

population-based preventive strategies for targeting the relevant molecular pathways.

FUTURE STUDIES

Evidence from other complex traits suggests that, with larger sample sizes, GWAS will reveal many more loci harbouring common sequence variants underlying respiratory diseases. Other studies will usefully focus on the role of rare sequence variants and structural genomic variants in respiratory disease. Understanding precisely how the molecular pathways highlighted by these genetic studies influence the development and progression of disease, and how they can be modified, provides a major challenge for the coming decade.

Funding This work was supported by the Medical Research Council (G0902313).

Competing interests None.

Contributors The literature review and drafting of the manuscript was wholly undertaken by the named authors.

Provenance and peer review Commissioned; internally peer reviewed.

REFERENCES

1. **McCarthy MI**, Abecasis GR, Cardon LR, *et al*. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet* 2008;**9**:356–69.
2. **Moffatt MF**, Gut IG, Demenais F, *et al*. A large-scale, consortium-based genome-wide association study of asthma. *N Engl J Med* 2010;**363**:1211–21.
3. **Pillai SG**, Ge D, Zhu G, *et al*. A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. *PLoS Genet* 2009;**5**:e1000421.
4. **Hancock DB**, Eijgelsheim M, Wilk JB, *et al*. Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. *Nat Genet* 2010;**42**:45–52.
5. **Repapi E**, Sayers I, Wain LV, *et al*. Genome-wide association study identifies five loci associated with lung function. *Nat Genet* 2010;**42**:36–44.

Pulmonary puzzle

A 67-year-old woman with fever, multiple lung opacities, visual impairment and acute respiratory failure



CASE PRESENTATION

A 67-year-old woman presented to the emergency room in acute respiratory failure. She had a 4-month history of dry cough, fever, intense fatigue, progressive dyspnoea and recent visual impairment. Her prior medical history included a mitral valve replacement in 2005 due to post-endocarditis mitral regurgitation. On examination, the patient was in hypoxemic acute distress. She was intubated and mechanically ventilated. A chest x-ray (figure 1A) just prior to endotracheal intubation revealed bilateral air space disease and high-resolution CT of the chest (figure 1B) revealed irregular nodules, bilateral areas of conglomerate masses with air bronchograms of peribronchovascular orientation surrounded by ground glass opacities and no mediastinal lymphadenopathy. Laboratory findings indicated mild normocromic and normocytic anaemia, haemoglobin 10 g/dl, lymphopenia 168 cells/mm³, C-reactive protein 157 mg/litre (0.0–3.0 mg/litre). Tests for HIV, serum

cytoplasmic antineutrophil cytoplasmic antibody, antinuclear antibody and rheumatoid factor were negative. A transesophageal echocardiogram displayed a bioprosthetic mitral valve with mild stenosis, no evidence of endocarditis, and minimum regurgitation with negative blood cultures. MRI of the brain displayed bilateral optic neuritis.

An open lung biopsy was performed: angiocentric nodules comprised a mixture of lymphocytes with variable numbers of associated plasma cells and histiocytes (figure 2A). The lymphocytic infiltrate was mainly composed of small and intermediate size cells that were CD3 positive T lymphocytes. Scattered large atypical cells (figure 2B) were CD20 positive B lymphocytes. The polymorphic lymphoid infiltrate showed a distinctive predilection to infiltrate vessel walls (figure 2C), resulting in thickening of the lumens of affected vessels (figure 2D).

QUESTION

What is the diagnosis?

See page 280 for the answer

Leticia Barbosa Kawano-Dourado,¹

Alexandre de Melo Kawassaki,¹ Vera Luiza Capelozzi,²

Marcos Soares Tavares,¹ Carmen Sílvia Valente Barbas³

¹Pulmonary Division, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil; ²Pathology Division, University of São Paulo Medical School, São Paulo, Brazil; ³Pulmonary Division, Heart Institute (InCor), University of São Paulo Medical School and Hospital Israelita Albert Einstein, São Paulo, Brazil

Figure 1 (A) Chest x-ray (anteroposterior view) just prior to endotracheal intubation revealed midline sternotomy metallic wires, bilateral mass-like opacities predominating in the middle and lower lung zones. (B) High-resolution CT of the chest revealed nodules, bilateral areas of conglomerate masses with air bronchograms of peribronchovascular distribution surrounded by ground glass opacities.

