Lymphocytic interstitial pneumonia and pulmonary embolism in a patient with tetralogy of Fallot and common variable immunodeficiency: is there any link?

M A Valdivia-Arenas, N Sood

Division of Pulmonary, Critical Care and Sleep Medicine, Ohio State University, 201 Heart and Lung Research Institute, Columbus, Ohio, USA

Correspondence to: Dr M A Valdivia-Arenas, Division of Pulmonary, Critical Care and Sleep Medicine, Ohio State University, 201 Heart and Lung Research Institute, 473 West 12th Avenue, Columbus, OH 43210, USA; martin1990jbr@yahoo.com

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ABSTRACT

We report the simultaneous occurrence of lymphocytic interstitial pneumonitis and pulmonary embolism in a patient with tetralogy of Fallot and common variable immunodeficiency. An explanation based on the pathogenesis of these diseases is proposed to explain this "unfortunate coincidence".

A 45-year-old Caucasian woman with tetralogy of Fallot, surgically corrected at age 6 years, presented with severe dyspnoea and an acute episode of pleuritic right-sided chest pain, fevers of 102°F and chills. She was empirically treated with antibiotics and steroids for pneumonia twice in the previous 12 weeks, without improvement in her dyspnoea. She had a 20 pack-year smoking history but denied the use of illegal drugs or alcohol.

On admission she was afebrile, haemodynamically stable with an oxygen saturation of 78% on room air. The lungs exhibited diffuse expiratory ronchi and wheezes. A grade II/VI systolic ejection murmur and an early diastolic murmur were noted at the upper left sternal border. Extremities revealed distal cyanosis, but no clubbing or oedema. White blood cell count was 20 000/mm³ with 96% neutrophils and 3% lymphocytes and β -natriuretic peptide level was 256 pg/ml.

CT angiogram of the chest showed right middle lobe acute pulmonary embolus, with extensive bilateral ground glass opacities (fig 1A). Transthoracic echocardiography showed small residual ventricular septal defect, right to left shunt at the atrial level and a right ventricular systolic pressure of 64 mm Hg. Treatment with heparin was instituted on admission. Because of the presence of the bilateral infiltrates and persistent hypoxaemia, bronchoalveolar lavage was performed 3 days later showing 50% alveolar macrophages, 45% neutrophils, 5% lymphocytes but no organisms. Cultures were negative. Surgical lung biopsy showed diffuse infiltration of the alveolar septa by lymphocytes and diffuse intra-arterial thrombosis (fig 1B).

HIV testing was negative. Antinuclear antibody and rheumatoid factor were negative. Antiphospholipid antibodies were positive. Serum IgG immunoglobulins were significantly reduced. Total IgG was 510 mg/dl (normal 650–1600), IgG2 75 mg/dl (normal 150–640), IgG3 19.7 mg/dl (normal 20–110) and IgG4 4.6 mg/dl (normal 8–140). IgA was 202 mg/dl (normal 80–320 mg/ml). Pulmonary function tests showed restriction and

a reduction in diffusing capacity of moderate degree (forced expiratory volume in 1 s/forced vital capacity (FEV₁/FVC) 76%, FEV₁ 40% predicted, total lung capacity (TLC) 70% predicted, carbon monoxide transfer factor (Tlco), 52% predicted). Subsequently, she was treated with prednisone 60 mg/day for 3 months and intravenous immunoglobulins 24 g/month (0.5 mg/kg), with significant symptomatic, radiological and lung function improvement (FEV₁/FVC 91%, FEV₁ 78% predicted, TLC 81% predicted, Tlco 54% predicted). She remains on oral anticoagulation (fig 1C).

