Sarcoidosis and aspergillosis: a tough combination

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CPA is a serious complication of sarcoidosis contributing to fibrosis, respiratory failure and haemoptysis http://ow.ly/cMyQ30bNG4z

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It should have been a wake-up call. Thirty years ago, Tomlinson and Sahn [1] found that seven out of 12 (58%) patients with aspergillosis complicating sarcoidosis died over a 2 year period. Three years earlier, Wollschlager and Khan [2] had found evidence of aspergillosis in 12% of 100 consecutive sarcoidosis referrals, and aspergillomas were found in 53% of the 19 patients with fibrocystic aspergillosis. Yet the literature was almost silent on this topic despite an estimated global prevalence of 1.2 million patients with sarcoidosis [3], until 2008. In that year, Hours *et al.* [4] surveyed pulmonary cavitary sarcoidosis and its complications in their tertiary care service for sarcoidosis in Paris, France. They found that 3.9% had cavitary lesions and 2.1% an aspergilloma. This team have followed that report up in this issue of the *European Respiratory Journal* with a detailed study of chronic pulmonary aspergillosis complicating pulmonary sarcoidosis [5]. Others have noted the complexity of this dual pulmonary condition [6].

Sarcoidosis remains an enigmatic disorder of uncertain aetiology. Early reports focused on the cutaneous manifestations, and it was Cæsar Boeck in Oslo who emphasised the multisystem nature of the disease in 1916, including pulmonary disease [7]. The Kveim test was introduced in 1941. Wurm, Reindell and Heilmeyer demonstrated the benefits of a radiographic staging system for sarcoidosis, which was adapted and expanded by others, including Citron, Siltzbach, Chrétien and DeRemee [8]. Aspergilloma complicates stage III or fibrocystic/cavitary pulmonary sarcoidosis. Predicting which patients with sarcoidosis will develop fibrosis or cavitation is currently not possible, just as the prediction of who will develop aspergillosis is equally obscure.

Chronic pulmonary aspergillosis (CPA) comprises four entities: chronic cavitary (CCPA), simple aspergilloma, *Aspergillus* nodule and – the most severe – chronic fibrosing (CFPA) or destroyed lung [9]. In the context of cavitary sarcoidosis, defining CCPA is difficult because cavitary sarcoidosis is similar in appearance to CCPA, until a fungal ball is visible. Uzunhan *et al.* [5] have, for the first time, defined the different CPA phenotypes in sarcoidosis based on imaging and *Aspergilllus* IgG serology, with additional data on culture and also documented outcomes. In a 25 year cohort of 3137 sarcoidosis patients, 80 were identified with CPA (2.6%) and 65 were analysed in detail. An aspergilloma was seen in 41 (68%) patients, 60 (92%) had positive *Aspergillus* IgG serology and 48 (81%) grew *Aspergillus* spp. from a respiratory sample. Only four (7%) were *Aspergillus* IgG serology-only positive using multiple tests evolved over the 25 years of their study. Nine out of 34 (26%) patients had detectable *Aspergillus* antigen

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in the blood. CPA was present at the diagnosis of sarcoidosis in 10 (15%) of cases and developed over time in the remainder.

In most patients, CPA was classifiable – simple aspergilloma was seen in 17 (31%), CCPA in 27 (49%) and a mixed pattern including CFPA in 8 (15%) [5]. Compared with other underlying disease entities, this is a higher proportion of simple aspergilloma and CFPA. *Aspergillus* nodules are found in fewer than 10% of patients with CPA [10], and, in sarcoidosis, nodules are uncommon as the main radiological presentation [11].

Sarcoidosis is more common in black people living in the USA and London. Elsewhere, whether African heritage is a risk factor for sarcoidosis is not known. In this large French cohort, a substantial proportion of those with cavitary sarcoidosis (39%) [4] and with CPA complicating sarcoidosis (34%) were black [5]. It is not clear if black people are more or less likely to develop CPA in sarcoidosis than others.

