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Combined pulmonary involvement in hereditary lysozyme amyloidosis with associated pulmonary sarcoidosis: a case report.

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Abstract. Sarcoidosis is a multisystem inflammatory disorder of unknown cause which can affect any organ system. Autosomal dominant lysozyme amyloidosis is a very rare form of hereditary amyloidosis. The Arg64 variant is extraordinarily rare with each family showing a particular pattern of organ involvement, however while Sicca syndrome, gastrointestinal involvement and renal failure are common, lymph node involvement is very rare. In this case report we describe the first reported case of sarcoidosis in association with hereditary lysozyme amyloidosis.*(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 321-324)*

Key words: Amyloidosis, Sarcoidosis

Introduction

Sarcoidosis is a multisystem inflammatory disorder of unknown cause, which is manifested by the presence of non-caseating granulomas in affected organ tissues. It commonly affects young and middle-aged adults and predominantly affects the lungs and intra-thoracic lymph nodes and has a varying course (1). Sarcoidosis can affect any organ system and present in virtually any manner and the formation of granulomas is the fundamental abnormality (2). A common presentation is that of Lofgren's syndrome, however up to 50% of cases diagnosed are asymptomatic at presentation (3). The most common chest radiographic findings at the time of diagnosis are bilateral hilar lymphadenopathy with pulmonary infiltration being a rare pattern (4).

Autosomal dominant lysozyme amyloidosis is a very rare form of hereditary systemic non-neuropathic amyloidosis first described in 1993. It is also called familial visceral amyloidosis (5). In these cases lysozyme is the amyloidogenic precursor protein and the condition is generally a slowly progressive one and there have been 4 reported lysozyme mutations associated with it; W64R/Arg64 (as described in this case reports), I56T, D67H and F57I.The Arg64 variant has only been reported in a few cases since it was first described in 2002 (6,7).

There is no known correlation between the type of mutation and the clinical symptoms. Each family shows a particular pattern of organ involvement, however while Sicca syndrome, gastrointestinal involvement, hepatic involvement and renal failure are common, lymph node involvement has only been described in single cases (5,7).

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Case Report

A 37 year old female presented to the Emergency Department in December 2008 with an episode of minor haemoptysis and central pleuritic chest pain of sudden onset. This had been preceded by flu-like symptoms for three days. She was a smoker with a twenty pack year history. She had a longstanding Sicca syndrome and history of bleeding gastric ulcers. A gastric biopsy several years previously had demonstrated amyloid infiltration.

She had an extensive family history of hereditary lysozyme Arg64 amyloidosis and was diagnosed 8 years ago after her mother died of renal failure and an autopsy had revealed the disease as the underlying pathological cause. Six of her nine siblings were positive for the mutation as were several of her maternal aunts and uncles.

Physical examination did not reveal any significant positive findings. White cell count was 11.2 x 10^9, haemoglobin was 10.3 g/dl and C-reactive protein increased to 117 mg/l (normal < 4mg/l). Other routine blood tests where normal. A chest x-ray and a CT thorax were done.

The chest x-ray showed marked mediastinal and bihilar lymphadenopathy, confirmed on a CT thorax (see Fig.1a/1b). To investigate the haemoptysis a bronchoscopy was performed, and the bronchial mucosa appeared inflamed but no specific cause for the haemoptysis was noted. No bronchoalveolar lavage was performed at the time.

The histology of endobronchial biopsies (Fig. 2a) revealed eosinophilic deposits surrounding the blood vessels which were positive for Congo red staining in keeping with amyloid deposition. (Fig. 2b). Immunohistochemical staining of the amyloid deposits was performed using monospecific antibodies reactive with serum amyloid A protein (SAA), lysomen (LYS) and with kappa and labda immunogloublulin light chains. The amyloid stained with antibodies to lysosyme (LYS) and this staining was abolished by prior absorption of the antibody with the pure antigen.

A mediastinoscopy was subsequently performed to obtain lymph node biopsy. Histology from mediastinal lymph nodes demonstrated non-caseating granuloma in keeping with sarcoidosis. (Fig. 3). Congo red staining was negative.

