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### Chronic lymphocytic leukaemia and concomitant relapsing polychondritis: a report on one treatment for the combined manifestation of two diseases

SIR, We report the case of a 60-yr-old patient who suffered from chronic lymphocytic leukaemia (CLL) with concomitant relapsing polychondritis. Polychondritic exacerbations were regularly observed with CLL progression and included bilateral painful swellings of the external ear cartilage and of the trachea, disseminated inflammatory polyarthritis, ocular inflammation and a palatal ulceration (Fig. 1). All manifestations of polychondritis and CLL responded well to chlorambucil/prednisone initially, and to cyclophosphamide during later stages of the disease, while the response to methotrexate was poor and treatment with bendamustine was complicated by tumour lysis syndrome and subsequent acute renal failure. Treatment with cyclophosphamide repeatedly induced remissions for both diseases, but was regularly accompanied by serious infectious complications. Relapsing polychondritis is rare and is generally diagnosed clinically if the patient develops at least three of the following signs: bilateral chondritis of the external ears, inflammatory polyarthritis, ocular inflammation, nasal chondritis, vestibular/auditory malfunction and respiratory tract chondritis. Notably, its 5-yr mortality may be as high as 30%, due to collapse of laryngeal and tracheal cartilaginous supporting structures, or cardiovascular involvement. Mild cases may respond to NSAIDs. More severe cases are usually treated with prednisone and may require additional immunosuppressive agents, e.g. cyclophosphamide [1].

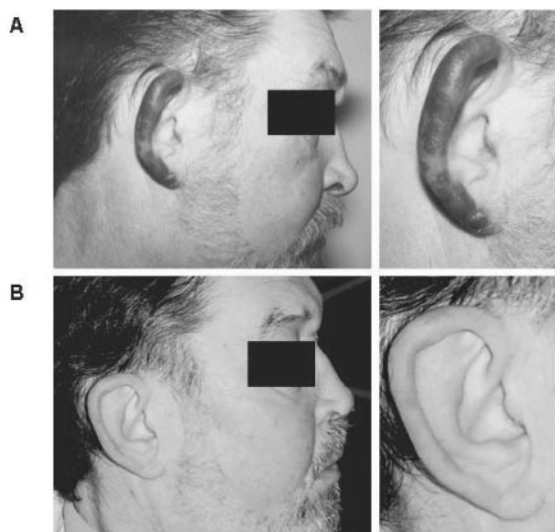


FIG. 1. Pain and a purple swelling of the external ear are the most common first clinical signs of relapsing polychondritis. The swelling may extend into the ear canal and induce ear infections, hearing loss and balance disturbances with vertigo and vomiting. During later stages of polychondritis, the destruction of supporting cartilaginous tissue may become visible as floppy ears occurring together with auditory and vestibular abnormalities, a flattened nose bridge (saddle nose) or, less frequently, with visual disturbances due to recurring inflammation, which may lead to blindness. The two pictures at the top (A) show our patient prior to treatment, while the pictures at the bottom (B) show our patient after one cycle of chlorambucil. This figure may be viewed in colour as supplementary data at *Rheumatology Online*.

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1. Kent PD, Michet CJ Jr, Luthra HS. Relapsing polychondritis. *Curr Opin Rheumatol* 2004;16:56–61.

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### Adalimumab-induced asthma

SIR, A 51-yr-old lady with a 15-yr history of erosive seropositive rheumatoid arthritis (RA) was treated with adalimumab, having failed multiple DMARDs. Prior to this she had no personal or family history of asthma or atopy and had never smoked.

Within 2 weeks of starting adalimumab she developed a diurnal bronchial wheeze with shortness of breath. This persisted and was reported at review 8 weeks later. Pulmonary function tests (PFT) showed an obstructive pattern, forced expiratory volume in 1 s (FEV<sub>1</sub>) reduced by 49% of predicted and a significant bronchodilator response of 25% improvement in FEV<sub>1</sub> (15% improvement indicates reversible airways disease) (Table 1). A raised transfer coefficient (KCo) of 1.88 mmol/kPa/min/l (117% predicted) was also noted, which is typical of asthma. A full blood count showed a new eosinophilia of  $1.0 \times 10^9/l$  (normal range 0.0–0.4) and a raised immunoglobulin E of 384 kU/l (normal range 0–81).

