

- 3 Zauli D, Grassi A, Ballardini G, Contestabile S, Zucchini S, Bianchi FB. Thyroid autoimmunity in chronic idiopathic urticaria: implications for therapy. *Am J Clin Dermatol* 2002;3:525–8
- 4 Fiebiger E, Maurer D, Holub H, *et al.* Serum IgG autoantibodies directed against the α -chain of Fc ϵ R1; a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest* 1995;96:2606–12
- 5 Volpe R, Row VV, Ezrin C. Circulating viral and thyroid antibodies in subacute thyroiditis. *J Clin Endocrinol Metab* 1967;27:1275
- 6 Leznoff A, Josse RG, Denburg J, *et al.* Association of chronic urticaria and angioedema with thyroid autoimmunity. *Arch Dermatol* 1983;119:636–40
- 7 Kandeel AA, Zeid M, Helm T, *et al.* Evaluation of chronic urticaria in patients with Hashimoto thyroiditis. *J Clin Immunol* 2001;21:335–47

Pathophysiological insights from a case of reversible pulmonary arterial hypertension

D Mukerjee MRCP E Kingdon MRCP¹
M Vanderpump FRCP² J G Coghlan FRCP³

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When pulmonary hypertension develops in the presence of connective tissue disease, it may be reversible by prompt immunosuppressive therapy.

CASE HISTORY

A previously fit man of 46 reported six months of fatigue, ankle swelling, numbness in the feet and dyspnoea on mild exertion. He had never smoked. On examination he had moderate gynaecomastia and there were several 6 mm nodules on the anterior chest wall. He was in right heart failure, with a parasternal heave and a loud pulmonary component of the second heart sound. Additional abnormalities were ascites, 5 cm splenomegaly, loss of light touch and vibration sense in the lower limbs (with absent ankle jerks), and papilloedema. Haemoglobin was 15.2 g/dL, white cells $8.9 \times 10^8/L$, platelets $852 \times 10^9/L$, erythrocyte sedimentation rate 85 mm/h, C-reactive

protein 33 mg/L. Tests for autoantibodies, including ANCA, were negative. The endocrine profile indicated hypogonadism (luteinizing hormone 21 IU/L [normal 1–10], follicle stimulating hormone 17 IU/L [1–7], testosterone 6 nmol/L [10–35] and hypothyroidism (thyrotropin 11.1 mU/L, free T3 6.9 pmol/L)). A chest X-ray was normal, as were CT and MRI of the brain. Cerebrospinal fluid protein was slightly raised at 1.1 g/L and nerve conduction studies pointed to a demyelinating sensorimotor neuropathy. Echocardiography showed pulmonary artery hypertension (systolic pressure 40 mmHg) and right ventricular hypertrophy. On histological examination, a skin lesion was seen to contain several glomeruloid haemangiomas. This conjunction of abnormalities fulfilled the criteria for POEMS (polyneuropathy-organomegaly-endocrinopathy-M band-skin changes) syndrome. Cardiac catheterization confirmed the pulmonary arterial hypertension. Acute administration of Iloprost (epoprostenol) reduced pulmonary vascular resistance by 57% (Table 1).

The patient was started on warfarin and a calcium channel antagonist in high dosage. Immunosuppressive therapy for the POEMS was prednisolone 30 mg and azathioprine 150 mg daily. Testosterone and thyroxine replacement was also initiated. The calcium channel antagonist had to be stopped because of intolerance. After ten months on this regimen he had improved clinically. However, when the azathioprine was withheld because of nausea and vomiting there was a recurrence of ascites, ankle swelling and dyspnoea. Immunosuppression was reintroduced with mycophenolate mofetil 1 g twice daily and prednisolone 30 mg daily, to which he responded with full resolution of the decompensation. Repeat right heart catheterization three months later showed haemodynamic improvement with mean pulmonary artery pressure 25 mmHg (Table 1). 3 years after the original diagnosis of pulmonary arterial hypertension, and still taking mycophenolate mofetil and prednisolone, the patient remains well with good exercise tolerance.

COMMENT

POEMS or Crow–Fukase syndrome is a multisystem disorder first defined by Nikanishi *et al.*¹ Recently, Miralles *et al.*² studied 2714 cases and showed that this syndrome is indistinguishable from the rare variant of osteosclerotic myeloma with polyneuropathy. Overproduction of pro-inflammatory cytokines and the endothelial-cell-specific mitogen and potent angiogenic peptide vascular endothelial growth factor (VEGF) has been demonstrated.³ The expression of VEGF in glomeruloid lesions of the skin and kidney in POEMS is noteworthy since similar expression has been reported in plexiform lesions of other patients with pulmonary arterial hypertension. In our

Departments of Rheumatology, ¹Nephrology, ²Endocrinology and ³Cardiology, Royal Free Hospital, Pond Street, London NW3 2QG, UK

