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Radiological Features of Cystic Fibrosis

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1. Introduction

With patients with cystic fibrosis (CF) living longer and reaching adulthood, conditions before not frequently encountered now play a larger role in the spectrum of CF related symptoms and complaints which continue to challenge clinicians in both outpatient and acute settings. It is in this context that the radiologist and different radiological imaging modalities can aid the clinician in order to establish an accurate diagnosis and steer appropriate treatment. In this chapter, we present a comprehensive review of common and not so common radiological features of both pulmonary and extra-pulmonary manifestations of CF.

With a huge variety of scans available at one's finger tips, or to be more precise, at the end of an electronic request form, it is vital that clinicians are familiar with the different existing imaging modalities, what information to expect from each one of them and the most appropriate scan to request to answer the specific clinical question, taking into consideration the patient's characteristics and needs- in other words, how to make best use of their Radiology Department. In this way, the required information can be obtained most rapidly and efficiently by using the correct test or tests performed in the correct order.

Chest radiographs are usually the exam of choice for the initial assessment and sequential follow-up of pulmonary disease in adult CF patients. It employs a very small dose of ionizing radiation and can be of great value in the detection of new infiltrates in acute infective exacerbations or diagnosing complications such as a pneumothorax. Plain radiography is also much used in patients complaining of acute abdominal pain, although findings can be non-specific and patients may require further imaging to characterize the abdominal pathology. An abdominal radiograph delivers a higher radiation dose and therefore should not be performed unnecessarily. Barium studies are not commonly used and it is believed that barium may cause obstruction in CF patients due to the thick intraluminal secretions. On the other hand, hypertonic oral contrast is used in some patients for the treatment of distal intestinal obstructive disease (DIOS). Air and contrast enemas continue to be used for the reduction of intussusception.

Ultrasound imaging does not carry any radiation hazard and has the added advantage of being relatively cheap and readily available. It can be useful in the chest in the assessment of pleural effusion or collection, but is most valuable for the evaluation of abdominal organs (e.g. liver, gallbladder, kidneys, spleen) and in patients with acute abdominal pain or suspected bowel pathology, such as DIOS, appendicitis or intussusception. The disadvantage of this modality is that it is completely operator dependent and sometimes images obtained are suboptimal due to patient related factors, such as obesity or overlying distended bowel gas.

Cross-sectional imaging techniques include computed tomography (CT) and magnetic resonance imaging (MRI). CT delivers high radiation – a chest CT is equivalent to over 200 chest radiographs in terms of radiation dose – and this needs to be considered, especially when dealing with young individuals such as CF patients. Chest CT imaging will be superior to plain radiograph in the assessment of initial or mild lung disease, in cases of poor clinical response when complications are suspected such as atypical mycobacteria infection and in pre-transplant evaluation. With the modern multi-detector CT scanners, the whole chest can be scanned in 10 to 20 seconds during a single breath-hold and therefore the exam is usually well tolerated even by the most breathless patient.

Much confusion is still seen when physicians request lung high resolution computed tomography (HRCT). The term high resolution implies a better quality scan, but in reality refers to 12 to 20 incremental ultra-thin 1 or 1.5mm thick image slices of the lung that are obtained at evenly spaced intervals through the chest and is indicated for the evaluation of diffuse interstitial or bronchial disease. It does not scan the whole volume of the chest and therefore is not appropriate for the assessment of lung nodules, malignancy, mediastinal lymphadenopathy or pleural disease, which are only fully imaged with a full lung volume spiral scan. HRCT increases the radiation dose delivered and should be limited to specific patients.

Abdominal CT imaging can be of great aid in the patient with acute abdominal pain in which the initial ultrasound scan was non-diagnostic. It is the scan of choice for the evaluation of the pancreas and therefore pancreatitis. MRI continues to be very expensive and not as accessible as CT. Its main indication is the assessment of hepatobiliary disease and cholangiopancreatography (MRCP). It is, as ultrasound, radiation free, but scans are sometimes prolonged and not always tolerated by those who are claustrophobic.

2. Pre-natal imaging

The use of radiological imaging in the aid of pre-natal diagnosis of CF and post-natal complications is well documented. Foetuses with CF have been associated with hyperechogenic foetal bowel detected by ultrasound during the second and third trimesters of pregnancy. Bowel is considered hyperechogenic if its echogenicity (brightness) is equal to or greater than that of the adjacent iliac bone (Al-Kouatly et al., 2001). Although this can be a normal finding, identified in 0.1-1.8% of foetuses, the risk of diagnosis of CF is greater if associated with bowel dilatation or the absence of an identifiable gallbladder (Hertzberg et al., 1996; Scotet et al., 2002).

3. The nose and sinuses

The upper airways are very frequently affected in CF, with over 75% of patients reporting some kind of sinus or nasal symptom such as nasal or sinus obstruction, nasal discharge, post-nasal drip and facial pain (Cepero et al., 1987). Sinusitis should be considered in all CF patients with nasal symptoms. A common cold is often suspected and can occur in CF patients, but when symptoms affect the CF patient only and no other member of the family, sinusitis is likely to be the cause. There is poor correlation between the severity of symptoms and imaging findings (Sakano et al., 2007). Indications for CT imaging include evaluation of the severity of the disease and pre-operative evaluation.

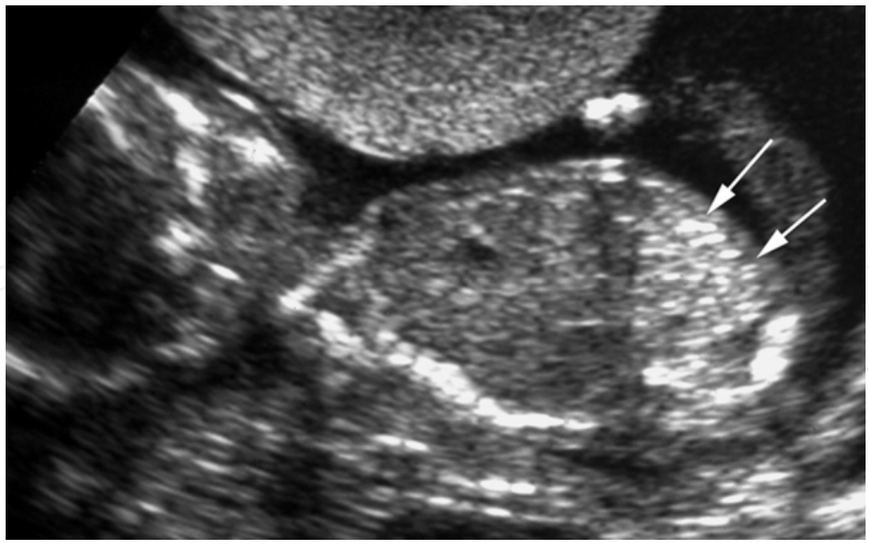


Fig. 1. Sagittal ultrasound view of a foetus with hyperechogenic bowel (arrows).