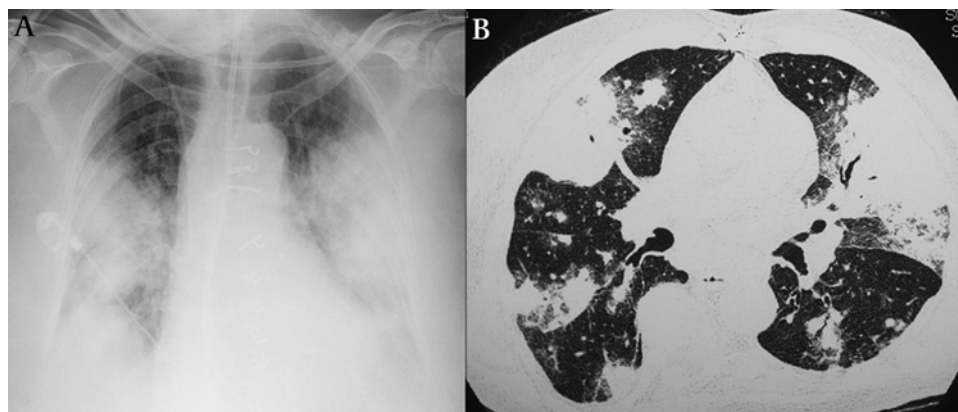
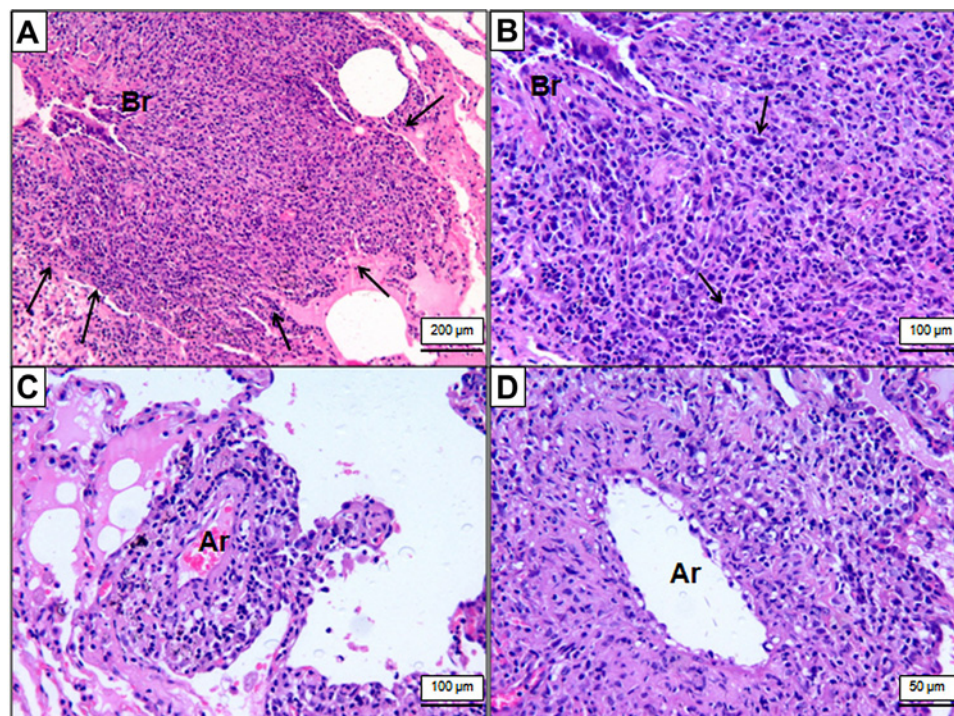


Figure 2 Low magnification photomicrograph illustrating a zone of pulmonary parenchyma displaying a dense cellular infiltrate forming angiocentric nodules (A, arrows). A high-magnification view illustrating a polymorphic lymphocytic infiltrate that includes isolated large atypical cells (B, arrows). A transmural infiltrate of lymphoid cells involving a pulmonary artery is shown in panels (C) and (D). Hematoxylin-eosin stain. Ar, artery; Br, bronchioli.



Correspondence to Dr Leticia Barbosa Kawano-Dourado, Pulmonary Division, Heart Institute (InCor), University of São Paulo Medical School, Av Dr Eneas Carvalho de Aguiar, 44, São Paulo 05403-000, Brazil; leticiakawano@hotmail.com

Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was provided by CAPPesq.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data about the case report are available upon request from the corresponding author.

Published Online First 27 October 2011

Thorax 2012;**67**:273–274. doi:10.1136/thoraxjnl-2011-200573

Competing interests None.

