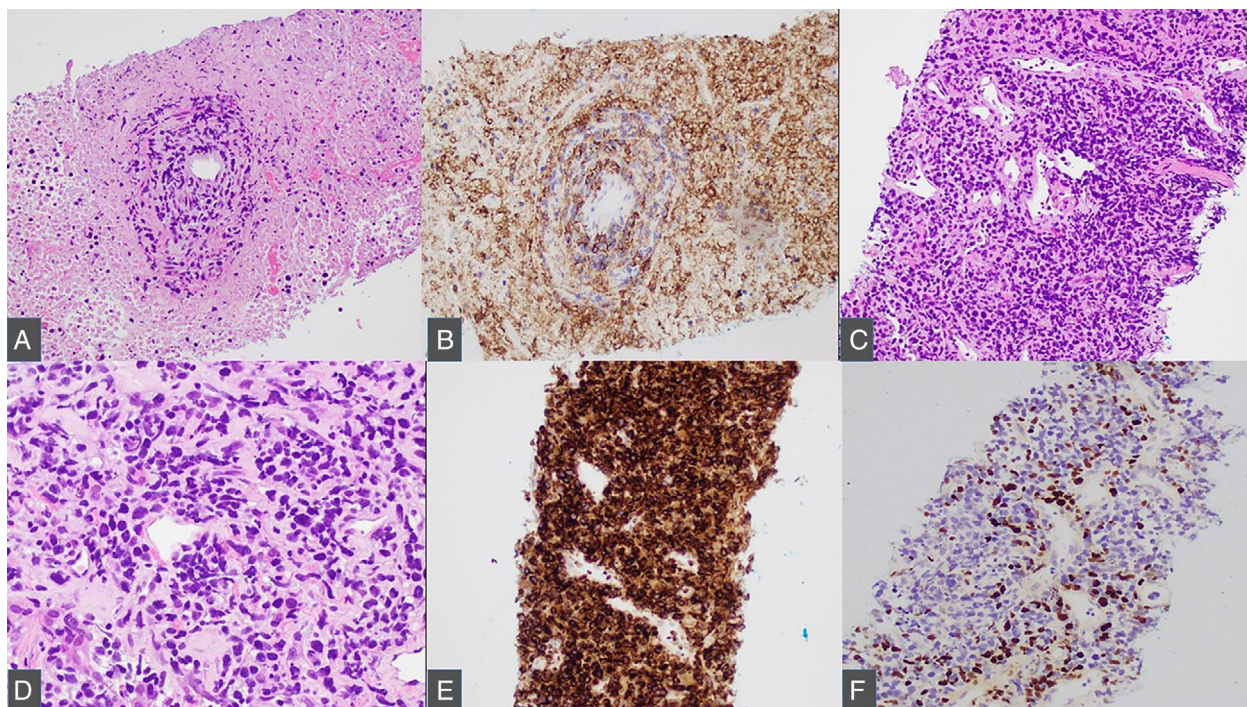


Figure 2. Case 1: histopathology of lung core biopsy. (A) Atypical lymphoid cells within the wall and subintima of a vessel with surrounding necrosis (haematoxylin and eosin (H&E), 200× magnification). (B) CD20 positivity in viable atypical cells and “ghost cells” in the surrounding necrosis (200× magnification). (C) Viable lung with diffuse interstitial lymphoid infiltrate (H&E, 200× magnification). (D) Angiotropic large atypical lymphocytes with large hyperchromatic irregular nuclei and background smaller lymphocytes (H&E, 400× magnification). (E) BCL-2 diffuse positivity (100× magnification). (F) EBV-encoded RNA in situ hybridization (EBER ISH)-positive large cells (200× magnification).