Imaging will reveal abnormalities even if not clinically manifested, such as small hypoplasic sinuses - often adult CF patients have no frontal sinus cavity - thickened nasal turbinates and thickened mucosa of the sinuses. Chronic inflammation and thickening of the mucosa of the nasal cavities and sinuses result in formation of inflammatory polyps and the accumulation of mucus in obstructed sinuses. Many patients undergo surgery to remove polyps and enlarge the outlet of obstructed sinuses, but relief tends to be temporary due to the recurrent nature of the disease.

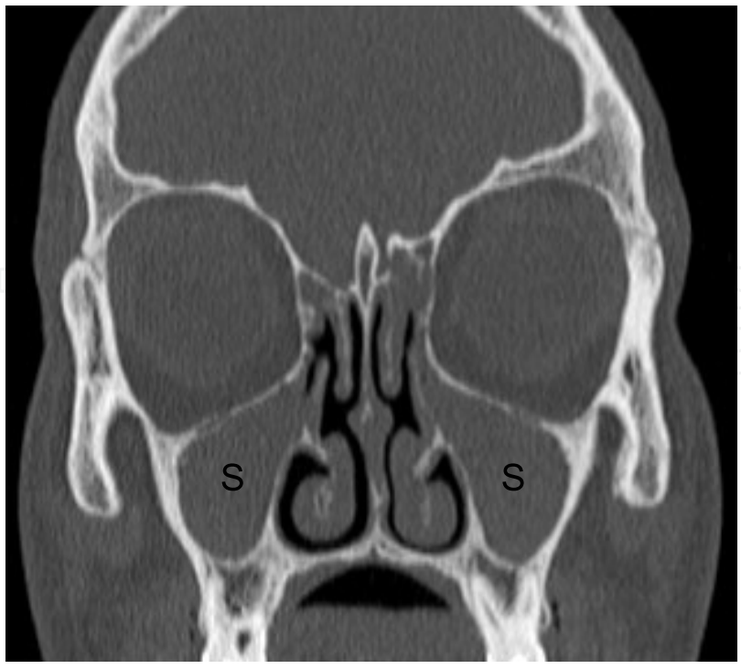


Fig. 2. Coronal CT image at the level of the nasal cavities showing complete opacification of the maxillary sinuses (S) in a case of recurrent sinusitis.

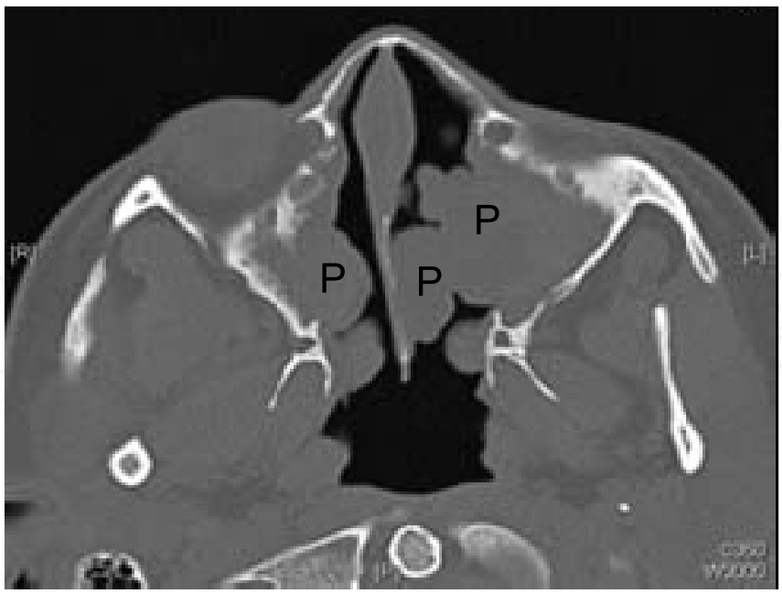


Fig. 3. Axial CT image at the level of the nasal cavities showing opacification of the maxillary sinuses and rounded densities in the nasal cavities (P) in a severe case of nasal polyposis.

4. Pulmonary manifestations

4.1 Bronchiectasis

Repeated chest infections are the hallmark of CF. These are usually associated with *Pseudomonas aeruginosa* or *Staphylococcus aureus* infection and clinically manifested by increased cough, sputum production, breathlessness and fatigue (Marshall, 2004). Classically CF initially affects the upper lobes, but severe cases will show diffuse bilateral disease affecting all of the lungs. Chest radiographs will reveal degrees of hyperinflation, dilated bronchi with thickened walls (cylindrical or cystic bronchiectasis) associated with well defined areas of air space opacification, as in lobar pneumonias, or nodules due to mucoid impaction, atelectasis, cavities and hilar lymphadenopathy. Pneumothorax is also frequently seen and can be recurrent (Hansell et al., 2005).

Chest radiographs are generally sufficient for regular clinical management and usually there is little visible radiographic change associated with clinical exacerbations. On the other hand it is now well established that CT imaging can give valuable information for the monitoring of disease progression and assessment of treatment response. Studies have shown a close relationship between HRCT findings and clinical and pulmonary functional evaluation of patients (Hansell et al., 2005). More severe cases may also show signs of right heart failure with pulmonary arterial hypertension and cor pulmonale.

4.2 Allergic bronchopulmonary aspergillosis

In patients with increased wheeze and asthma-type symptoms, and chest symptoms failing to improve despite antibiotic treatment, allergic bronchopulmonary aspergillosis (ABPA) should be suspected. Imaging can reveal transient and recurring areas of consolidation on

chest radiographs, often due to atelectasis from mucoid plugging and bronchial obstruction, which subsequently improve after steroid therapy. Evaluation of ABPA in patients with CF is limited as imaging findings that are used to establish the diagnosis of ABPA in patients with asthma are common in patients with CF (Hansell et al., 2005).