The patient was treated for a presumed lower respiratory tract infection on the basis of the inflammatory changes on the bronchoscopy together with elevated CRP and symptoms resolved on oral antibiotics (co-amoxiclav) which she received for five days. Cultures from the bronchoscopy grew a moderate growth of Strep. pneumoniae and a scanty growth of Staph. aureus. Cultures for tuberculosis and fungi were negative. Follow-up chest x-rays had fully returned to normal after 6 months without any further therapy. (Fig.4)

Discussion

Lung involvement has never been reported in hereditary lysozyme amyloidosis. An association with

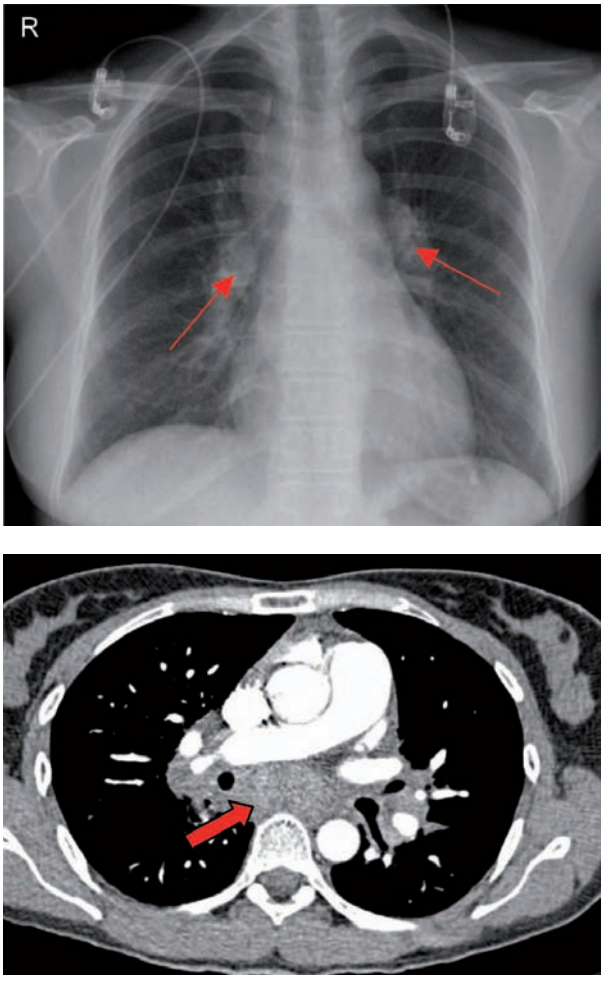

Fig. 1. A) Chest Radiograph at time of initial presentation. Figure 1a demonstrates bi-hilar lymphadenopathy and mediastinal lymphadenopathy in the carinal region. The remainder of the lung fields are clear. B) CT Thorax time of initial presentation. Figure 1b further demonstrates the extent of the mediastinal lymphadenopathy as indicated by the arrows.

sarcoidosis is not known either. There have been previous case reports of sarcoidosis and amyloidosis co-existing, however these cases are very rare (8-10). The occurrence of two rare diseases occurring in the same patient as two distinct disorders in this case highlights the importance of obtaining a tissue diagnosis in the case of unusual organ involvement.

Reports, which describe the association between sarcoidosis and AA amyloidosis, suggest that the sarcoidosis-related inflammatory process may be implicated in the pathogenesis of amyloidosis. A discordance between cellular and humoral immunity may be a contributing factor to the production of clones of amyloid-producing plasma cells (10-13). To date there have been no previous reports of sarcoidosis in association with Autosomal dominant lysozyme amyloidosis and the possibility that two rare diseases have occurred co-incidentally and are unrelated remains a possibility.

Pulmonary involvement is recognised in amyloidosis but mediastinal involvement is rare and should prompt a search for alternative diagnosis as in our case (13). The marked lymphadenopathy resolved spontaneously in our case following a brief course of antibiotics at the time of initial presentation. Resolution of such adenopathy in sarcoidosis is well recognised. No specific cause was identified for

