Large granular lymphocyte leukaemia

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INTRODUCTION

Over the past decade, pulmonary hypertension has become an exciting and rapidly-progressing sub-specialty within respiratory medicine, with advances in the understanding of both its pathogenesis and treatment. Rare associations with pulmonary arterial hypertension (PAH) can help to elucidate common underlying mechanisms of all forms of PAH. The authors report two cases of PAH in association with large granular lymphocyte (LGL) leukaemia, one of which was curable.

DISCUSSION

Case reports one and two illustrate two cases of PAH in association with LGL-leukaemia that prompt interesting questions about the pathogenesis of PAH, the treatment of LGL-leukaemia and the pulmonary vascular response to leukaemia remission.

Eighty-five percent of LGL-leukaemias are a clonal proliferation of CD4-/CD8+ T cells, with abundant cytoplasm and prominent azurophil granules, and the remaining 15% are proliferations of natural killer cells.

The association between PAH and LGL-leukaemia has only been reported in three cases in two reports. Rossoff et al (1997) described a patient with PAH, LGL-leukaemia and splenectomy. A wedge biopsy demonstrated plexogenic changes characteristic of idiopathic pulmonary hypertension. Following cladribine therapy, the leukaemia went into remission and his PAH regressed significantly. The authors suggest a parallel between LGL-associated PAH and human immunodeficiency virus (HIV) associated PAH in which there is also an excess of CD8+ T cells.

In the second report, two patients with aggressive LGL-leukaemia and severe PAH had lung biopsies showing infiltration by leukaemic cells which constitutively expressed Fas ligand (FasL) (Lamy et al, 2000). The interaction between FasL and the Fas receptor induces apoptosis, and the authors proposed that FasL overexpression may lead to endothelial apoptosis, which may trigger endothelial and smooth muscle cell proliferation. The histological differences between these two case reports are probably accounted for by the degree of aggression of the leukaemia and need not provoke two separate mechanisms of disease.

The authors of this case report propose another potential mechanism. Voelkel and Tuder (1996) have suggested that primary pulmonary endothelial injury or dysfunction may lead to endothelial and smooth muscle inflammation and proliferation resulting in the plexogenic arteriopathy of idiopathic pulmonary hypertension. A minimum threshold of major histocompatibility complex (MHC) class I expression is required to inhibit natural killer pathways. A reduced

CASE REPORT 1

A 38-year-old man was diagnosed with low-grade large granular lymphocyte (LGL) leukaemia in 1995 and observed until March 2000 when he developed pulmonary arterial hypertension (PAH) coincident with a rise in his LGL count. He was started on methotrexate and cyclosporin in June 2000 and referred to Papworth Hospital. Methotrexate was stopped because of neutropenia. Computed tomography (CT) pulmonary angiography and high resolution CT excluded both acute and chronic thromboembolic pulmonary hypertension. Lung windows showed minor discrete interstitial changes with septal thickening and ground glass opacities at both lung bases. This was thought possibly to represent leukaemic infiltration. Echocardiography and right heart catheter were performed to exclude any valvular or congenital heart disease. There was no clinical and/or laboratory evidence of other secondary causes of PAH, such as autoimmune disease, human immunodeficiency virus (HIV) or liver disease, and he had not taken any drugs that may have induced PAH. Surgical lung biopsy was not undertaken because of high perioperative risk. He had 27x10^9/litre gammadeltaT-cell LGLs, typed as Vdelta5 Jdelta1. He was started on a nebulized prostacyclin analogue, iloprost, but discontinued this within 3 months without seeking medical advice. His progress is shown in *Table 1*. Follow-up CT at 1 year showed resolution of the interstitial changes.

CASE REPORT 2

A 47-year-old man was diagnosed with LGL-leukaemia in 1991. Initial treatment included beta-interferon, prednisolone and splenectomy. After multiple transfusions in 1996, he entered spontaneous remission. He was referred to Papworth Hospital in July 2002 with PAH and an 18-month history of dyspnoea. Immunophenotyping identified LGLs as CD8+TCRVbeta7.1 (19% of CD8+ T cells). Thirty percent of CD4+CD25+ T-cells expressed Vbeta12 and were thought to be regulating the LGL proliferation. Secondary causes of PAH were excluded. Surgical lung biopsy was not undertaken because of high perioperative risk. Nebulized iloprost was commenced and his condition remained stable with an increase in six-minute walking distance. He was changed to oral bosentan, a endothelin antagonist, in March 2004 because of the inconvenience of nebulization. His progress is shown in *Table 1*.