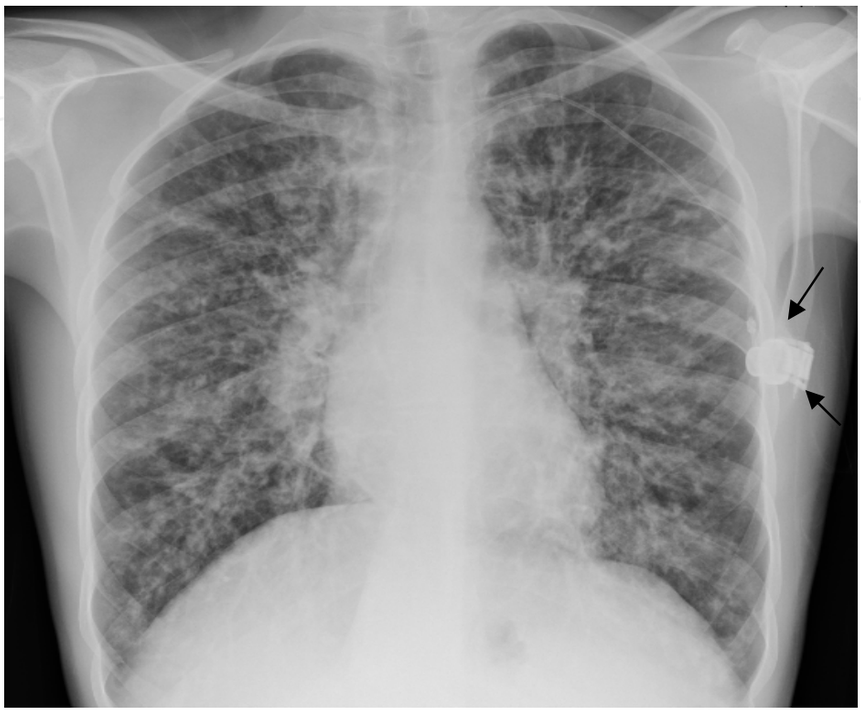
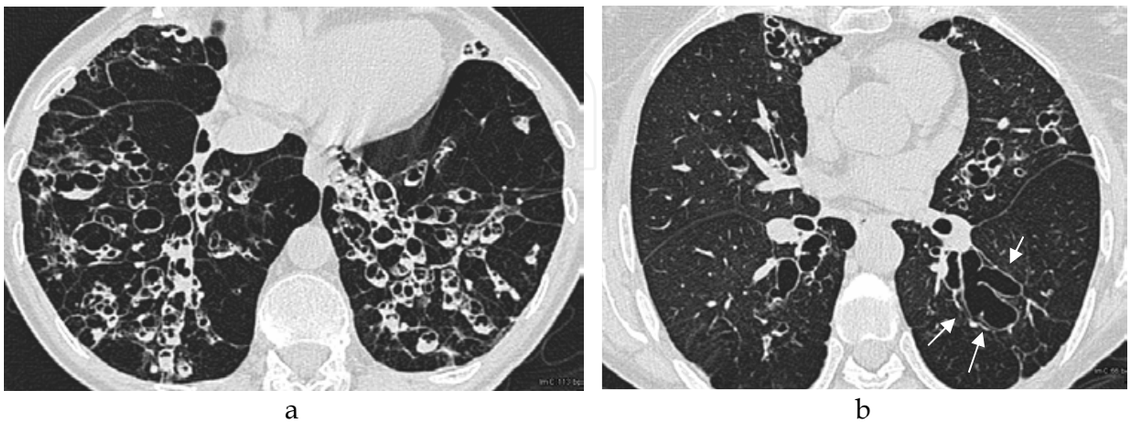


Fig. 4. Chest radiograph of a CF patient with hyperinflated lungs and severe bilateral and diffuse bronchiectasis seen as ring shadows and tram-track opacities that converge to the lung hila, which correspond to dilated thick walled bronchi. Note the port-a-cath device in the left chest wall and catheter in the distal superior vena cava used for the administration of intravenous antibiotics (arrows).



a b

Fig. 5. Lung axial CT images demonstrating classic rounded cystic bronchiectasis throughout both lungs (fig. 5a) and varicose type bronchiectasis (arrows) (fig. 5b). The bronchi are dilated, thick walled and some contain mucus.



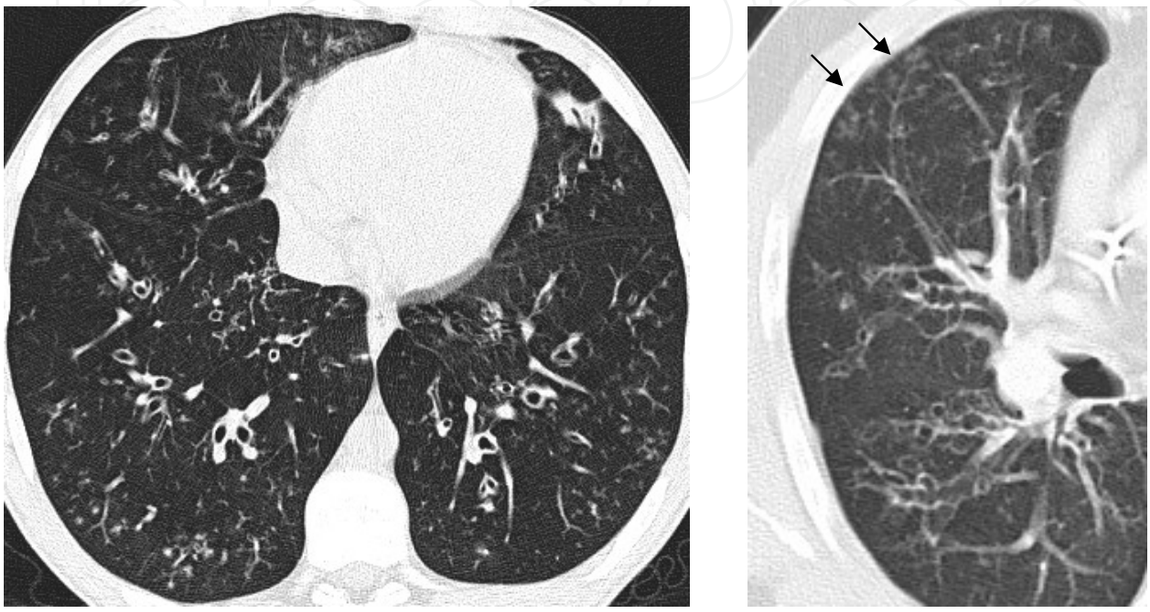
Fig. 6. Chest radiograph of CF patient with ABPA. There are bilateral widespread bronchiectasis, but the upper lobe bronchi are filled with mucus which was a new feature in comparison to previous radiographs. Clinical evaluation and elevated serum IgE and positive serum precipitins to Aspergillus confirmed the diagnosis of ABPA which improved with steroid treatment.

4.3 Non-tuberculous mycobacteria

Non-tuberculous (atypical) mycobacteria (NTBM) are increasingly isolated from CF patient's airways, although not always considered clinically significant. It is estimated that the lungs of 10% of adult CF patients are infected with NTBM. These bacteria consist of a range of organisms that differ in their virulence. Common varieties that infect CF lungs include *Mycobacterium fortuitum*, *Mycobacterium kansasii*, *Mycobacterium xenopi*, *Mycobacterium avium intracellulare* and *Mycobacterium cheloni* (*Mycobacteria abscessus*). *Mycobacterium abscessus* is especially important due to its high virulence, resistance to treatment and being one of the relative contra-indications for lung transplant.

