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References

1 **Günther A**, Mosavi P, Heinemann S, *et al*. Alveolar fibrin formation caused by enhanced procoagulant and depressed fibrinolytic capacities in severe pneumonia. Comparison with the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2000;**161**:454–62.
2 **Schultz MJ**, Millo J, Levi M, *et al*. Local activation of coagulation and inhibition of fibrinolysis in the lung during ventilator-associated pneumonia. *Thorax* 2004;**59**:130–5.
3 **Liaw PC**, Ferrell G, Esmon CT. A monoclonal antibody against activated protein C allows rapid detection of activated protein C in plasma and reveals a calcium ion dependent epitope involved in factor Va inactivation. *J Thromb Haemost* 2003;**1**:662–70.
4 **Levi M**, Ten Cate H. Disseminated intravascular coagulation. *N Engl J Med* 1999;**341**:586–92.
5 **Bernard GR**, Vincent JL, Laterre PF, *et al*. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;**344**:699–709.

Surgery for difficult persistent asthma

A 35 year old non-smoking woman was referred to hospital for advice regarding poorly controlled atopic asthma. Despite good compliance with fluticasone 2 mg/day, a long acting β_2 agonist, anticholinergic agent, nebulised bronchodilators plus theophylline, she experienced persistent symptoms necessitating frequent courses of oral corticosteroids. It became apparent that her asthma control deteriorated before menstruation—a pattern which was not influenced by premenstrual or continuous oral corticosteroids. Trials with various combined oral contraceptive pills failed to improve asthma control. Some improvement was observed with 6 months of treatment with a gonadorelin analogue (goserelin); although premenstrual symptoms did persist, exacerbations were less marked resulting in a significant reduction in oral corticosteroid use. Gonadorelin analogues produce an initial phase of stimulation followed by downregulation of gonadotrophin releasing hormone receptors, thereby reducing the release of gonadotrophins and subsequent inhibition of oestrogen production. On discontinuation of goserelin (contraindicated for use longer than 6 months) symptomatic asthma recurred, requiring repeated monthly courses of oral corticosteroids. Following discussion with the patient and her gynaecologist, it was decided that, given the cyclical severity of symptoms, the need for frequent oral corticosteroids, and partial success with a gonadorelin analogue, definitive surgical treatment should be considered.

Four years after initial referral a bilateral oophorectomy and subtotal hysterectomy was performed without complication and an oestrogen alone hormone replacement was implanted. In the year following surgery the patient had a single exacerbation of asthma that coincided with the end of the effectiveness of her oestrogen implant (with consequent rise in gonadotrophin levels due to lack of suppression by oestrogen). She was subsequently commenced on regular oestrogen only hormone replacement therapy to good effect. One year after surgery the patient has discontinued alternate day oral prednisolone, is asymptomatic, and maintained on 250 μg/day fluticasone combined with salmeterol.

This unusual case highlights the importance of enquiring about the possible temporal relationship between worsening asthma control and the menstrual cycle. Premenstrual exacerbations of asthma are well recognised and do not always respond to more aggressive anti-inflammatory treatment. Some success has been observed with the institution of oral oestrogen and intramuscular progesterone administration.[1 2] We believe this to be one of the first documented cases of difficult asthma where marked improvement in asthma control has been achieved after a beneficial therapeutic trial of a gonadorelin analogue, followed by bilateral oophorectomy and subtotal hysterectomy plus oestrogen replacement. An initial improvement in asthma control was observed when gonadotrophin levels were low (as a result of the gonadorelin analogue) and a deterioration occurred when gonadotrophin levels were likely to have been rising (towards the end of the effectiveness of the oestrogen implant). This, in turn, suggests that high (or rapidly increasing) gonadotrophin levels, rather than oestrogen/progesterone, were implicated in adversely affecting asthma activity.

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References

1 **Beynon HL**, Garbett ND, Barnes PJ. Severe premenstrual exacerbations of asthma: effect of intramuscular progesterone. *Lancet* 1988;**2**:370–2.
2 **Myers JR**, Sherman CB. Should supplemental estrogens be used as steroid-sparing agents in asthmatic women? *Chest* 1995;**106**:318–9.

Is there a relationship between *Mycobacterium tuberculosis* strain type and TB paradoxical reaction?

