Apical pulmonary lesions due to Marfan syndrome misdiagnosed as pulmonary tuberculosis

Prem P Gupta, Krishan B Gupta, Joginder S Gulia, Rohtas Yadav, Sanjeev Kumar, Dipti Agarwal

Abstract

A 55-year-old male with chest symptoms and apical pulmonary lesions was diagnosed as a case of sputum smear-negative pulmonary tuberculosis at a peripheral health centre in India on the basis of Revised National Tuberculosis Control Programme Guidelines—he was put on antitubercular chemotherapy. He had no radiological or clinical improvement with antitubercular treatment, so the patient was referred to our institute.

On evaluation, we found that the patient had multisystem involvement with typical features of Marfan syndrome and a suggestive history in other blood-relatives. Upper lobe fibrosis, bronchiectasis, emphysematous changes, multiple blebs, small pneumothorax, pleural fibrosis and pleural thickening were seen which were due to Marfan syndrome rather than tuberculosis. The present case seems to signify the search for alternative aetiologies in similar clinico-radiological presentations if, after 3 months, cultures for Mycobacterium are still negative (despite sputum induction and/or bronchoscopy with biopsies) and the patient is having no radiological improvement.

Case report

A 55-year-old man was diagnosed to have sputum smear-negative pulmonary tuberculosis at a peripheral health centre in India on the basis of clinical history of dyspnoea on exertion, cough with scanty expectoration and fever along with a chest radiograph suggestive of right upper zone lesions (Figure 1A). He was a non-smoker and never consumed alcohol. There was no exposure to agents leading to fibrosis at workplace or at home. He was categorised to WHO category III and antitubercular treatment was started. However, there was no clinical or radiological improvement and he was referred to our institute for further management.

We observed that the patient fulfilled the diagnostic criteria described for the Marfan syndrome. He provided a family history suggestive of similar disorder that he could recall over four generations involving male members—his grandfather, father, paternal uncles (all three affected), himself, along with two brothers and two sons.

The known aetiological associations of upper lobe fibrosis including pneumoconiosis, sarcoidosis, ankylosing spondylitis, extrinsic alveolitis, and other conditions were considered but not found in present case. He had pectus excavatum (Figure 1B), mild scoliosis with winging of left scapula (Figure 1C), reduced extension at the elbows (<170°), pes planus, increased arm span to height ratio >1.05 (armspan was 188 cm and the height was 178 cm) (Figure 1D), reduced upper-
segment to lower-segment ratio, presence of wrist and thumb signs, and joints hypermobility.

He also had malar hypoplasia, enophthalmos, and retrognathia (Figure 1E). His ophthalmic examination revealed ectopia lentis and flat cornea. There was no skin involvement.

Figure 1. [Panel A] Digital chest radiograph showing non-homogenous opacities over right upper zone leading to misdiagnosis to smear-negative pulmonary tuberculosis; [Panel B] The patient had pectus excavatum chest deformity; [Panel C] Mild scoliosis with winging of scapula; [Panel D] An increased arm span/height ratio over 1.05 and; [Panel E] Marfan like facial expression: malar hypoplasia, enophthalmos, and retrognathia

His complete blood count, routine biochemical tests including blood sugar and urinalysis were within normal limits. He had a negative tuberculin test both at 48 and 72 hours. He had no Mycobacterium in sputum when analysed through Ziehl Neelsen stained smear and also on radiometric rapid culture (BACTEC system). The spirometry was suggestive of restrictive pattern with decrease in FVC and FEV\textsubscript{1} but with a normal FEV\textsubscript{1}/FVC ratio.
Computed tomography of thorax showed right apical pulmonary lesions suggestive of fibrosis and traction bronchiectasis along with volume-loss on right side. High-resolution CT thorax study was undertaken. It showed lung parenchymal fibrosis, traction bronchiectasis, areas of parenchymal destruction and honeycombing (Figure 2A), multiple subpleural blebs in apical segments of right upper lobe and paraseptal emphysema (Figure 2B), and a small right pneumothorax.

Bilateral pleural fibrosis and pleural thickening were also seen. Magnetic resonance imaging of lumbosacral spine revealed no dural ectasia (Figure 2C).

Figure 2. [Panel A] HRCT thorax axial scans revealing lung parenchymal fibrosis, traction bronchiectasis, areas of parenchymal destruction and honeycombing; [Panel B] HRCT thorax axial scan showed multiple subpleural blebs in apical segments of right upper lobe and paraseptal emphysema; [Panel C] Magnetic resonance imaging of lumbosacral spine showing no dural ectasia.
He had no abnormality in cardiovascular system apart from mild mitral valve regurgitation (Figure 3).