The chronology of events and absence of previous respiratory disease suggested an adverse reaction to adalimumab. Introducing methotrexate was considered to suppress this presumed immunological side-effect, but due to previous severe rashes with methotrexate this was not pursued. Therefore inhaled beclomethasone 200 µg twice daily was added.

Within 3 days her symptoms had improved and within 2 weeks they were completely controlled by beclomethasone. Subsequent PFT on beclomethasone whilst still on adalimumab were much improved, with a FEV<sub>1</sub> of 2.021 and a FEV<sub>1</sub>/forced vital capacity (FVC) ratio of 81.8%.

Unfortunately, after an initial good response to adalimumab with a greater than 50% reduction in swollen and tender joint count, the RA persistently flared. Adalimumab was stopped after 5 months of treatment. The patient subsequently stopped

TABLE 1. Pulmonary function test before and after bronchodilator

| Test                      | Two weeks after starting adalimumab |       |            | Three months after stopping all medication |       |            |
|---------------------------|-------------------------------------|-------|------------|--------------------------------------------|-------|------------|
|                           | Before                              | After | Change (%) | Before                                     | After | Change (%) |
| FEV <sub>1</sub> (l)      | 1.41                                | 1.76  | 25         | 2.1                                        | 2.2   | 4.5        |
| FVC (l)                   | 2.09                                | 2.22  | 6          | 2.6                                        | 2.7   | 3.5        |
| FEV <sub>1</sub> /FVC (%) | 67.4                                | 79.3  | 18         | 79.1                                       | 82.1  | 1.0        |

the beclomethasone inhaler with no return of symptoms. PFT 3 months after stopping all medication had returned to normal (Table 1). Eosinophils also returned to normal within 3 weeks of stopping the drug.

Adalimumab is a fully human recombinant monoclonal anti-tumour necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) antibody recently licensed for the treatment of moderate to severely active RA. Like all anti-TNF- $\alpha$  drugs, adalimumab has recognized side-effects, increased susceptibility to infection being the most worrying.

This is the only Committee on Safety of Medicines (CSM)-reported adverse event of asthma with adalimumab to date in the UK. Further information from Abbott Laboratories revealed that in the pivotal trials of adalimumab asthma has been reported as an adverse event in 0.3% of adalimumab-treated patients compared with 0.1% of placebo-treated patients. Neither treatment nor the pre-existence of asthma was recorded; however, no patient had to stop adalimumab.

A possible explanation of the new onset of asthma in these patients lies in the contrasting inflammatory responses in RA compared with asthma and other allergic diseases. Among T-helper cells (Th), two opposite poles of immune responses can be distinguished based on secretion of cytokines: the Th1 cytokine pattern, with predominant secretion of interferon  $\gamma$  (IFN- $\gamma$ ) and TNF- $\alpha$ , and induction of a cellular immune response. In contrast, the Th2 cytokine pattern has predominant secretion of interleukin (IL)-4, IL-5 and IL-13 and induction of the humoral immune response. Atopic disorders show a raised level of IgE and a Th2 cytokine response [1], whilst RA is considered to be a Th1-polarized disease [1–5].

The generation of a Th2 immune response is inhibited in the presence of Th1 cytokines and vice versa [6]. Based on reciprocal inhibition of the development of Th1 and Th2 responses, it has been suggested that Th1- and Th2-polarized diseases mutually exclude one another. We hypothesize that active RA in this case produced a Th1 cytokine response, which suppressed the clinical expression of asthma. However, once the TNF- $\alpha$  blocking drug was introduced, the Th1 response was suppressed, allowing the Th2-activated pathway to express itself clinically as asthma.