Given the fact that chest symptoms in CF are common principally due to bronchiectatic lungs that are chronically infected with CF bacteria (mainly *P. aeruginosa*), determining the pathogenicity of NTBM is often challenging. In addition, the treatment of these bacteria is difficult with high rates of re-infection and recurrence, and long duration of treatment (12 to 18 months) that uses a combination of antibiotics often containing rifampicin, which is known to induce liver enzymes and therefore interferes with many CF drugs (antibiotics, insulin and contraceptive agents). For all these reasons, CF physicians seek confirmation of the pathogenesis of atypical mycobacteria prior to treatment. Mycobacteria is considered to play a role if the same species grows in the sputum on more than one occasion and symptoms persist after treating *P. aeruginosa*. Chest radiology using HRCT scans is therefore called upon to increase the degree of diagnostic certainty.

HRCT signs are often subtle and include one or more of the following: small centrilobular nodules and nodular changes in the periphery of the lungs, tree-in-bud opacities, new lung abscesses (Field et al., 2004; Olivier et al., 2003). Presence of one of more of these radiological signs together with chest and systemic symptoms that do not respond to anti-pseudomonas antibiotics would justify the start of treatment. Repeating the HRCT scan in 3 to 4 months after commencing the treatment is useful in showing radiological response.



a b

Fig. 7. Lung axial CT image showing bronchiectasis, ground-glass and tree-in-bud opacities in both lung bases associated with non-tuberculous mycobacteria infection (fig. 7a). Close-up of tree-in-bud in the right middle lobe (arrows) (fig. 7b).

5. Abdominal manifestations

5.1 The pancreas

Autolysis of the pancreas due to viscous pancreatic enzymes and obstructed pancreatic ducts is known to start during intra-uterine life (Sturgess, 1984). This leads to fibrosis, atrophy and replacement of the pancreas by fat (Sequeiros et al., 2010) which clinically results in exocrine pancreatic insufficiency and malabsorption in up to 90% of patients (Rosenstein et al., 1998).

Pancreatitis can be the first manifestation of CF and is a rare complication among patients with CF with a reported incidence of approximately 1.24%. It mainly occurs during adolescence and young adulthood and is much more common among patients with preserved pancreatic tissue (De Boeck et al., 2005) and therefore considered pancreatic sufficient (10.3% of cases), but it can also occur among patients with pancreatic insufficiency (0.5% of cases). Pancreatitis is an important differential diagnosis that should be considered in the context of a CF patient presenting with acute abdominal pain.

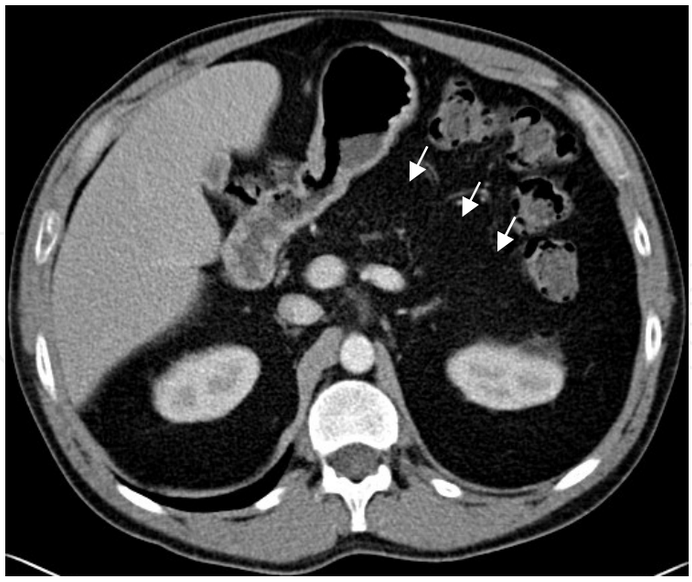


Fig. 8. Abdominal axial CT image of a CF patient at the level of the splenic vein showing the pancreas completely substituted by fat (arrows).

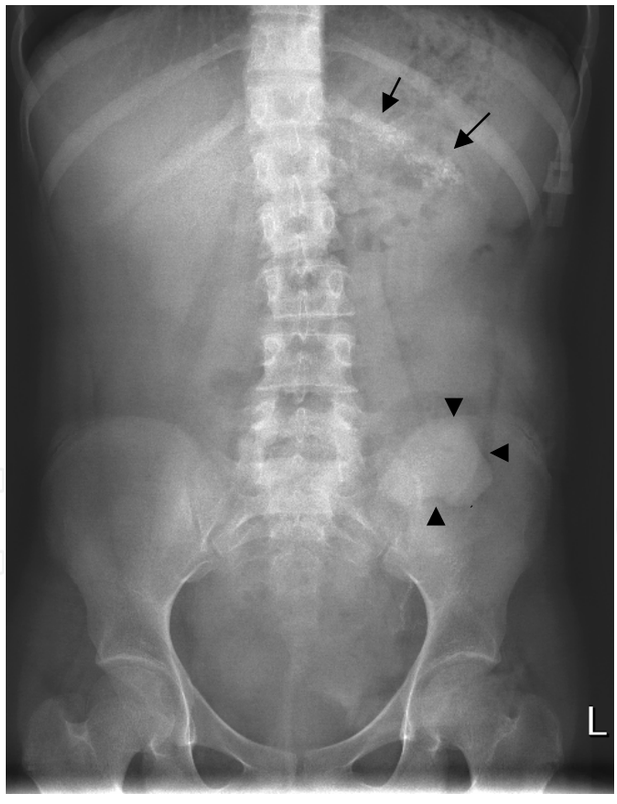


Fig. 9. Radiograph of the abdomen shows typical pancreatic calcifications secondary to CF related chronic pancreatitis in the left upper quadrant adjacent to the spine (arrows). Note the shadow in the left iliac fossa representing an ileostomy due to surgical management of previous bowel obstruction (arrow heads).

Pancreatic cysts are a relatively common finding in CF and can vary in size and number. Rarely, cysts can replace the entire pancreas in a condition called pancreatic cystosis, which can cause pain through mass effect (van Rijn et al., 2007). In such cases, surgical resection of the pancreas may be necessary.