**Figure 3. Echocardiography of the patient showing mitral valve regurgitation**

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**Final diagnosis:** Marfan syndrome with pleuro-pulmonary manifestations

**Discussion**

Marfan syndrome is a systemic disorder of connective tissue caused by mutation in fibrillin-1 gene (FBN 1 gene) on chromosome 15 (15 q 21.1) that encodes for a glycoprotein called fibrillin-1. Fibrillin-1 is a major building block for 10–12 nm microfibrils forming elastin fibres that are found throughout the body but are particularly abundant in suspensory ligaments of the lens, aorta, and ligaments—understandably the areas worst affected in Marfan syndrome.

Marfan syndrome is a hereditary disorder having an autosomal dominant inheritance. The case where neither of parents has been affected is described occurring due to *de novo* mutation in approximately one out of four of all cases with Marfan syndrome. It has a worldwide distribution with an estimated prevalence of about 1 in 10,000 individuals though some regional variations occur.

The mutation in fibrillin-1 gene (FBN 1 gene) has been suggested to exert a dominant negative effect whereby mutant fibrillin monomers impair the global function of the microfibrils. Many aspects of the disease are caused by altered regulation of transforming growth factor β (TGFβ), a family of cytokines that affect cellular performance, highlighting the potential therapeutic use of TGFβ antagonists. However, it is not recommended to diagnose Marfan syndrome on the basis of
molecular findings as all fibrillin-1 gene mutations do not lead to Marfan syndrome and, moreover, molecular diagnosis is not ubiquitously available.

The diagnosis of this syndrome is made using Marfan Syndrome Diagnostic Criteria also described as ‘Ghent Criteria’ named after the name of the city in Belgium.\(^1\)

Marfan syndrome is a multisystem disorder with manifestations characteristically involving the cardiovascular, skeletal, and ocular systems. The pulmonary involvement is less common and seen in 10% of patients with Marfan syndrome. The incidence of spontaneous pneumothorax in these patients is almost 100 times higher than in normal populations. Widening of the distal airspaces with or without discrete bullae/blebs can predispose to spontaneous pneumothorax, which is found in 4–15% of patients with the disorder.\(^3\)

Mechanical considerations suggest that, similar to a suspended coil spring, the largest alveoli and the greatest stress in the lung occur in the apex—a potential mechanism for localisation of interstitial alterations in Marfan syndrome, idiopathic apical fibrosis, centrilobular emphysema, and ankylosing spondylitis.\(^4\) Moreover, as the pulmonary connective tissues are also weak in Marfan syndrome this could account for emphysema and apical bullae/blebs leading further to recurrent pneumothoraces.

Several reports suggest an increased susceptibility to pulmonary infection and bronchiectasis in patients with Marfan syndrome. Apical pulmonary fibrosis is speculated due to healing of pulmonary lesions in the apical parts of the lungs, the site where mechanical damage is expected to be maximal. Honeycombing in pulmonary parenchyma has also been described in Marfan syndrome.\(^5\)

As the present patient was seen initially at a peripheral health centre in a region where the prevalence of tuberculosis is very high and even the Revised National Tuberculosis Control Programme (RNTCP) provide guidelines to treat smear-negative symptomatic patients with persisting radiological opacities, it was not difficult to see why this patient was prescribed antitubercular treatment.

In regions with high prevalence of tuberculosis, initial therapy with antitubercular drugs in patient with radiological and/or clinical features suggestive of tuberculosis seems to have a rationale as more harm could be caused by withholding treatment than the occasional inappropriate use of antitubercular treatment; however, it require a search for alternative diagnosis if after 3 months, cultures for *Mycobacterium* are still negative (despite sputum induction and/or bronchoscopy with biopsies) and the patient is having no radiological improvement.

The identification of non-tuberculosis aetiologies like pneumoconiosis, allergic bronchopulmonary aspergillosis, sarcoidosis, ankylosing spondylitis, extrinsic alveolitis, cystic fibrosis, cyanotic pseudo-fibrosis, bronchocentric granulomatosis and other conditions leading to upper lobe fibrosis is very important in later scenario. The present case appears to serve as a validation of this point.
Author information: Prem P Gupta, Professor, Respiratory Medicine; Krishan B Gupta, Sr Professor, Respiratory Medicine; Joginder S Gulia, Associate Professor, Otorhinolaryngology; Rohtas Yadav, Sr Professor, Radiodiagnosis; Sanjeev Kumar, Ex-Resident, Respiratory Medicine; Dipti Agarwal, Assistant Professor, Physiology; Postgraduate Institute of Medical Sciences, University of Health Sciences, Rohtak, India

Correspondence: Professor Prem Parkash Gupta, 9J/17, Medical Enclave, PGIMS, Rohtak, India, PIN-124001. Email: gparkas@yahoo.co.in

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