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Propionibacterium acnes isolated from lymph nodes of patients with sarcoidosis

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Abstract. Propionibacterium acnes has been repeatedly suggested as a candidate causative agent of sarcoidosis. It is the only microorganism that has been isolated from sarcoid lesions by bacterial culture so far and this has been described in Japanese patients only. We report two non-Japanese patients in whom mediastinoscopy was performed in order to obtain lymph node tissue for histopathology, which was suggestive for sarcoidosis. Bacterial culture of these uncontaminated mediastinal lymph nodes revealed P. acnes in both patients. As shown in these two cases, P. acnes can be isolated from sterile biopsied sarcoid lymph nodes of non-Japanese patients and supports the belief that there is an etiologic link between P. acnes sarcoidosis. Further elucidation could provide an opening to novel strategies using antibiotics for treating sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 271-274)*

Key words: propionibacterium acnes, sarcoidosis, mediastinoscopy

Introduction

Sarcoidosis is a multisystem granulomatous disease that affects individuals worldwide. The incidence differs between geographical regions and aggregation in specific races occurs, being roughly three times more common in blacks (1). It usually develops before the age of 50 years, with the highest incidence observed in the third and fourth decades of life (1). The organs most commonly affected are the lungs and its draining lymph nodes (2).

Despite intensive research, the etiology of sarcoidosis has not been resolved yet. Sarcoidosis might result from the exposure of genetically susceptible individuals to an environmental agent. Because sarcoidosis can be clinically similar to infectious granulomatous diseases, microbial etiologies are considered (3). Propionibacterium acnes, which is a rod bacterium indigenous to the skin and mucosal surfaces, has been repeatedly linked to sarcoidosis (2, 4) and is so far the only microorganism isolated from sarcoid lesions by bacterial culture (5, 6). These two studies were performed in Japanese patients.

We present two non-Japanese patients with sarcoidosis in whom P. acnes was isolated from mediastinal lymph nodes after mediastinoscopy by bacterial culture.

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Case presentation

Case 1

A 39-year-old Turkish male with a 2-year history of fatigue was referred to our department under suspicion of a granulomatous disease as computed tomography (CT) of the chest showed mediastinal lymphadenopathy and multiple pulmonary nodules with perilymphatic distribution. He had previously been diagnosed with psoriasis. Involuntary weight loss and night sweats were not present. Physical examination did not reveal any abnormalities. Laboratory investigations, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and the serum angiotensin converting enzyme (ACE), were within normal limits, whereas the IFN-γ-release assay (IGRA) for tuberculosis revealed a positive result. Ziehl-Neelsen staining of sputum was negative. Findings from bronchoalveolar lavage were not indicative for sarcoidosis. Endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA) was not suspicious for malignancy and did not reveal granulomatous inflammation. He underwent mediastinoscopy with mediastinal lymph node biopsies, which revealed non-caseating granulomas (Figures 1 and 2), indicative for sarcoidosis. P. acnes was isolated from these lesions by bacterial culture (Brucella blood agar, incubated for 48 hours at 35°C in an anaerobic jar with mixture of CO_2, H_2 and N_2), whereas Mycobacterium tuberculosis was not cultured. Treatment was not indicated and during follow-up he was in good clinical condition and was not disabled by his illness.

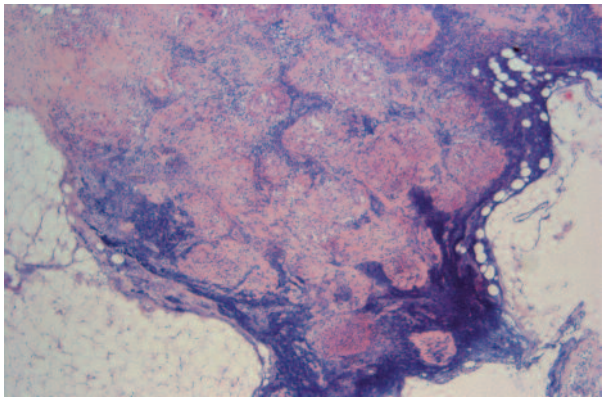

Fig. 1. Multiple granulomas lying in fatty tissue surrounded with lymphocytes. Haematoxylin eosin staining 25x

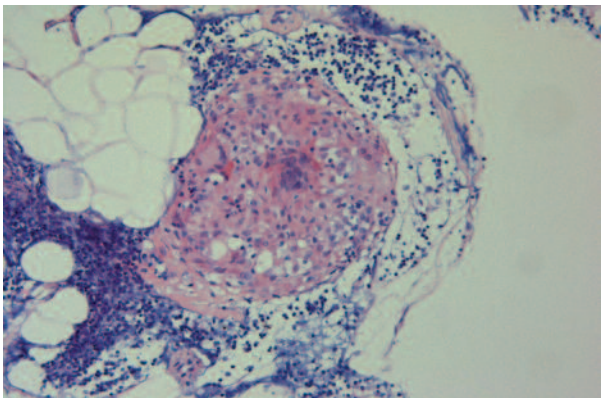

Fig. 2. Non-caseating epitheloid cell granuloma with (central and at the left) a giant cell. Haematoxylin eosin staining, 100x