Paradoxical reaction (PR) in tuberculosis (TB) is defined as transient worsening of symptoms and signs or the appearance of new lesions after beginning appropriate antituberculosis chemotherapy. Recent studies suggest that PR occurs in 10–35% of patients. It is more common and more severe in HIV co-infected individuals with disseminated disease.[1] PR is thought to be an immune mediated phenomenon but the reasons for its occurrence are unknown.[1]

Infection by *Mycobacterium tuberculosis* (MTB) results in highly variable outcomes between individuals. The characterisation of MTB strains by molecular typing techniques suggests this may be a reflection of the infecting organism, as well as host response and environmental factors. MTB strains with distinct genotypes have been shown to evoke different immunopathological events in mouse models[2] and variable clinical manifestations in human population based studies.[3] Furthermore, individual strain types have been linked to particular clinical outcomes; for example, a significant association was seen between the Beijing MTB lineage and transient fever unrelated to disease severity, toxicity, or drug resistance in early treatment.[4]

We sought to investigate the hypothesis that the risk of PR may be strain dependent as defined by IS*6110* restriction fragment length polymorphism (RFLP) typing.

Between January 2002 and December 2003 all adult patients seen at our centre with culture positive MTB had IS*6110* RFLP typing performed on one isolate. A case note review was performed retrospectively for clinical evidence of PR.[1] IS*6110* RFLP typing was undertaken using a modification of the standard international protocol.[5] All patterns were entered onto a database using Bionumerics Edition 3.0 package (Applied Maths, Kourtrai, Belgium). Comparison of DNA fingerprints and cluster analysis of profiles was performed by calculation of the Dice coefficient; optimisation was set at 1% and position tolerance at 1.2%. A cluster was defined as a series of isolates with 100% identity. A putative lineage was identified as a series of isolates with 70% or greater similarity.[6]

145 patients had isolates that were typed. 100 (69%) sets of notes were reviewed. 45 were excluded (24 were unavailable or incomplete; 21 patients were lost to follow up or care was transferred). Of the 100 patients' notes reviewed, 52 were male, age range 16–81 years. 48% were black African, 16% Asian, and 19% from the UK. Table 1 shows the TB site and HIV status of the patients. PR occurred in 20 patients (20%) (HIV positive 10/26 (38%); HIV negative or unknown 10/74 (14%)). All patients with PR had distinct IS*6110* RFLP profiles suggesting 20 separate strains.

There was only one identified lineage with a similarity of 70% within the whole patient cohort. This was not associated with increased risk of PR. The group comprised 10 patients who were all black African, only one of whom had a PR. The similarity is likely to represent an original strain of African descent (data not shown).

IS*6110* typing is the recognised gold standard for MTB strain typing and has widespread application in epidemiological and outbreak investigations of TB.[5] Using this method we found one lineage, but no association between strain type and PR. The power of our study is limited by its small sample size and retrospective nature. However, the rate of PR (20% and three times higher in HIV positive subjects: 38% *v* 14%) is in line with previous work.[1] IS*6110* typing is not a definitive phylogenetic marker and other molecular techniques such as single nucleotide polymorphism may demonstrate an association.

The possibility exists that paradoxical TB reactions may be a consequence of specific host response genes. Particular MHC haplotypes have been linked to ''immune reconstitution disease'' in HIV positive patients starting antiretroviral therapy.[7] A larger study

Table 1 Site of TB and HIV status of patients with and without clinically evident paradoxical reactions (PR)

	Pulmonary TB		Lymph node TB		Other primary site		
	HIV+	HIV−/NK	HIV+	HIV−/NK	HIV+	HIV−/NK	Total
PR	7	3	2	6	1	1	20
No PR	10	46	4	8	2	10	80

NK, not known.

is needed to focus on both strain type and consequent host immune response.

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References

1 **Breen RA**, Smith CJ, Bettison H, *et al.* Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax* 2004;**59**:704–7.
2 **Dormans J**, Burger M, Aguilar D, *et al.* Correlation of virulence, lung pathology, bacterial load and delayed type hypersensitivity responses after infection with different Mycobacterium tuberculosis genotypes in a BALB/c mouse model. *Clin Exp Immunol* 2004;**137**:460–8.
3 **Dale JW**, Bothamley GH, Drobniewski F, *et al.* Origins and properties of Mycobacterium tuberculosis isolates in London. *J Med Microbiol* 2005;**54**:575–82.
4 **Van Crevel R**, Nelwan RHH, de Lenne W, *et al.* Mycobacterium tuberculosis Beijing genotype strains associated with febrile response to treatment. *Emerg Infect Dis* 2001;**7**:880–3.
5 **Maguire H**, Dale JW, McHugh TD, *et al.* Molecular epidemiology of tuberculosis in London 1995–7 showing low rate of active transmission. *Thorax* 2002;**57**:617–22.
6 **McHugh TD**, Batt SL, Shorten RJ, *et al.* Mycobacterium tuberculosis lineage: a naming of the parts. *Tuberculosis (Edinb)* 2005;**85**:27–136.
7 **Price P**, Keane NM, Stone SF, *et al.* MHC haplotypes affect the expression of opportunistic infections in HIV patients. *Hum Immunol* 2001;**62**:157–64.