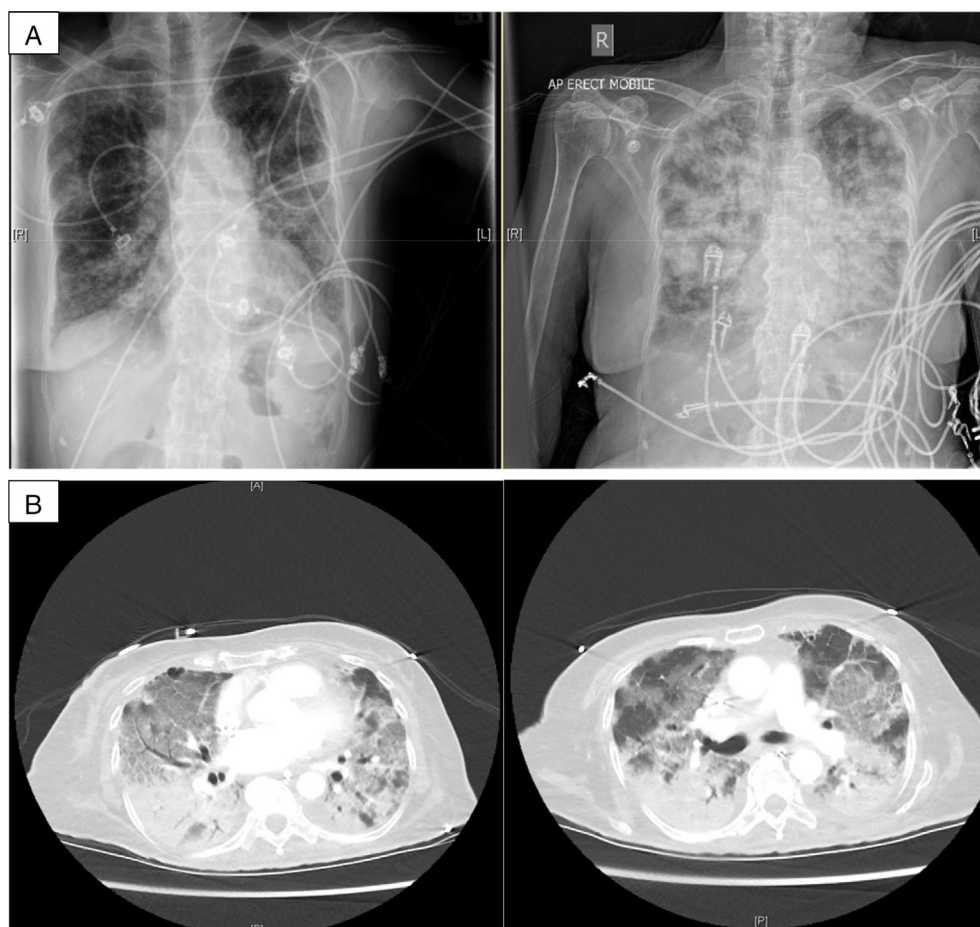


Figure 3. Case 2: radiological images taken during admission (chest X-ray (CXR) and computed tomography (CT) chest). (A) CXR on day 1 (left) and day 2 (right) of admission, depicting rapidly progressive infiltrates. (B) CT chest on day 3 of admission, depicting significant ground-glass opacities with mass-like consolidations.

Both white cell count ($16 \times 10^9/L$) and C-reactive protein (CRP, 136 mg/L) were elevated. Chest X-rays (CXRs) (Fig. 3) demonstrated patchy air-space changes that had rapidly progressed.

Initial management included Hi-Flow oxygen and antibiotics of ceftriaxone and azithromycin. However, the patient continued to deteriorate quickly. She was moved to the intensive care unit (ICU) with ongoing high oxygen requirements, failing non-invasive ventilation. She had to be intubated due to progressive hypoxic respiratory failure within 24 h of clinical presentation. Severe nature of her condition warranted the use of hydrocortisone and change of antibiotic to piperacillin-tazobactam.

CT chest showed confluent consolidation within the right lower lobe and patchy air-space opacifications within the right upper and left lower lobes. There were also enlarged mediastinal, right hilar, and supraclavicular lymph nodes (Fig. 3). Microbiology showed positive PCR

of rhinovirus on nasopharyngeal swab. Bronchoscopy confirmed rhinovirus.

Her admission was further complicated with *Clostridium difficile* gastroenteritis resulting in commencement of oral vancomycin. She received pulsed methylprednisone for three consecutive days. On the eighth day of admission, the decision to palliate was made as significant deterioration ensued despite maximal medical therapy.

A limited post-mortem lung tissue biopsy was performed. Both respiratory syncytial virus (RSV)-type B and rhinovirus were detected on viral PCR of lung biopsy specimen. Histopathology (Fig. 4) showed mixed, polymorphous atypical lymphoreticular infiltration with prominent angiocentricity, diffuse bronchovascular distribution, and hilar lymph node involvement. There was transmural infiltration of small- and medium-sized vessels by atypical lymphocytes. Immunohistochemical stains showed that the large atypical cells were positive for CD20, CD79a, BCL-2,