Correspondence to: Dr D Mukerjee, 63a Princess May Road, Stoke Newington, London N16 8DF, UK

E-mail: devmukerjee@hotmail.com

Table 1 Results of cardiac catheterization before and after immunosuppressive treatments

Catheterization	mPAP	mRAP	PCWP	MAP	PVR	SVO ₂	Ao	CI
First								
Before Iloprost	36	6	6	112	375	79	98	6.4
After Iloprost	32	2	6	107	214	83	98	9.7
Second	25	3	11	109	167	81	98	6.7

mPAP=Mean pulmonary artery pressure (mmHg); mRAP=mean right atrial pressure; PCWP=pulmonary capillary wedge pressure (mmHg); PVR=pulmonary vascular resistance (dyn s cm⁻⁵); SVO₂=mixed venous oxygen saturation in m d⁻¹; Ao=aortic oxygen saturations in m d⁻¹; MAP=mean arterial pressure (mmHg); CI=cardiac index (L min⁻¹ m⁻²)

patient there was rapid clinical improvement, together with a large decrease in peripheral vascular resistance, when the immunosuppressive regimen was changed to mycophenolate mofetil plus prednisolone. Treatment with a combination of prednisolone, methotrexate, ciclosporin and cyclophosphamide has similarly led to resolution of pulmonary arterial hypertension secondary to systemic lupus erythematosus (SLE). Endothelial immune deposits have been demonstrated in some SLE-related cases of pulmonary arterial hypertension⁵ but no such deposits have been found in POEMS or systemic sclerosis related cases. One explanation for this discrepancy may be that the pathogenesis of pulmonary artery hypertension in connective tissue diseases is heterogeneous. Triggers might include at one end of the spectrum cytokine-mediated vasoconstriction with dysregulation of TGFβ and VEGF expression (which might respond to immunosuppression)⁶ and at the other end irreversible vascular remodelling and fibrosis. Reversible vasculopathy with overproduction of proinflammatory cytokines and VEGF and decreased expression of TGFβ has been previously described in POEMS.^{7,8} However, there has been no established link between TGFβ dysregulation and defects in the BMPR2 gene in this condition. The challenge for management is to identify pulmonary arterial hypertension at a stage when it will still respond to definitive therapy.

REFERENCES

- Nakanishi T, Sobue I, Toyokura Y, *et al.* The Crow–Fukase syndrome: a study of 102 cases in Japan. *Neurology* 1984;**34**:712–20
- Miralles GD, O’Fallon JR, Talley NJ. Plasma cell dyscrasia with polyneuropathy. The spectrum of POEMS syndrome. *N Engl J Med* 1992;**327**:1919–23
- Soubrier M, Dubost JJ, Sere AF, *et al.* Growth factors in POEMS syndrome: evidence for marked increase in VEGF. *Arthritis Rheum* 1997;**40**:786–7
- Hirose S, Hosoda Y, Furuya S, *et al.* Expression of VEGF and its receptors correlates closely with formation of plexiform lesion in human pulmonary hypertension. *Pathol Int* 2000;**50**:472–9
- Sanchez O, Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary hypertension secondary to connective tissue diseases. *Thorax* 1999;**54**:273–7

- Paciocco G, Bossone E, Erba H, *et al.* Reversible pulmonary hypertension in POEMS syndrome—another etiology of triggered vasculopathy? *Can J Cardiol* 2000;**16**:975–81
- Gherardi RM, Belec L, Soubrier D, *et al.* Overproduction of proinflammatory cytokines balanced by their antagonists in POEMS syndrome. *Blood* 1996;**87**:1458–65
- Lesprit P, Godeau B, Francois-Jerome A, *et al.* Pulmonary hypertension in POEMS syndrome. A new feature mediated by cytokines. *Am J Respir Crit Care Med* 1998;**157**:907–11

Lymphadenopathy after joint replacement for osteoclastoma

A J Stewart BM MRCP B M Southcott MB BS FRCR
E Raweily MB BS FRCPath¹

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Lymphadenopathy after tumour resection is an important indicator of recurrence, but other explanations must be excluded.

CASE HISTORY

The patient was a man of 46 who in 1995 had sustained a fracture of the right medial femoral condyle apparently due to an aneurysmal bone cyst. He was treated with open reduction and internal fixation with a bone graft. The knee became increasingly painful and swollen, and in March 1997 X-rays showed a destructive tumour involving the whole of the lower end of the femur with extension into the soft tissue medially and posteriorly. The patient was keen to

Charing Cross Hospital, Fulham Palace Rd, London W6 8RF; ¹Section of Cellular Pathology, Department of Pathology, Mayday University Hospital, Croydon CR7 7YE, UK

Correspondence to: Dr A Stewart
E-mail: astewart@hhnt.org