5.2 Hepatobiliary disease

Hepatobiliary manifestations are common in CF and include fatty infiltration of the liver (steatosis), focal biliary cirrhosis with portal hypertension, microgallbladder and gallstones. Patients are more frequently asymptomatic, but liver disease is the second most common cause of death in CF (2.2% of deaths) and approximately 6-8% of individuals with CF have potentially fatal liver disease that requires liver transplantation (Genyk et al., 2001). It is thought to be a consequence of thickened secretions and abnormal bile flow within the liver causing bile duct obstruction. Signs of liver disease usually develop before or at puberty (Feigelson et al., 1993).



Fig. 10. Abdominal axial CT image at the level of the pancreas showing a small cyst in the tail of the pancreas (arrows).

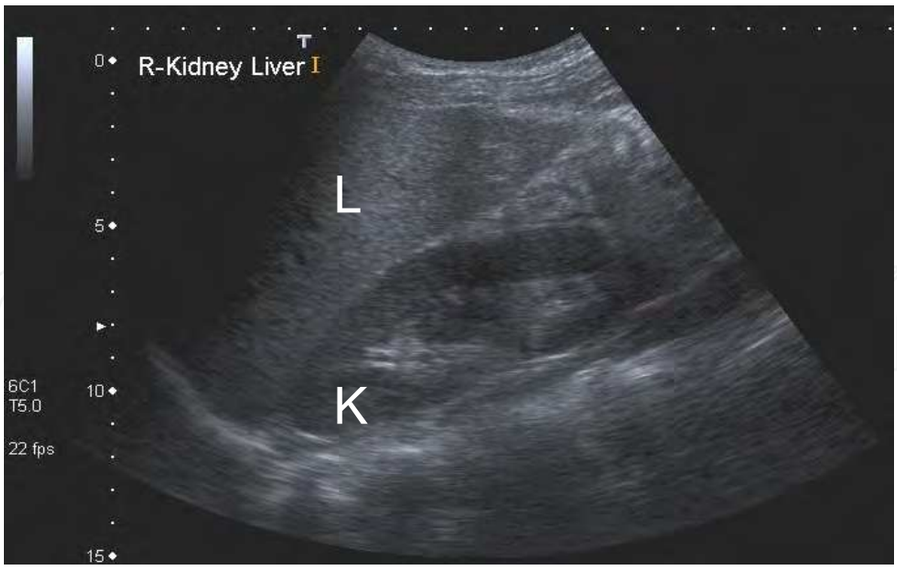


Fig. 11. Abdominal ultrasound image demonstrating echogenic (bright) liver due to diffuse fatty infiltration (L). A normal liver would look as dark as the adjacent right kidney (K).

Biliary calculi are present in 4-12% of patients. These are most commonly composed of cholesterol and thought to be a consequence of pancreatic insufficiency and the production of thick lithogenic bile (Agrons et al., 1996).

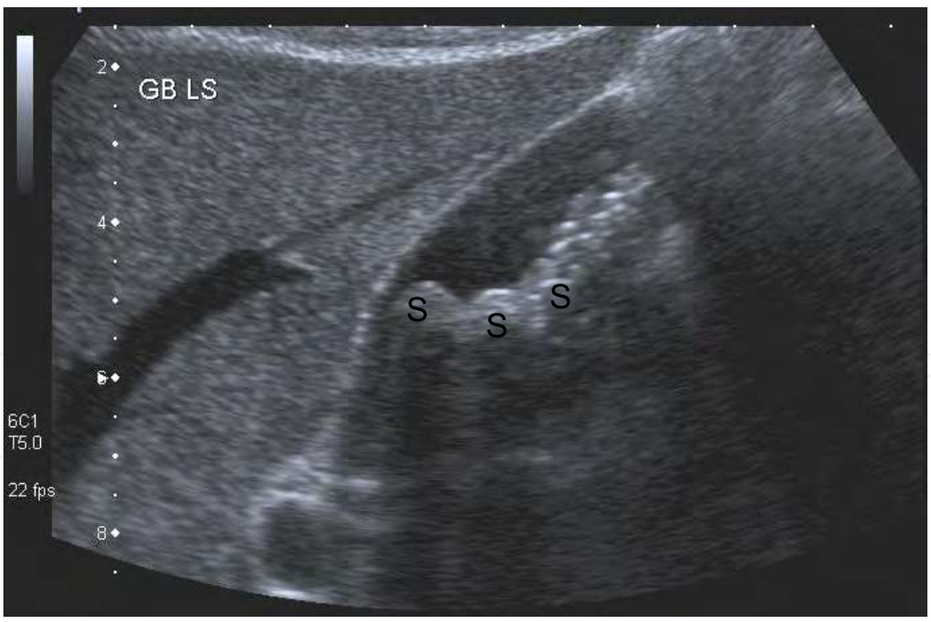


Fig. 12. Abdominal ultrasound image of a thin walled, non complicated gallbladder containing several stones (S).

Splenomegaly as a result of portal hypertension can be seen as massive enlargement of the spleen causing pain, dyspnoea and signs of hypersplenism and sometimes complicated with splenic infarcts or subcapsular haematomas.

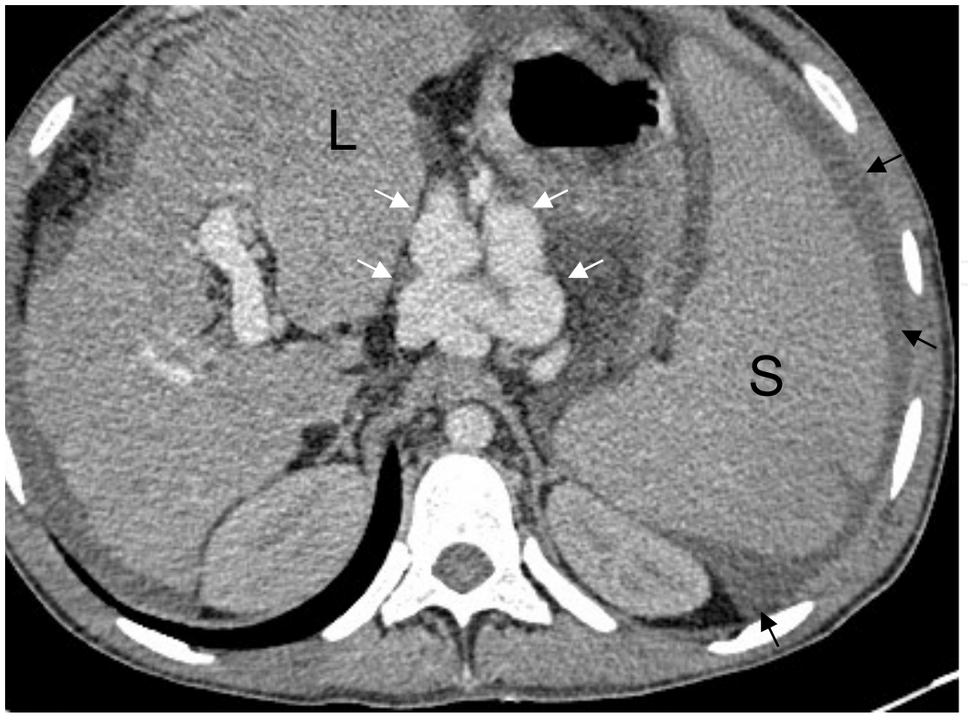


Fig. 13. Axial CT image of the abdomen showing a lobulated, macronodular cirrhotic liver (L), ascites (black arrows), splenomegaly (S) and varices (white arrows) due to portal hypertension.