Case 2

A 42-year-old Moroccan male presented with a 4-year history of cough and weight loss of 10 kg in the past 3 years. In 2011 he was diagnosed with Helicobacter pylori infection for which he received conventional eradication therapy. The physical examination was unremarkable. The serum ACE level was 60 U/L and ESR was 26 mm/hr. Other laboratory tests, including complete blood count and CRP, were within normal limits. IGRA for tuberculosis was negative. High resolution CT showed bilateral pulmonary nodules, mediastinal and perihilar lymphadenopathy and interlobular septa thickening, which can be seen in patients with sarcoidosis. Histological examination of tissue acquired during EBUS-TBNA did not demonstrate malignancy or granulomatous inflammation. Mediastinoscopy with mediastinal lymph node biopsies revealed non-caseating granulomas, from which P. acnes was isolated. Therapy was not started and lung function tests as well as radiology remained stable during follow-up.

Discussion

We report two non-Japanese cases in which P. acnes was isolated from sarcoid lymph nodes by bacterial culture. These lymph nodes biopsies were obtained during mediastinoscopy, which means that contamination is highly unlikely given the sterile conditions of the procedure. Multiple studies have

linked P. acnes to sarcoidosis (2, 4) and results of a recently conducted meta-analysis supported an association between P. acnes and some cases of sarcoidosis (7). The presented cases seem to underline this association, as P. acnes is the only microorganism that has been isolated from sarcoid lesions (5, 6).

In order to obtain a comprehensive overview of P. acnes isolation from sarcoid lymph nodes by bacterial culture we performed a PubMed literature search. The following MeSH terms were used: "Propionibacterium acnes", "sarcoidosis" and "biopsy". Spelling variations were also used. Two eligible articles were identified. Both studies were Japanese and one was published in 1978 and the other in 1984. In one study (5), P. acnes was cultured from 78% of sterile biopsied lymph nodes in patients with sarcoidosis and only 20% in patients with other diseases. In the other study (6), the findings were comparable, with 70%, and 29% positive cultures, respectively.

Both patients in our case series were not born in The Netherlands, but immigrated to our country from Turkey and Morocco. To our knowledge, our cases are the first non-Japanese patients in whom P. acnes has been isolated from sarcoid lymph nodes by bacterial culture. Interestingly, an international collaborative study investigating the possible link between P. acnes and sarcoidosis using quantitative polymerase chain reaction (PCR), already found no difference between Japanese and European patients regarding expression of P. acnes in sarcoid lymph nodes (8).

Other studies using quantitative PCR or in situ hybridization, have also tried to clarify the possible etiologic link between P. acnes and sarcoidosis and have suggested that P. acnes resides in sarcoid lesions (9) and might be related to the cause of granulomatous inflammation in sarcoidosis (10). Some P. acnes is also found in lymph nodes from patients without sarcoidosis by bacterial culture (5, 6, 11) and by PCR (9), and it is the most common commensal bacterium in the lungs and lymph nodes from individuals without sarcoidosis (11). However, isolation of P. acnes from lymph nodes is much more frequent in patients with sarcoidosis compared to patients without this disease (5, 6).

It is not known how this commensal bacterium could become pathogenic. Data from cord blood mononuclear cells indicate that P. acnes is mitogenic to T lymphocytes, which might mean that P. acnes is not directly pathogenic but acts as an adjuvant stimulating ongoing immune response initiated by an unrelated antigen (12).

Another hypothesis, in which sarcoid granuloma formation results from hypersensitivity to endogenous P. acnes, has been suggested (2). P. acnes can cause a latent infection in lungs and lymph nodes and persists there in a cell wall-deficient form. Certain environmental conditions can activate this latent form, which then proliferates in cells at the site of latent infection. Granuloma formation might then be induced by an Th1 immune response to one or more antigens of P. acnes in patients hypersensitive to this endogenous bacterium (2, 13).

These hypotheses of mitogenic and antigenic activity, respectively, provide alternative approaches for the treatment of sarcoidosis. For example, observational studies and case reports have demonstrated that antibiotic agents to which P. acnes is sensitive or antibiotics with immunomodulatory or anti-inflammatory effects can be effective for treating sarcoidosis (14-16).

The presented cases show that P. acnes can be isolated from sarcoid lymph nodes of non-Japanese patients by bacterial culture and support the thought that P. acnes plays a role in the etiology of sarcoidosis. Both mitogenic and antigenic activity have been suggested. Further clarification of the precise role of P. acnes might lead to novel treatment strategies.

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