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threshold for MHC-unrestricted CD8+ T cell killing by LGL-leukaemias can cause anaemia since red cell precursors express marginal levels of MHC class I (Handgretinger et al, 1999).

This cytotoxic attack might also be directed against the endothelium of larger pulmonary vessels that characteristically express low levels of MHC class I versus the pulmonary capillary bed (Page et al, 1992). There is therefore a possible common mechanism for the development of the red cell aplasia and PAH in LGL-leukaemia.

In case one both haemodynamics and LGL count undoubtedly improved with cyclosporin, suggesting clear disease association between LGL and PAH. Furthermore, his response suggests only a small degree of pulmonary vascular remodelling, with the major cause of elevated vascular resistance being related to reversible vascular inflammation or infiltration. Although he started treatment with nebulized iloprost, he discontinued this within 3 months. This short period of vasodilator therapy will not have been responsible for any significant remodelling of the pulmonary vasculature or long-term reduction in pulmonary vascular resistance.

The lack of response in case two may reflect an independent mechanism for the PAH or substantial remodelling of the pulmonary vascular bed. Alternatively, chemotherapy may be crucial in reducing cytokine-driven vascular proliferation.

In case two, multiple transfusions led ultimately to control of his disease in 1996, probably through the generation of a CD4+ T-cell subset regulating the Vbeta7.1-LGL population, as proposed by Bushell et al (2003). Therefore any immunomodulatory treatment, such as cyclosporin, would be inappropriate since it could potentially attenuate this regulatory effect.

CONCLUSIONS

The authors have presented two cases of PAH associated with LGL-leukaemia. Therapy was tailored to each case, avoiding pitfalls of inappropriate treatment in one and providing the benefits of treatment in the other. HM

Acknowledgements
The authors acknowledge the help of Dr JL Smith, Wessex Immunology, Southampton University Hospitals NHS Trust, UK, in the molecular typing of the gammadeltaT-cell LGL.

Conflict of interest: None

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TABLE 1.
Echocardiographic, 6-minute walk, haemodynamic and haematological progress

	Case 1					Case 2					
Date	6.00	10.01	3.02	2.03	2.04	7.02	11.02	2.03	5.03	3.04	7.04
Treatment		CyA	CyA	CyA	CyA		Ilo	Ilo	Ilo	Ilo	Bos
NYHA status	IV	II	I	I	I	II	II	II	II	II	II
Echocardiography											
RVSP (mmHg+RAP)	87	57	42	N/A	41	128	156	115	151	N/A	118
Six-minute walk (m)	160	440	560	N/A	443	340	400	380	380	460	494
Right Heart Catheter											
mPAP (mmHg)	57	30	N/A	19	N/A	55	67	N/A	N/A	N/A	57
CI (litres/minute/m²)	1.8	2.4	N/A	2.7	N/A	1.5	1.7	N/A	N/A	N/A	1.8
SvO_2 (%)	N/A	71	N/A	72	N/A	64	67	N/A	N/A	N/A	73
Full Blood Count											
Hb (g/dl)	9.0	11.4	11.0	12.2	14.2	16.7	17.9	18.3	16.1	16.0	16.2
WCC (x10⁹/litre)	30	5.5	4.8	4.1	3.4	8.8	7.8	6.5	7.9	7.2	9.0
Lymphocytes (x10⁹/litre)	29	4.6	3.9	3.6	2.4	4.4	3.6	3.6	4.1	3.2	4.6
Platelets (x10⁹/litre)	65	216	212	192	195	203	257	233	257	223	254
LGL count (x10⁹/litre)	27	3.6	N/A	3.4	N/A	0.3	N/A	0.3	N/A	N/A	N/A

CyA, Cyclosporin A; Ilo, nebulized iloprost; Bos, oral Bosenatn; NYHA, New York Heart Association; RVSP, right ventricular systolic pressure; RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; CI, cardiac index; SvO_2, mixed venous oxygenation saturation; Hb, haemoglobin; WCC, white cell count; LGL, large granular lymphocyte.