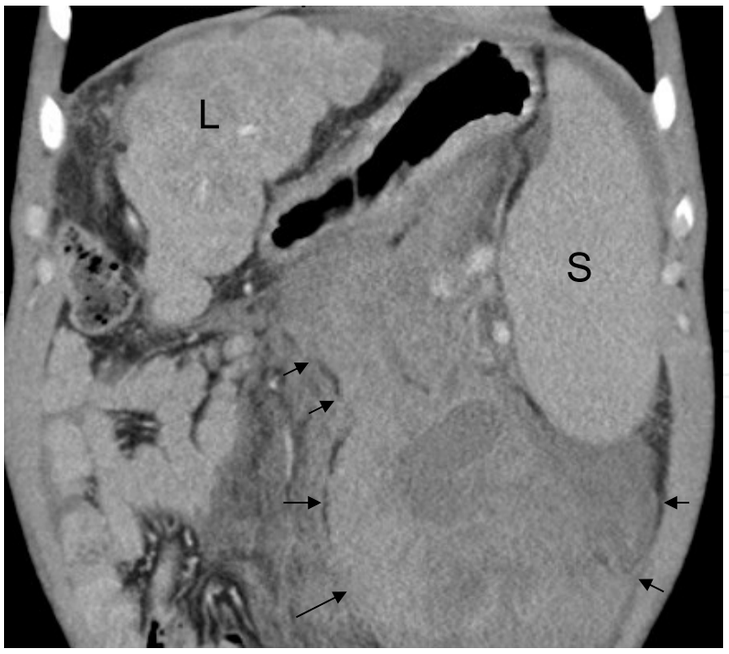


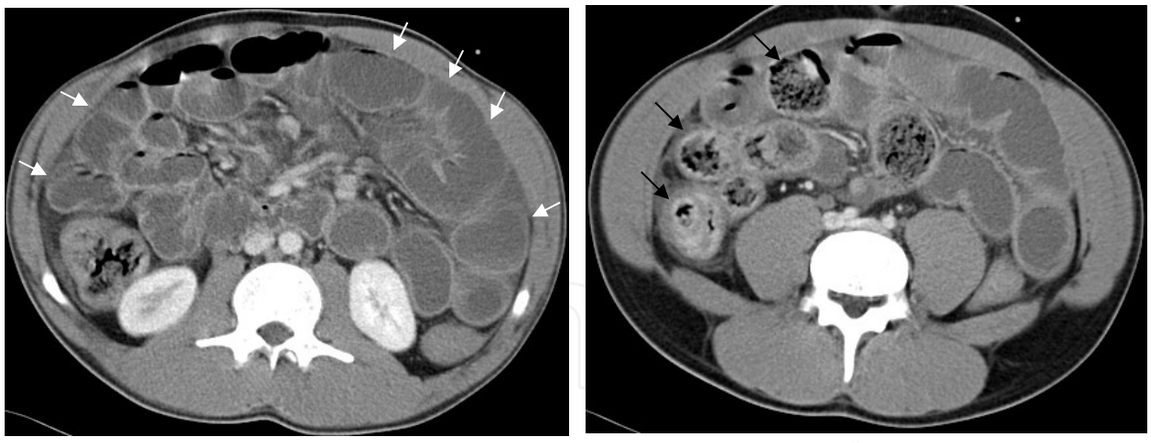
Fig. 14. Coronal CT image of the abdomen showing a large fatal spontaneous splenic haematoma (arrows) in a CF patient with severe portal hypertension and splenomegaly (S). Note the lobulated macronodular cirrhotic liver (L).

5.3 Meconium ileus

Bowel blockage of the newborn or meconium ileus is seen in 15-20% of neonates with CF and 25% of infants with meconium ileus prove to have CF (Hen et al., 1980). Meconium is composed of materials swallowed by the foetus during pregnancy, such as intestinal epithelial cells, mucus and amniotic fluid. In CF, mucus glands of the small intestine produce thick secretions and therefore the meconium sometimes becomes abnormally sticky and inspissated, causing a mechanical obstruction within the segment of the ileum. Classically, above the obstruction the bowel is greatly distended with fluid content, while below this level, the distal ileum and colon are collapsed. Soon after birth, usually in 24 to 48 hours, the newborn will present with abdominal distension and vomiting.

5.4 Distal intestinal obstructive syndrome

Distal intestinal obstructive syndrome or DIOS is the equivalent of meconium ileus in adults. It affects up to 15% of CF patients as a result of thickened intraluminal secretions, undigested food secondary to exocrine pancreatic insufficiency and impaired bowel motility (Speck & Charles, 2008). Patients complain of recurrent episodes of abdominal pain and distension, nausea and vomiting. Ultrasound imaging will reveal ditlated loops of small bowel containing "swirling" intraluminal echogenic material without forward propulsion motion in keeping with obstruction. Abdominal radiograph and CT show dilated small bowel loops with fluid levels and faecal material within the small bowel ("small bowel faeces").



a b

Fig. 15. Axial CT scan of the abdomen of CF patient with acute abdominal obstruction after weeks of stopping to take exocrine pancreatic enzymes. Images show dilated loops of small bowel containing fluid (white arrows) (fig. 14a) and faecal material within the distal ileum in the right iliac fossa (black arrows) (fig. 14 b) - "small bowel faeces". Surgical intervention was necessary and revealed an obstructed ileum with inspissated secretions and undigested food.



Fig. 16. CF patient with diagnosed DIOS managed clinically with hydration and oral hypertonic solution. Abdominal radiograph shows dilated loops of small bowel filled with ingested oral Gastrografin contrast agent.



Fig. 17. Abdominal radiograph showing a pre-term infant with meconium ileus who was subsequently diagnosed with CF. He presented with marked abdominal distension at 3 days of life. There are markedly dilated loops of small bowel and no air is seen in the colon or rectum.



Fig. 18. Contrast enema in a neonate infant with meconium ileus. As is typical of the condition, the colon is small secondary to distal ileal obstruction and there is also small bowel dilatation. There are filling defects in the colon and terminal ileum representing meconium pellets (arrows).