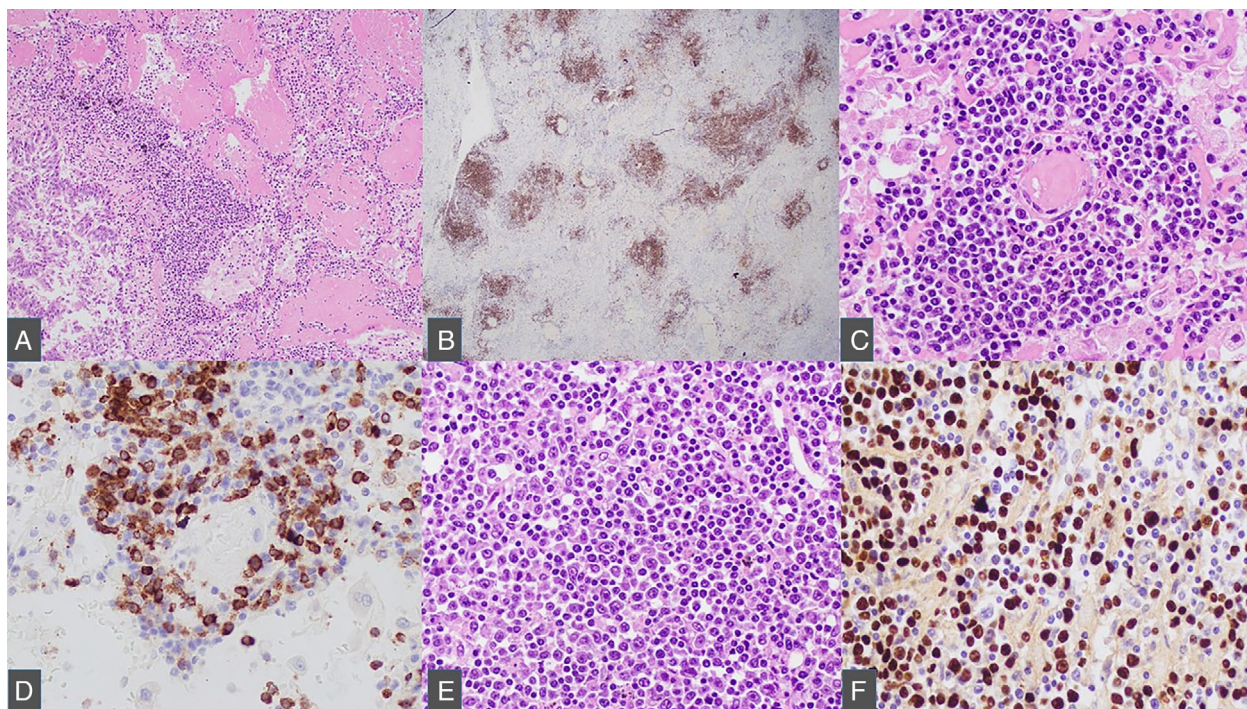


Figure 4. Case 2: histopathology of post-mortem lung. (A) Lung parenchyma with acute phase diffuse alveolar damage (right side) and adjacent polymorphous atypical lymphoreticular infiltrates (haematoxylin and eosin (H&E), 40× magnification). (B) CD20 highlighting angiocentric distribution of the atypical B lymphocytes (20× magnification). (C) Transmural infiltration of a small vessel by atypical lymphocytes replacing media and intima (H&E, 400× magnification). (D) Angiotropic CD79a positivity (400× magnification). (E) Lymph node effacement by mixed large and small lymphocytes (H&E, 400× magnification). (F) EBV-encoded RNA in situ hybridization (EBER ISH)-positive large cells (400× magnification).

and occasionally CD30. EBER ISH showed diffusely positive staining in more than 50 cells/HPF. Adjacent lung showed diffuse alveolar damage pattern injury. These features were consistent with EBV-associated lymphoproliferative disorder PLG grade III—high-grade disease.

Discussion

PLG is an uncommon angiocentric and angiodestructive EBV-associated B-cell lymphoproliferative disorder with a prominent T-cell reaction [3]. Immunodeficient patients may have an abnormal host immune response to clearance of EBV with consequential clonal proliferation of atypical EBV-infected B cells. Simplistically, EBV genome products can lead to cell growth promotion and apoptosis inhibition [4]. This results in considerable white blood cells infiltration around blood vessels causing damage and tissue destruction subsequently.

Majority of the PLG cases involve the lungs (>90%). Other organ systems that may be involved concomitantly or separately include the skin (20–50%), kidney (15–32%), and nervous system (20–38%). The less commonly involved include the liver, gastrointestinal tract, eyes, and spleen [2,5].

Generally, the risk factors include EBV infection, underlying immunodeficiency with or without contribution from genetic or familial factors predisposition, and being on immunosuppressive drugs. Immune defect conditions (e.g. X-linked severe combined immunodeficiency, post-allograft transplantation, or HIV infection) can lead to an increased risk of developing PLG and therefore the higher incidence in this group of patients [6]. In the literature, few cases of PLG had been ascribed to usage of immunosuppressives such as azathioprine and methotrexate with possible resolution following cessation of the offending drugs [7].