Bosentan in inoperable chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a devastating disease in which the pulmonary vasculature becomes obstructed by organised fibrotic material, presumed to be the consequence of incomplete resolution of pulmonary emboli. The ensuing increased pulmonary vascular resistance and right ventricular dysfunction results in severe exercise limitation, symptomatic right heart failure, and markedly impaired survival.

Recent studies suggest that the frequency of this condition is higher than previously appreciated, occurring in up 3.8% of patients following acute pulmonary embolism after 2 years.[1] The treatment of choice is pulmonary endarterectomy (PEA), a potentially curative surgical procedure in which the fibrotic material is removed from the proximal pulmonary arteries during periods of circulatory arrest.[2]

However, in response to increased flow and shear stress through vascular segments unobstructed by proximal thrombotic material, some individuals also develop a small vessel arteriopathy. This so called ''distal CTEPH'' has a pathophysiology not dissimilar to that of idiopathic pulmonary arterial hypertension.[3] In such patients, PEA may be unsuccessful in alleviating the pulmonary hypertension, and at the present time there is no licensed medical treatment for this condition.

As the national referral centre for PEA for the UK, we sought to assess the efficacy of the oral endothelin receptor antagonist bosentan in patients with distal CTEPH. This agent has established efficacy in pulmonary arterial hypertension, and in distal CTEPH endothelin-1 is thought to play an equally important role in the progressive nature of pulmonary vascular remodelling.[4]

Twenty patients with established distal CTEPH were recruited to the study, 15 deemed inoperable because of the distribution of their disease on imaging and five with persisting pulmonary hypertension following PEA. All subjects received open label bosentan 125 mg twice daily for at least 3 months. Assessments of change in 6 minute walk distance (6MWD), modified New York Heart Association Classification (NYHA), and haemodynamics were made. After at least 3 months of treatment there were significant improvements in 6MWD, NYHA classification, cardiac index, total pulmonary resistance, and pulmonary vascular resistance (table 1). All patients were alive at 3 months and no significant adverse events were reported as a result of the treatment. In particular, hepatic transaminases, which were monitored on a monthly basis, remained within the acceptable range in all participants.

Although uncontrolled, these preliminary data suggest that treatment with bosentan in this otherwise progressive condition results in improvement in exercise capacity, function, and haemodynamic prognostic markers. It is likely that, by inhibiting the action of endothelin-1, bosentan reduces the abnormal endothelial and smooth muscle cell proliferation stimulated by high shear stress within non-occluded pulmonary arterioles. This gradual reversal of vascular remodelling is the most likely reason for the reduction in pulmonary vascular resistance and right ventricular afterload and improved cardiac output observed in our subjects.

Pulmonary endartectomy remains the treatment of choice for proximal CTEPH. However, in patients with established distal arteriopathy deemed unsuitable for this surgical intervention, bosentan may offer an option by which to delay the progression of this otherwise devastating disease.

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References

1 **Pengo V**, Lensing AW, Prins MH, *et al.* Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med* 2004;**350**:2257–64.
2 **Klepetko W**, Mayer E, Sandoval J, *et al.* Interventional and surgical modalities of treatment for pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;**43**(12 Suppl S):73–80S.
3 **Moser KM**, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. *Chest* 1993;**103**:685–92.
4 **Bauer M**, Wilkens H, Langer F, *et al.* Selective upregulation of endothelin B receptor gene expression in severe pulmonary hypertension. *Circulation* 2002;**105**:1034–6.

Table 1 Mean (SD) 6MWD and cardiac haemodynamics at baseline and after at least 3 months of treatment with bosentan

	Baseline	3 months	Change from baseline	p value
NYHA class II/III/IV	5/14/1	8/11/1		
6MWD (m)	262 (106)	307 (100)	45 (53)	0.001
CI (l/min/m^2)	1.9 (0.62)	2.3 (0.59)	0.4 (0.3)	>0.001
TPR (dyne.s/cm^5)	1165 (392)	918 (275)	−247 (322)	0.003
PVR (n = 15) (dyne.s/cm^5)	964 (406)	690 (271)	−274 (300)	0.005
mPAP (mm Hg)	48 (13)	45 (11)	−3 (7.6)	0.09
mRAP (mm Hg)	9.4 (6.5)	7.7 (4.8)	−1.6 (6.6)	0.28
Mixed venous saturations (%)	59 (8.6)	63 (7.7)	3.8 (9.6)	0.15

6MWD, 6 minute walk distance; CI, cardiac index; TPR, total pulmonary resistance; PVR, pulmonary vascular resistance; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure. Two sided p values as indicated.