5.5 Intussusception

Intussusception is more common in CF patients than in the general population and is seen in 1% of paediatric patients. It is rare in adulthood and comprises 5% of all intussusceptions and 1% of bowel obstructions (Nash et al., 2011). Intussusception can cause similar symptoms of acute abdominal pain as DIOS and is an important differential diagnosis that should be considered in acute obstruction as it may require surgical intervention, whilst DIOS is often managed non-surgically with hydration and oral hypertonic solutions (Speck & Charles, 2008). Intraluminal inspissated mucus, undigested food or enlarged lymphoid follicles can initiate an intussusception. Imaging reveals a bowel-within-bowel configuration which is pathognomonic of the condition (Gayer et al., 1998).



Fig. 19. Axial CT scan of the abdomen at the level of the iliac bones. Imaging reveals rounded structure with classic "bowel-within-bowel" configuration in the right iliac fossa in keeping with intussusception (arrows).

5.6 Fibrosing colonopathy

Fibrosing colonopathy is characterised clinically by right iliac fossa pain, where a thickened loop of bowel can sometimes be felt on clinical examination. It has been reported in association with children prescribed high strength pancreatic enzyme supplements, although the aetiology is not completely clear. Imaging has a limited role demonstrating non-specific large bowel wall thickening and final diagnosis is usually obtained with histology, which depicts submucosal fibrosis (Stacey et al., 1997).

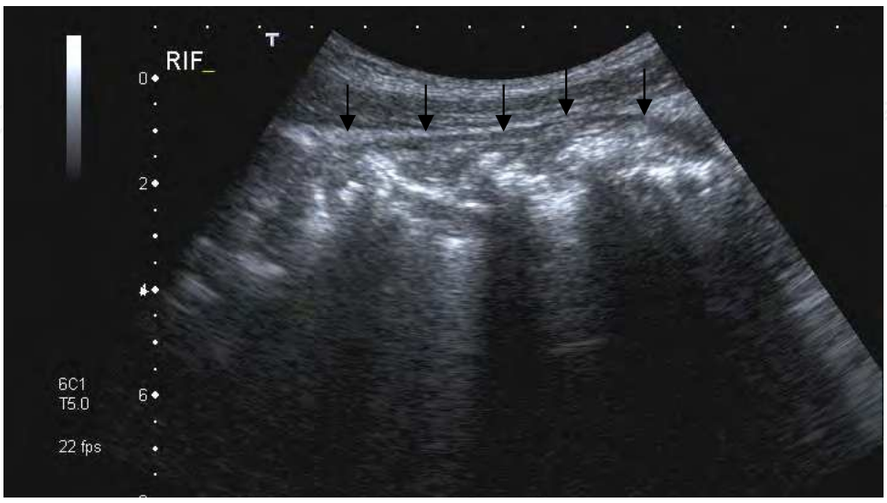


Fig. 20. Ultrasound image of the right iliac fossa showing a thick walled ascending colon (arrows) in a symptomatic CF patient.

5.7 Appendicitis

Appendicitis is relatively uncommon in CF, with a reported incidence of 1-2% compared to 7% in the general population. The cause of this is thought to be a protective effect of inspissated secretions against appendicitis (McCarthy et al., 1984). Although uncommon, it should always be considered in acute abdominal pain as a delayed diagnosis could result in subsequent rupture and abscess formation. Imaging features are similar to those seen in the general population.

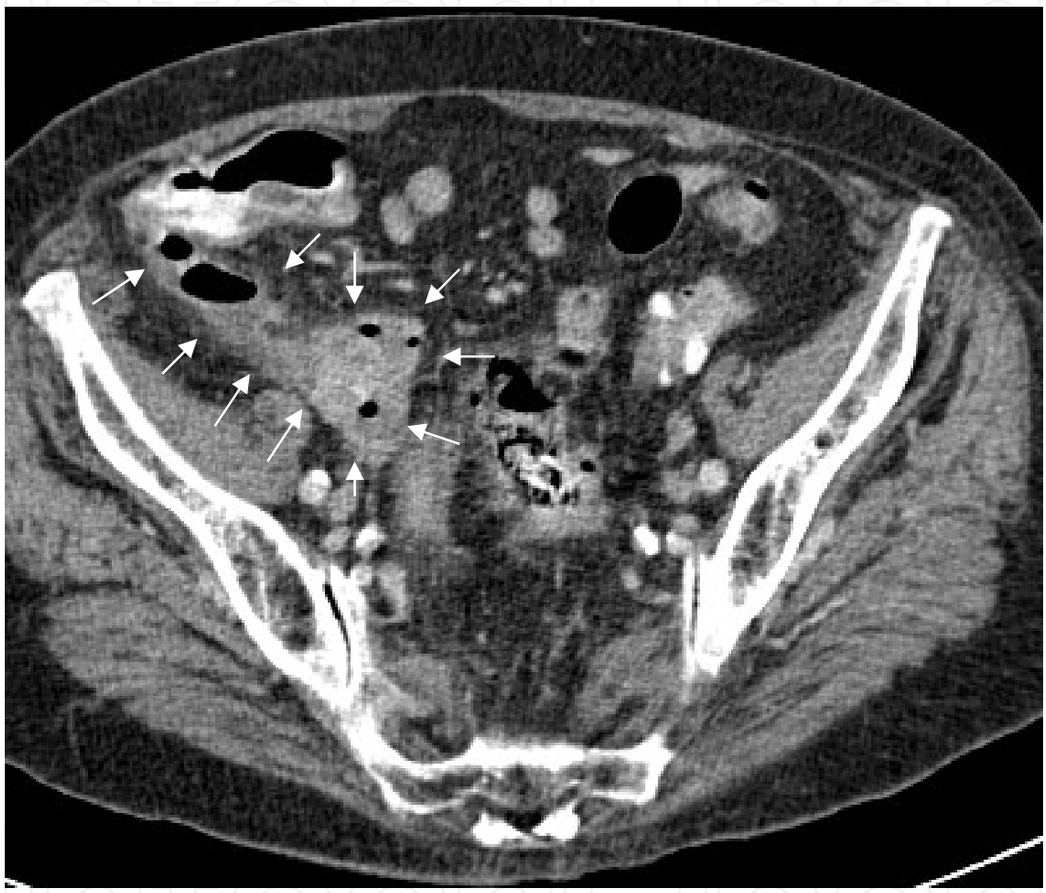
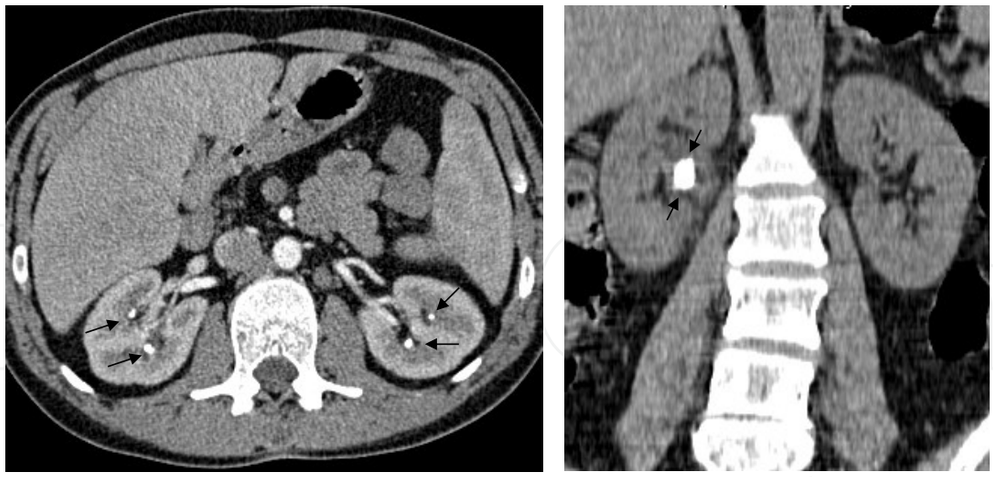