Any age can be affected as shown in our case reports; however, PLG typically inflicts in those between the ages of 30 and 60 years old, that is, typically middle-aged patients. Preponderance of the disease is generally seen in males, with a male to female ratio of 2:1 to 3:1 with more diagnosed in the Western society [3].

PLG should be suspected in symptomatic patients (commonly cough, rash/subcutaneous nodules, dyspnoea, and neurological abnormalities such as ataxia or cranial nerve disorder) alongside constitutional symptoms with chest imaging depicting nodular opacities. Cutaneous lesions (erythematous nodules, papules, or plaques) can be the initial manifestation of PLG [8].

Routine pathology tests are usually non-diagnostic. Screening for immunodeficiency would be justified (e.g. HIV screening or serum Ig levels). Generally, EBV serology shows evidence of previous infection and EBV viral load being slightly elevated. On CT imaging, most PLG patients had preponderance of pulmonary nodules or masses within the lower lungs, perilymphatic distribution affecting peribronchovascular and subpleural regions alongside central low attenuation, and ground-glass halo and peripheral enhancement of these lesions (indicative of central necrosis, haemorrhage, and angio-invasive nature, respectively). The lung nodules may show waxing and waning appearance over time. Another useful imaging modality is ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET/CT. ^{18}F -FDG PET/CT can detect multisystem involvement and guide site of tissue biopsy, monitor response to treatment, and identify recurrence of PLG during surveillance (but do note of reported variable FDG avidity/uptake within the lesions) [9,10].

Histopathology forms the cornerstone in diagnosing PLG. A triad of mixed lymphoid infiltrates, transmural infiltration of vasculature by the lymphoid cells (“angiitis”), and focal areas of necrosis within the lymphoid infiltrates are the classical histopathological features seen. The “granulomatosis” term is used to describe the focal areas of necrosis seen within the lymphoid infiltrates but typical well-formed granulomas may not be seen [11]. Tissue biopsy is generally obtained from lung lesions (due to disease predilection) via video-assisted thoracoscopic surgery (VATS) or open thoracotomy and less often from skin lesions (if present). Adequate amount of tissue biopsy procurement is crucial to ascertain the diagnosis and grading its severity; transbronchial biopsy or transthoracic needle aspirate may yield small samples inadequate for proper analysis [12].

Immunophenotyping and genetic analysis go in tandem with histopathology to establish a firm PLG diagnosis. Characteristically, EBV-positive B cells express CD20 along with positive in situ hybridization for EBER. B-cell monoclonality can be demonstrated particularly in severe disease. Also, CD3 staining T-cell marker with usually CD4 T-helper cells are seen within the lymphoid infiltration of vessel walls [2].

Severity of PLG ranges from grades 1 to 3 as per the WHO recommendation. The grading in essence relates to the proportion of EBV-positive B cells relative to reactive background lymphocytes and extent of necrosis. Low grade (grade 1 or 2), asymptomatic, and confined to lungs may be suggestive of a more favourable prognosis. Whilst high grade (grade 3), symptomatic with progressive, or extensive multiorgan disease (particularly involving nervous system) may be suggestive of an unfavourable prognosis.

Treatment is not well defined. Management ranges from observation or immune-modulation (interferon alpha-2b) for low grade to using steroids and chemotherapy for high

grade. High-grade PLG disease would generally be treated more intensely as equivalent to high-grade lymphoma such as diffuse large B-cell lymphoma (DLBCL). Multiagent chemotherapy with anti-CD20 monoclonal antibody—rituximab—would be an option for high-grade PLG patients [2]. Those patients with drug-induced PLG, discontinuing the inciting drug, would be the foremost management if possible, followed by close clinical observation alongside surveillance imaging.

Clinical course of PLG is variable. Spontaneous remission may be seen in about 20% of patients but the disease is generally progressive in most patients. Overall, the prognosis is poor with a reported mean survival of two- and five-year mortality rate ranging between 60% and 90% [13].

In conclusion, our cases highlight the importance of considering the rare entity of PLG as a possibility for progressive pulmonary infiltrates especially in those immunosuppressed. PLG management is much dependent on the grade, extent, and symptom burden of the disease. Higher grade would typically warrant a more aggressive management as the risk of mortality can be woeful if PLG goes undiagnosed.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Author Contribution Statement

Dr Pradeep Balakrishnan is the lead author, corresponding author, and is reviewer of the article. Dr Matthew Ing contributed to writing of the cases, and is reviewer of the article. Dr Zaid Househ was the anatomical pathologist involved in care of the patients, contributed to histopathology images preparation, and is reviewer of the article. Dr Ajantha Raguparan was involved in care of the patients as the respiratory consultant, and is reviewer of the article.

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