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Pictorial Review

Pulmonary complications of cystic fibrosis

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The life expectancy of patients with cystic fibrosis (CF) has steadily increased over recent decades with a corresponding increase in the frequency of complications of the disease. Radiologists are increasingly involved with managing and identifying the pulmonary complications of CF. This article reviews the common manifestations of CF lung disease as well as updating radiologists with a number of less well-known complications of the condition. Early and accurate detection of the pulmonary effects of CF are increasingly important to prevent irreversible lung damage and give patients the greatest possibility of benefiting from the new therapies becoming available, which correct the underlying defect causing CF.

Introduction

Cystic fibrosis (CF) is an incurable autosomal recessive disease that affects approximately 1 in 2500 live births among caucasians.[1] CF is caused by a mutation in the gene coding for the CF transmembrane conductance regulator (CFTR) protein, which is expressed in many different organs and acts primarily as a chloride channel.[1] CFTR dysfunction in the lung leads to dehydration of the airway surface liquid, reduced mucociliary clearance, and a cycle of pulmonary infection and inflammation. In the majority of cases, CF leads to progressive respiratory failure and premature death.

Improvements in CF care have led to an increase in median life expectancy to 37 years of age and children born with CF in this century are predicted to live beyond the age of 50 years.[2] As a result, the CF population is increasing and the presence of pulmonary complications is likely to become more commonplace. Early recognition and appropriate management of these complications is essential for the continued improvement in survival of patients with CF. Additionally, new drugs targeting the underlying CFTR defect are becoming available, which raise the possibility of slowing disease progression.[3,4] Radiologists have a vital role to play in the management of CF to help allow patients to benefit from these new personalized medicines. Imaging studies have the further benefit of allowing clinicians to target both diagnostic and therapeutic interventions most effectively.

In this article, we review the full spectrum of pulmonary manifestations of CF from common features, such as bronchiectasis and pneumothorax, through to lesser-known conditions, such as the “Cepacia syndrome” and idiopathic progressive lung collapse. The role of computed tomography (CT) and chest radiography in management will also be discussed.

Bronchiectasis and small airway disease

Bronchiectasis refers to abnormal, permanently dilated airways and is the hallmark of CF lung disease. A cycle of recurrent infection and inflammation complicates the development of bronchiectasis, which typically affects the upper lobes in CF, as shown in Fig 1. Recent data have

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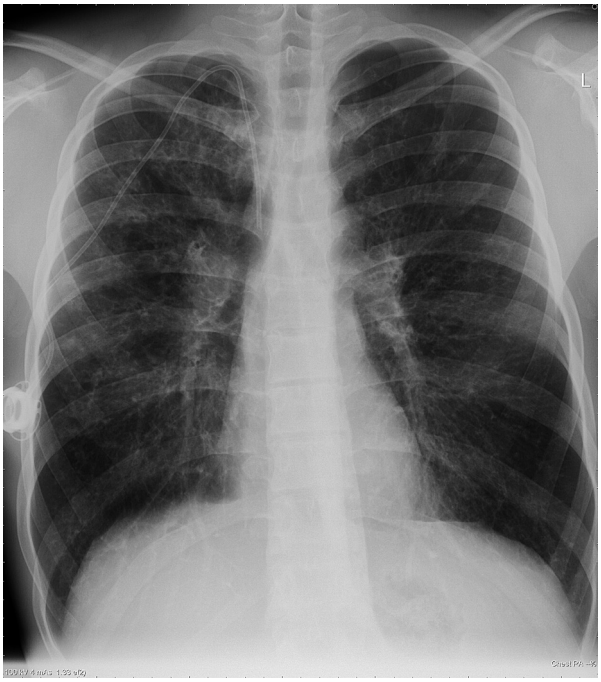

Figure 1 Typical chest radiograph of a patient with CF demonstrating bilateral generalized bronchial wall thickening, tram-lining indicating bronchiectasis, and the presence of a TIVAD in the right hemi-thorax.

shown a significant correlation between the extent of bronchiectasis and reduced survival amongst patients with CF.[5]