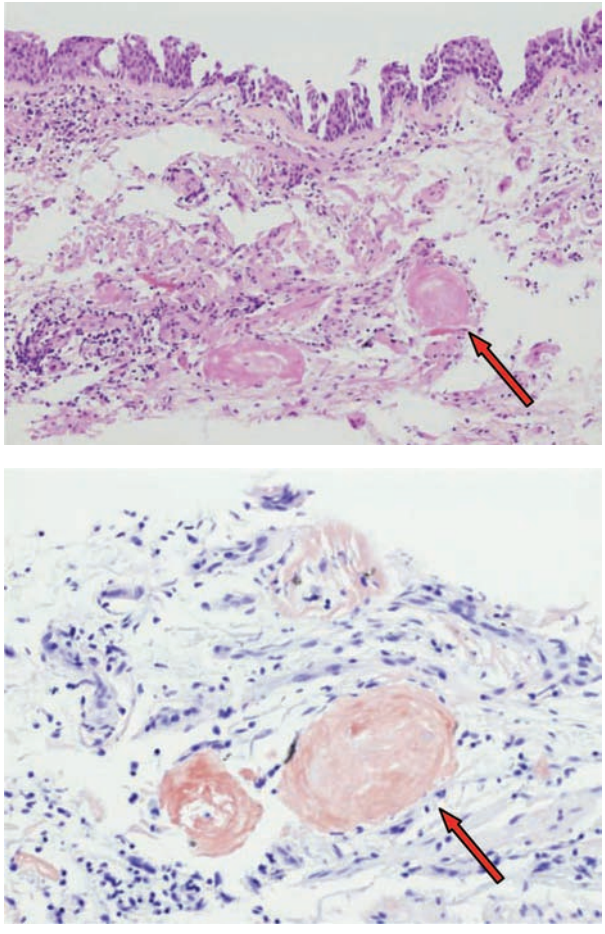

Fig. 2. A) Endobronchial Biopsy. Endobronchial biopsy demonstrating eosinophilic deposits surrounding the blood vessels as indicated by the arrow. B) Congo Red Stain on Endobronchial Biopsy. Endobronchial biopsy staining positive for Congo Red Stain indicating amyloid deposition.

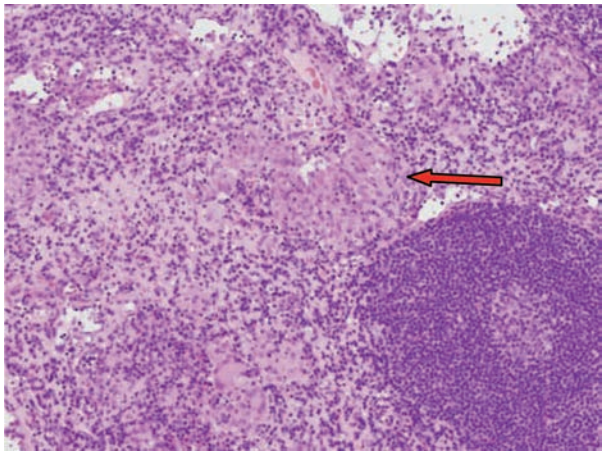

Fig. 3. Mediastinal Lymph Node Biopsy. Mediastinal lymph node biopsy demonstrating non-caseating granuloma consistent with sarcoidosis.

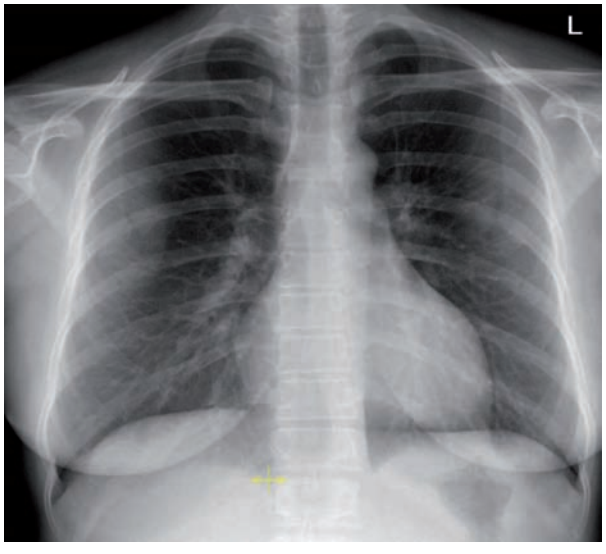

Fig. 4. Follow up Chest Radiograph after 6 months. Repeat Chest Radiograph after 6 months demonstrated complete resolution of lymphadenopathy.

the haemoptysis in our patient though the bronchial mucosa was inflamed It might be justified to hold off on specific treatment and monitor the clinical course in similar cases of sarcoidosis associated with amyloidosis.

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