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Chronic beryllium disease: azathioprine as a possible alternative to corticosteroid treatment

To the Editor:

Chronic beryllium disease (CBD) is a chronic granulomatous disease that mainly affects the lungs. It occurs after beryllium exposure in genetically susceptible individuals with, most commonly, the HLA-DPβ1 (Glu69) polymorphism [1]. Beryllium particles are slowly washed out, causing delayed onsets of the disease and flare ups long after exposure to beryllium [2, 3].

The clinical, radiological and pathological presentation of CBD is very similar to sarcoidosis. Thus, misdiagnosis is not uncommon, as reported by FIREMAN *et al*. [4] and MÜLLER-QUERNHEIM *et al.* [5]. These authors managed to correct the diagnosis of chronic sarcoidosis to CBD in 4–6% of patients, thanks to a careful retrospective screening for beryllium exposure [4, 5].

In CBD, lungs are damaged by diffuse noncaseating granulomas and this may lead to fibrosis. The US Beryllium Case Registry determined the following specific criteria for CBD diagnosis: a beryllium exposure history; relevant clinical and radiological signs (breathlessness, reduced pulmonary capacity and diffuse interstitial opacities); evidence of beryllium sensitisation with positive beryllium lymphocyte proliferation test in blood or in bronchoalveolar lavage (BAL); and histopathological features such as noncaseating granulomas or mononuclear tissue infiltration without any infection. Long-term prognosis of CBD is poor with a mortality rate ranging from 5.8% to 38%. Current treatment of CBD relies on both beryllium exposure cessation and corticosteroid therapy. Corticosteroid therapy is efficient on the granulomatous component and leads to a significant clinical, radiological, biological and functional improvement [6]. However, the efficacy of corticosteroids doesn't last: relapses occur following cessation of therapy or dose lowering and long-duration treatment with possible severe side-effects is often necessary. Eventually, some patients might not respond as expected to corticosteroids, or develop progressive lung fibrosis despite this treatment [6, 7].

Herein, we report the first case of CBD successfully treated by azathioprine in a patient for whom corticosteroids were contraindicated.

A 43-yr-old nonsmoking male who had been exposed to beryllium for at least 3 yrs between 1992 and 1997 during his employment as a foundry worker presented to our clinic (Avicenne University Hospital, Bobigny, France). Diffuse interstitial opacities and lymphadenopathy were discovered on chest radiography in 1997. However, it was only in 2001 that CBD diagnosis was considered due to the occurrence of dyspnoea on exertion. Chest computed tomography (CT) evidenced diffuse ground-glass opacities, micronodules and discreet fibrotic lesions in the upper lobes (linear retractile opacities and traction bronchiectasis). A beryllium lymphocytes proliferation test was positive in both blood and BAL (biological index 13.43 and a beryllium statistical index >2.53). Pulmonary function tests (PFT) showed a restrictive impairment with a 40% lung volume reduction associated to a decrease of the diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) (fig. 1). The serum angiotensine converting enzyme (SACE) level was 70 UI (normal <40 UI). The BAL fluid cell count showed a significant hypercellularity (850,000 cells·mL^{-1}) and hyperlymphocytosis (66%). Genetically, the patient was Glu69 homozygous. There was no granuloma on bronchial biopsy but noncaseating

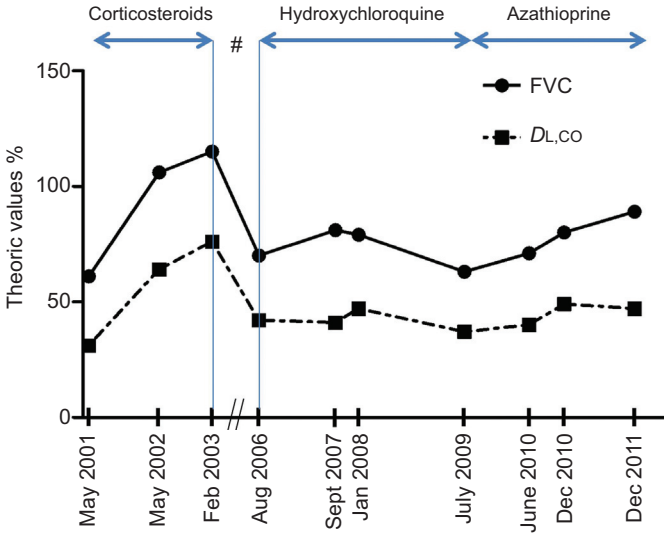

FIGURE 1. Functional evolution under treatment FVC: forced vital capacity; $D_{L,CO}$: diffusion capacity of the lung for carbon monoxide. #: lost to follow-up.