Contributors All authors significantly contributed to the formulation of the standard of care given the recent evidence-based review, and all were involved in writing and developing the document.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Fishwick D**, Barber CM, Bradshaw LM, *et al*; British Thoracic Society Standards of Care Subcommittee Guidelines on Occupational Asthma. Standards of care for occupational asthma. *Thorax* 2008;**63**:240–50.

2. **Nicholson PJ**, Cullinan P, Newman Taylor AJ, *et al*. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med* 2005;**62**:290–9.
3. **Occupational Asthma—Identification, Management and Prevention: Evidence Based Review and Guidelines**. British Occupational Health Research Foundation, 2010. ISBN 978-0-9564979-1-8. <http://www.bohrf.org.uk/downloads/OccupationalAsthmaEvidenceReview-Mar2010.pdf> (accessed 20 Sep 2011).
4. **Orriols R**, Costa R, Albanell M, *et al*. Reported occupational respiratory diseases in Catalonia. *Occup Environ Med* 2006;**63**:255–60.
5. **Tarlo SM**, Balmes J, Balkissoon R, *et al*. Diagnosis and management of work-related asthma: American College of Chest Physicians Consensus Statement. *Chest* 2008;**134**(Suppl 3):1S–41.

Pulmonary puzzles

ANSWER

From the question on page 273

Lymphomatoid granulomatosis (LYG) grade 1 was diagnosed. LYG is a rare T-cell rich, Epstein-Barr virus (EBV)-associated, B-cell lymphoproliferative disorder. Lung involvement is the predominant feature but extrapulmonary manifestations occur, especially skin and nervous system involvement such as optic neuritis.^{1 2} Systemic symptoms and lymphopenia are also described. Lung Involvement in LYG may be unilateral or bilateral and includes interstitial and alveolar compartments of the lung. The most common radiographic findings are multiple nodular opacities and masses with poorly defined margins distributed along the peribronchovascular bundle or interlobular septa.³ Reticular opacities associated with nodules, mediastinal lymphadenopathy and large conglomerate masses with air bronchograms are also observed.³

Histologic and immunohistochemical features are crucial for LYG diagnosis: mixed mononuclear cell infiltrate containing CD20-positive large B lymphocytes and numerous CD3-positive small lymphocytes, vascular infiltration, necrosis, and evidence of EBV infection.¹ Positivity for EBV infection in histological specimens ranges from 57 to 100% and therefore its absence does not rule out the diagnosis in proper clinical, radiological and histological scenarios, as was the case for our patient.^{1 4}

Grade 1 LYG contains only a few large B cells whereas numerous large B cells are present in grade 3 disease, which means worse prognosis. Current knowledge about LYG tends to categorise grades 2 and 3 as lymphomas, considering the

frequent presence of monomorphous foci of atypical B cells and the clinical behaviour.^{1 5}

The treatment of LYG is not well established. There has been a tendency to treat higher grade LYG with chemotherapy regimens for lymphomas but the treatment for grade 1 LYG is less clear.¹ There are some reports of spontaneous resolution and treatment success with interferon alfa-2b, corticosteroids, cyclophosphamide, and bone marrow transplant. Our patient was treated with corticosteroids, cyclophosphamide and rituximab with complete remission of lung lesions. The optic neuritis also remitted but the patient retained significant visual impairment. The patient was placed on prednisone and oral cyclophosphamide with slow tapering in the following 18 months. There have been no recrudescences in the last 3 years of follow-up.

Thorax 2012;**67**:280. doi:10.1136/thoraxjnl-2011-200573

REFERENCES

1. **Katzstein AL**, Dostader E, Narendra S. Lymphomatoid granulomatosis: insights gained over 4 decades. *Am J Surg Pathol* 2010;**34**:e35–48.
2. **Myers JL**, Kurtin PJ, Katzstein AL, *et al*. Lymphomatoid granulomatosis. Evidence of immunophenotypic diversity and relationship to Epstein-Barr virus infection. *Am J Surg Pathol* 1995;**19**:1300–12.
3. **Lee JS**, Tuder R, Lynch DA. Lymphomatoid granulomatosis: radiologic features and pathologic correlations. *AJR Am J Roentgenol* 2000;**175**:1335–9.
4. **Nicholson AG**, Wotherspoon AC, Diss TC, *et al*. Lymphomatoid granulomatosis: evidence that some cases represent Epstein-Barr virus-associated B-cell lymphoma. *Histopathology* 1996;**d29**:317–24.
5. **Pittaluga S**, Wilson WH, Jaffe ES. Lymphomatoid granulomatosis. In: Swerdlow SH, Campo E, Harris NL, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC, 2008:247–9.