Fig. 21. Abdominal axial CT image at the level of the right iliac fossa showing a distended, thickened appendix with an associated collection (arrows) in acute appendicitis.

5.8 Nephrolithiasis

Nephrolithiasis is another important differential diagnosis of acute abdominal pain as there is a reported increased frequency of renal stone disease in CF in comparison to the general population (3-6.3% in CF patients versus 1-2% in age-matched controls) (Gibney & Goldfard, 2003). As with non CF patients, pain can affect the loin region or anywhere from the loin to the groin, and patients may also complain of haematuria and notice the voiding of tiny grains of stone. Initial assessment can be made with a CT of the kidneys, ureters and bladder (CT KUB) to confirm the diagnosis or with an ultrasound scan if obstruction and hydronephrosis is suspected in a patient with know nephrolithiasis.



a b

Fig. 22. Axial CT scan of the abdomen of CF patient investigated for haematuria and recurrent abdominal pain with bilateral multiple kidney stones (arrows) (fig. 22a). Coronal CT scan of another patient showing a single stone in the right renal pelvis (arrows) (fig. 22b).

6. Hypertrophic pulmonary osteoarthropathy

This condition consists of a triad of clubbing, symmetric arthritis and periosteal new bone formation. Firstly associated with brochogenic carcinoma, it is also recognised in bronchiectasis, chronic lung inflammation and infection and CF, amongst others. Finger clubbing is the result of fibroelastic proliferation in the nail bed with thickening of the skin and subcutaneous tissues of the distal end of the fingers; synovitis leads to arthralgia and stiff swollen hands; periosteal new bone formation and cortical thickening affects long bones, more frequently the radius and ulna (Martinez-Lavin et al., 1993).

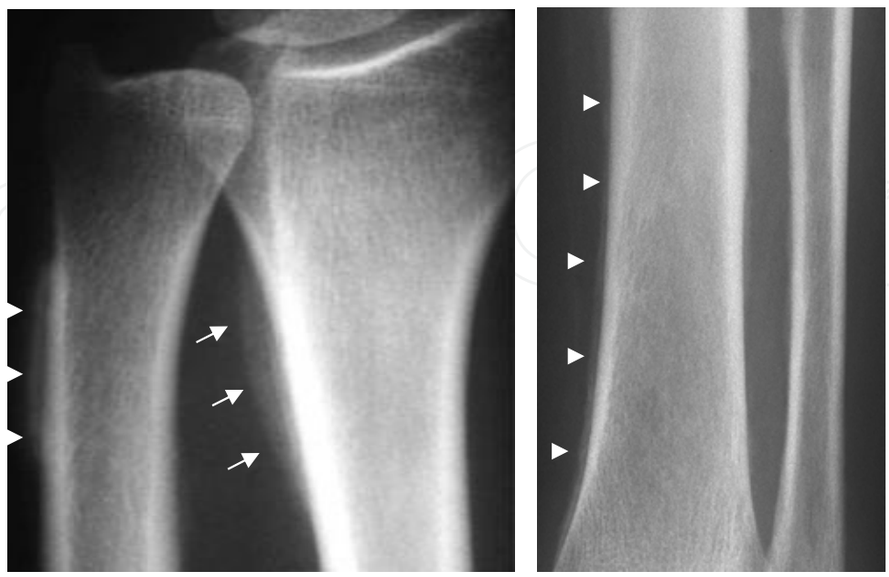


Fig. 23. Close-up radiographs of the distal long bones of the forearm and leg showing thickening of the cortical bone (arrows) as a result of chronic periostitis.

7. Conclusion

The lungs continue to account for the majority of CF complications and death, but with gastrointestinal complications becoming increasingly important and the ever growing availability of imaging facilities, clinicians and radiologists need to be aware of the larger spectrum of pathologies they might encounter and their radiological manifestations.

Imaging and close interaction between clinicians and radiologists is invaluable for the prompt and precise diagnosis of several CF related conditions. Some conditions can be diagnosed on the basis of imaging alone, avoiding unnecessary time wasting and invasive procedures, always reinforcing the necessity to maintain ionising radiation exposure to as low as reasonably achievable.

8. Acknowledgements

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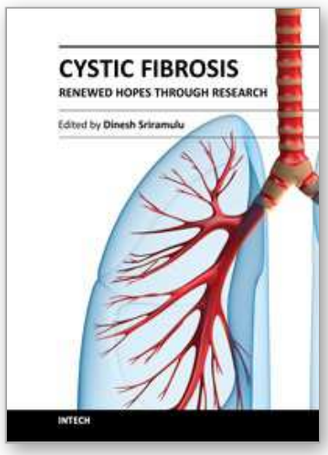
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Living healthy is all one wants, but the genetics behind creation of every human is different. As a curse or human agony, some are born with congenital defects in their menu of the genome. Just one has to live with that! The complexity of cystic fibrosis condition, which is rather a slow-killer, affects various organ systems of the human body complicating further with secondary infections. That's what makes the disease so puzzling for which scientists around the world are trying to understand better and to find a cure. Though they narrowed down to a single target gene, the tentacles of the disease reach many unknown corners of the human body. Decades of scientific research in the field of chronic illnesses like this one surely increased the level of life expectancy. This book is the compilation of interesting chapters contributed by eminent interdisciplinary scientists around the world trying to make the life of cystic fibrosis patients better.

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