Bronchiectasis is often sub-divided into cylindrical, varicose, and cystic bronchiectasis based on the pathological or radiographic findings. Signs of bronchiectasis on the chest radiograph include tram-lining and cystic lesions containing air–fluid levels. At CT, additional features of bronchiectasis include the "signet ring sign" where the internal bronchial diameter is larger than its corresponding artery; bronchial wall thickening; the presence of visible bronchi within 1 cm of the costal pleura or touching the mediastinal pleura[6] and a lack of normal tapering of the bronchi.[7] Fig 3 shows an example of the CT characteristics of severe bronchiectasis.

Due to the near-universal presence of bronchiectasis in older CF patients, it can be difficult to differentiate co-existing pulmonary abnormalities. Mucus plugging and the tree-in-bud appearance are commonly associated with bronchiectasis but are also features of allergic bronchopulmonary aspergillosis (ABPA) and infection with non-tuberculous mycobacteria (NTM). A high degree of suspicion for these conditions is required when reporting thoracic images from patients with CF.

In addition to causing bronchiectasis, CF also affects the small airways. Obstruction of the small airways with mucus typically causes peripheral air-trapping within the lung. This is seen as mosaicism on CT images. Studies in infants diagnosed with CF through newborn screening have shown that small airways disease is frequently detectable by CT even in the absence of clinical evidence of lung disease.[8]

Chronic endobronchial colonization

The lungs of CF patients are frequently colonized with a variety of characteristic organisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Burkholderia cepacia* complex.[1] It is impossible to differentiate these organisms based on radiological studies. *P. aeruginosa* becomes the dominant respiratory pathogen by the age of 18 years old,[9] and can be particularly difficult to eradicate once it has established biofilms within the lung. *B. cepacia* complex infection is often associated with accelerated lung function decline and has been responsible for devastating outbreaks within CF units.[10] The combination of *B. cepacia* bacteraemia and necrotizing pneumonia is known as the "Cepacia syndrome".[11] This is a dreaded and poorly understood condition associated with very high mortality. The radiological appearances of the Cepacia syndrome have not been described in detail in the literature. In the authors' experience, the chest radiograph in the Cepacia syndrome is characterized by progressive, bilateral, and diffuse nodular consolidation as shown in Fig 2.

Aspergillus-related lung disease

Aspergillus fumigatus is a fungus that is frequently isolated from the airways of patients with CF. The spectrum of *Aspergillus*-related lung disease includes allergic bronchopulmonary aspergillosis (ABPA), aspergilloma, and chronic necrotizing aspergillosis (also known as semi-invasive aspergillosis). Studies have indicated that 2–10% of patients with CF have ABPA.[12,13] Despite this high prevalence, ABPA can be very difficult to diagnose radiologically due to considerable overlap with the typical bronchiectasis and mucous plugging seen in most CF patients. Fig 3 illustrates a characteristic thoracic CT image from a patient with CF and ABPA.

The presence of central varicose bronchiectasis in CF may suggest a diagnosis of ABPA as an upper lobe predominance is more characteristic of CF itself.[14] Another feature that may help identify ABPA is the presence of high-attenuation mucous plugging using the paraspinal muscles as a reference (i.e., the mucous is higher density than the paraspinal muscles).[15] However, mimics of high-density mucous, such as haemorrhage and aspiration of radiodense material, should be considered in the differential.

Aspergilloma is an uncommon complication of CF, which is more commonly seen in patients with cavitary lung disease, such as those with previous tuberculosis or sarcoidosis.[16] Aspergillomas develop when *Aspergillus* spp. colonizes a pre-existing cavity. The initial radiological findings are of a cavity with thickened and irregular walls, which progresses into a fungal ball. The finding on CT of a solid lesion surrounded by air within a cavity, the air-crescent sign, is characteristic of an aspergilloma.[17]

Chronic necrotizing aspergillosis (also known as semi-invasive aspergillosis) is a further manifestation of *Aspergillus*-related lung disease, which usually affects patients with a mild degree of immunocompromise but can