There is a link between environmental fungal exposure and the development of sarcoidosis [12, 13] and some occupational exposures to fungi were quite common in those with CPA and sarcoidosis [5]. The overall importance of these associations has not been clarified, but could be relevant in the context of CPA as antifungal therapy is usually given. Uzunhan *et al.* [5] treated 85% of their patients with antifungal therapy for at least 6 weeks. Cough and the general symptoms of weight loss and fatigue improved in most patients.

Some patients with sarcoidosis are mildly immunocompromised, as evidenced by low CD4 cell counts and purified protein derivative anergy [14, 15], irrespective of corticosteroid therapy. We have found that many patients with CPA have reduced natural killer cells and gamma interferon and/or interleukin (IL)-12 production [16, 17]. Further immunological investigations of those with cavitary sarcoidosis and CPA complicating sarcoidosis are called for, as immunotherapy (*i.e.* gamma interferon replacement) may be beneficial.

Uzunhan *et al.* [5] report surgical resection in 11 patients, usually for haemoptysis. Despite this and 3 months of antifungal therapy after surgery, 10 (91%) relapsed, 6 to 45 months after surgery. This is a much higher relapse rate than for CPA overall, in which a 25% relapse rate has been documented [18]. A surgical solution for CPA in sarcoidosis should be one of last resort.

In their centre, the overall survival for CPA in sarcoidosis did not differ in this series from those with cavitary sarcoidosis – 74% at 5 years and 61% at 10 years [5]. These survival rates are much better than reported by Tomlinson and Sahn [1], but the earlier poor outcome could reflect corticosteroid use, which accelerates the progression of CPA in the absence of effective antifungal therapy. Our series of nearly 400 patients with CPA, just published, found that sarcoidosis patients with CPA had an outcome similar to other underlying diseases [19] and not as good overall as the French series (62% survival at 5 years, 47% at 10 years). Patients with CPA complicating non-tuberculous mycobacterial infection and chronic obstructive pulmonary disease fared worse overall [19].

The presence of a fungal ball or aspergilloma is a late feature of CPA. The presence of a fungal ball in the context of CCPA is a poor prognostic feature [19], especially if bilateral. Furthermore, antifungal resistance is more likely to develop in patients with higher fungal loads [20]. Mutations occur frequently in aspergillomas over time [21]. Given the difficulty in diagnosing CPA in sarcoidosis patients with cavitary disease, there is a case for proleptically screening patients for the development of *Aspergillus* IgG antibody to pick up sero-conversion before aspergillomas are visible radiologically. Earlier treatment could avoid haemoptysis, the development of general symptoms of CPA, and might improve outcome, as less fibrosis and development of CFPA is likely to occur with good antifungal therapy. This strategy needs prospective study.

Many genetic associations have now been made between CPA and certain immunological variants, namely the IL-1 pathway, IL-15, IL-10, vascular endothelial growth factor A (VEGF-A), transforming growth factor β1 (TGF-β1), DENND1B and PLAT [22–24]. In sarcoidosis, genetic variants in several pathways and genes have been found, including the IL-23/T helper (Th) 17 signalling pathway [25], butyrophilin-like 2 (BTNL2) [26], and annexin A11 (ANXA11) [27], although none is very strong. No genetic association work has yet addressed the different pulmonary phenotypes of sarcoidosis [28, 29]. If the CPA variants found in all populations are also found in sarcoidosis, then risk assessment using genetic testing might be a simpler and more comprehensive approach to excluding CPA risk, with a focus on those with genetic risks for CPA development.

CPA is one of the serious complications of sarcoidosis, partly because it contributes to fibrosis and respiratory failure and partly because of life-threatening and fatal haemoptysis. It also contributes to a worse quality of life. With an estimated annual incidence of 20 640 CPA cases and a prevalence of ~72 000

CPA patients with sarcoidosis [3], addressing the uncertainties in diagnosis and management of CPA is called for. Uzunhan *et al.* [5] provide an excellent basis for planning future studies.

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