granulomas with epithelioid and giant cells were found on videothoracoscopic lung biopsy, most likely located in the interstitial area of the alveolar septa. The diagnosis of CBD was then confirmed and prednisone treatment (1 $mg \cdot kg^{-1} \cdot day^{-1}$) was initiated in June 2001. The patient quit his job and, thus, was no longer exposed to beryllium.

Evolution was marked with a rapid and dramatic improvement with reduced dyspnoea, a decrease in CT ground-glass opacity and normalisation of both PFTs (fig. 1) and SACE level. This improvement was maintained until the corticosteroid dose was lowered to 7 mg of prednisone per day in February 2003. Unfortunately, the occurrence of psychotic troubles required heavy psychiatric medical treatment and corticosteroids had to be withdrawn. The patient was lost to follow-up between 2003 and 2006 and stopped taking his medication. He was not re-exposed to beryllium. In August 2006, he consulted his doctor following a relapse in breathlessness. A chest CT showed diffuse ground-glass opacities and wider upper lobe fibrotic lesions. Lung volumes were reduced by 30% and $D_{L,CO}$ was decreased to 42% of the predicted value (fig. 1). The SACE level was elevated

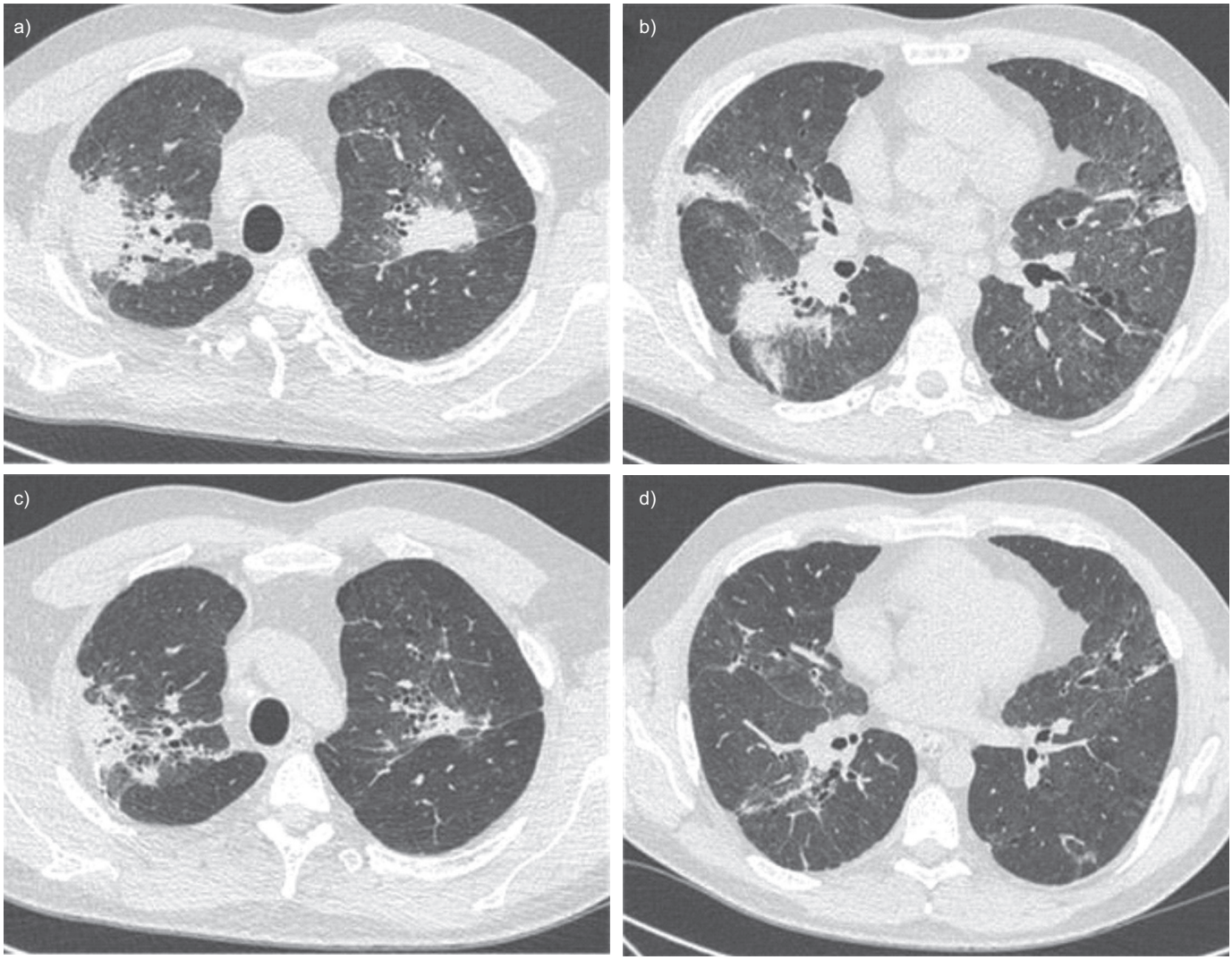

FIGURE 2. Radiological evolution a, b) before and c, d) under azathioprine treatment. There was a decrease of pulmonary consolidation and ground-glass opacities. Only fibrotic lesions are persisted.

(72 UI). Treatment with corticosteroids was impossible because of the patient's psychiatric instability. Hydroxychloroquine treatment (400 mg·day^{-1}) was then initiated. A significant, but only partial, clinical, radiological and functional improvement ensued, with a secondary relapse despite good observance.

In July 2009, the patient's condition worsened with PFT results comparable to those at first presentation (fig. 1). Treatment with azathioprine (150 mg·day^{-1}) was then started as hydroxychloroquine was withdrawn. This treatment allowed a significant gradual clinical, radiological and functional improvement (fig. 2), with almost normalised PFTs by December 2011 (fig 1). SACE level also normalised. Only stable fibrotic chest CT lesions and $D_{L,CO}$ abnormalities persisted. Treatment efficacy and tolerance were still excellent after 17 months and a reduction of azathioprine (100 mg·day^{-1}) was initiated.