This hypothesis would suggest a class effect. Indeed, asthma has been reported as an adverse event to the CSM for both infliximab and etanercept. There have been two reported cases of new onset asthma with etanercept and two exacerbations of asthma, one with each of etanercept and infliximab. Additionally, there have been another 25 cases of reported bronchospasm or wheezing, although most of these have been related to anaphylaxis.

Asthma appears to be a definite but rare side-effect of anti-TNF blockade. In all the adalimumab reported cases the asthma has been mild and adalimumab has not needed to be withdrawn. The details of the asthma adverse events to infliximab and etanercept are not available. In the absence of other guidelines, we followed the British Thoracic Society (BTS) guidelines for asthma [7] and added an inhaled steroid, which completely resolved the patient's mild symptoms.

We conclude that asthma in this patient was precipitated by the anti-TNF- $\alpha$  drug adalimumab. Although at no stage was the asthma severe enough for the drug to be stopped, we would recommend careful observation, particularly in patients with a personal or family history of asthma or atopy, and adherence to the BTS guidelines for asthma [7] if symptoms occur.

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1. Del Prete G. Human Th1 and Th2 lymphocytes: their role in the pathophysiology of atopy. *Allergy* 1992;47:450–5.
2. Simon AK, Seipelt E, Sieper J. Divergent T-cell cytokine patterns in inflammatory arthritis. *Proc Natl Acad Sci USA* 1994;91:8562–6.
3. Liblau RS, Singer SM, McDevitt HO. Th1 and Th2 CD4+ T cells in the pathogenesis of organ-specific autoimmune diseases. *Immunol Today* 1995;35:34–8.
4. Schulze-Koops H, Lipsky PE, Kavanaugh AF, Davis LS. Elevated Th1 or Th0-like cytokine mRNA in peripheral circulations of patients with rheumatoid arthritis. Modulation by treatment with anti-ICAM-1 correlates with clinical benefit. *J Immunol* 1995;155:5029–37.
5. Dolhain RJEM, van der Heiden AN, ter Haar NT, Breedveld FC, Miltenburg AMM. Shift toward T lymphocytes with a T helper 1 cytokine-secretion profile in the joints of patients with rheumatoid arthritis. *Arthritis Rheum* 1996;39:1961–9.
6. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. *Nature* 1996;383:787–93.
7. Higgins BG, Douglas JG. The new BTS/SIGN asthma guidelines: where evidence leads the way. *Thorax* 2003;58:98–9.

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### **Fatal streptococcal toxic shock syndrome in a patient with rheumatoid arthritis treated with etanercept**

SIR, We report the case of a 24-yr-old female with a 5-yr history of severe seropositive rheumatoid arthritis (RA) treated only with chloroquine and prednisone. Over the last 2 yr she had been maintained on prednisone 25 mg. Her physical exam revealed Cushingoid features in addition to persistent active joint inflammation in the small joints of the hands and wrists. In view of the severity of her disease it was decided to start her on methotrexate and etanercept. She received her first dose of etanercept 25 mg subcutaneously; the next day she started to complain of nausea, vomiting and diarrhoea associated with fever. She was managed with intravenous fluid and electrolyte replacement. Two days later she presented to the emergency room with fever, hypotension (blood pressure 80/50 mmHg) and generalized lethargy. She reported a history of a fall a few hours before with trauma to her right lower extremity. Her physical exam revealed swelling and erythema over the right knee and thigh. She was managed with fluid replacement and broad spectrum antibiotics. Her condition rapidly deteriorated and she went into shock with further drop in her blood pressure, tachycardia, tachypnoea and anuria. She was intubated, mechanically ventilated and was transferred to the intensive care unit. Her blood pressure did not pick up despite full-dose inotropes and flush fluids. Her right lower extremity rapidly became mottled with sloughing of the overlying skin. She had a cardiac arrest around 12 h after her admission to the emergency room. Two blood cultures revealed streptococcus group A.

The rapid development of a streptococcal toxic shock syndrome shortly after the initiation of etanercept therapy in a