DISCUSSION

Lymphocytic interstitial pneumonitis (LIP) is an infrequent cause of interstitial lung disease and has been associated with abnormalities of the immune system. It has been described in cases of hypogammaglobulinaemia, common variable immunodeficiency, monoclonal and polyclonal gammopathy, Sjögren's syndrome and HIV infection, among others.¹ Some patients have been successfully treated with prednisone and/or intravenous immunoglobulins, as previously reported.^{1–3}

The presence of immune system abnormalities has been described in patients with conotruncal malformations of the heart.^{4–6} Embryologically, both the thymus and cardiac outflow structures develop at the same time and all receive migrating cells from the neural crest. At the extreme of this spectrum is the DiGeorge anomaly (chromosome 22q11.2 deletion), characterised by abnormal facies, hypothyroidism, thymic aplasia and congenital heart defects, although a significant number of patients with tetralogy of Fallot may have a 22q11 deletion.⁷

Despite these immunological abnormalities, the association of LIP with tetralogy of Fallot has not been reported. Our patient also had evidence of pulmonary hypertension (PH) with a right ventricular systolic pressure of 64 mm Hg and a patent ventricular septal defect; she likely had a certain degree of PH before the acute event. The findings of in situ thrombosis are frequent in patients with PH. This process was supported by the widespread presence of intra-arterial thrombosis in the patient's lung biopsy. The occurrence of pulmonary embolism in our patient could be explained in part by the presence of antiphospholipid antibodies. Interestingly, the presence of antiphospholipid antibodies have been described in a patient with DiGeorge anomaly⁸ and in patients with PH, irrespective of its cause and severity.⁹

Figure 1 (A) CT angiogram of the chest showing right middle lobe acute pulmonary embolus, with extensive bilateral ground glass opacities. (B) Surgical lung biopsy showing diffuse infiltration of the alveolar septa by lymphocytes and diffuse intra-arterial thrombosis. (C) CT angiogram of the chest following treatment.

In conclusion, the occurrence of LIP in this patient can be explained by the underlying immunological abnormalities described in patients with tetralogy of Fallot and the occurrence of pulmonary embolism as a complication of these two diseases. No previous cases of LIP in association with tetralogy of Fallot have been reported. In our patient, the radiographic changes resolved with treatment, with resolution of her symptoms. This case also underscores the possible association between immune deficiency and tetralogy of Fallot.

Competing interests: None.

REFERENCES

1. **Cha SI**, Fessler MB, Cool CD, *et al.* Lymphoid interstitial pneumonia: clinical features, associations and prognosis. *Eur Respir J* 2006;**28**:364–9.
2. **Arish N**, Eldor R, Fellig Y, *et al.* Lymphocytic interstitial pneumonia associated with common variable immunodeficiency resolved with intravenous immunoglobulins. *Thorax* 2006;**61**:1096–7.
3. **Popa V**, Colby TV, Reich SB. Pulmonary interstitial disease in Ig deficiency. *Chest* 2002;**122**:1594–603.
4. **Khalil A**, Trehan R, Tiwari A, *et al.* Immunological profile in congenital heart disease. *Indian Pediatr* 1994;**31**:295–300.
5. **Radford DJ**, Lachman R, Thong YH. The immunocompetence of children with congenital heart disease. *Int Arch Allergy Appl Immunol* 1986;**81**:331–6.
6. **Radford DJ**, Thong YH. Facial and immunological anomalies associated with tetralogy of Fallot. *Int J Cardiol* 1989;**22**:229–39.
7. **Goldmuntz E**. DiGeorge syndrome: new insights. *Clin Perinatol* 2005;**32**:963–978, ix–x.
8. **Chang AD**, Tachdjian R, Gallagher K, *et al.* Type III mixed cryoglobulinemia and antiphospholipid syndrome in a patient with partial DiGeorge syndrome. *Clin Dev Immunol* 2006;**13**:261–4.
9. **Karmochkine M**, Cacoub P, Dorent R, *et al.* High prevalence of antiphospholipid antibodies in precapillary pulmonary hypertension. *J Rheumatol* 1996;**23**:286–90.