CBD is a granulomatous disease due to beryllium exposure in genetically susceptible individuals. CBD treatment relies on stopping beryllium exposure and corticosteroid therapy [8]. Despite frequent responses to such treatment, several limits are often observed, as in sarcoidosis, such as corticosteroid dependence, severe side-effects and, sometimes, pulmonary fibrosis progression.

To date, in CBD, unlike sarcoidosis, no therapy other than corticosteroids has been considered. We report the first case of a successful azathioprine treatment in a patient who had a contraindication to the use of corticosteroids. Azathioprine can also be used in sarcoidosis treatment as a corticosteroid-sparing agent thanks to its strong and delayed suppressive effect on T-lymphocytes proliferation and activation [9]. We have been able to demonstrate the efficacy of azathioprine in treatment of CBD allowing prolonged clinical, functional and radiologic control. Consequently, azathioprine could be considered in CBD in the presence of contraindication or when there is poor tolerance to corticosteroids, or perhaps as a corticosteroid sparing agent when prolonged high doses are necessary. Interestingly, we observed a partial and temporary efficacy of hydroxychloroquine, a drug known to reduce antigen presentation that also works in some sarcoidosis patients.

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Do tertiary paediatric hospitals deal with the same spectrum of paediatric pulmonary hypertension as multicentre registries?

To the Editor:

Although national [1–5] and international paediatric registries for pulmonary hypertension (PH) [6, 7] have been published recently, inclusion criteria and, therefore, the distribution of aetiologies and severity of cases have not always been comparable [8].