A 31-year-old female patient with chronic kidney disease presenting with persistent cough

Baijaeek Sain [1], Suranjan Mukherjee [2], Ritam Chakraborty [1] and Mithun Chaudhuri [3]

[1]Dept of Critical Care, AMRI Hospitals, Kolkata, India. [2]Dept of Pulmonology, AMRI Hospitals, Kolkata, India. [3]Dept of Radiology, AMRI Hospitals, Kolkata, India.

Corresponding author: Baijaeek Sain (baijaeeksain.natmed2018@gmail.com)

Shareable abstract (@ERSpublications)
Can you diagnose this 31-year-old woman with end-stage renal disease and a persistent cough? https://bit.ly/3s7n5VU

Cite this article as: Sain B, Mukherjee S, Chakraborty R, *et al*. A 31-year-old female patient with chronic kidney disease presenting with persistent cough. *Breathe* 2022; 18: 210141 [DOI: 10.1183/20734735.0141-2021].

Received: 5 Sept 2021
Accepted: 12 Feb 2022

Introduction

Pulmonary disorders may be due to intrinsic pulmonary pathology or secondary to a pathology in other organs, such as in the renal, cardiovascular or gastrointestinal systems [1, 2]. Patients with chronic kidney disease (CKD) can present with or may have pulmonary involvement due to fluid overload, anaemia, infection secondary to immunosuppression and, rarely, extra-osseous calcification [3]. Haemodialysis and renal transplantation help in improving the pulmonary symptoms and metabolic derangements in CKD patients, thereby averting such complications [4]. We herein present a case of a 31-year-old female with end-stage renal disease (ESRD) who presented with persistent cough.

Case summary

A female patient aged 31 years presented to our hospital with persistent dry cough for 3 weeks, worse on lying down and with regular sleep disruption. The patient denied any exertional breathlessness or wheeze and fever. There was no history of nasal symptoms, frequent cough and cold or any similar previous episodes. She was diagnosed to be a case of ESRD, on bi-weekly haemodialysis for about a year, with well-maintained renal parameters and awaiting renal transplantation. There was no suggestive occupational or exposure history. There was no suggestive family history. She was a non-smoker and non-alcoholic without any other comorbidities. At presentation, she was on torsemide, calcitriol, aspirin, clopidogrel, nifedipine, hydralazine, bisoprolol, recombinant erythropoietin beta and other supportive medications.

On examination there was no pallor, lymphadenopathy, pedal oedema or clubbing. The patient was haemodynamically stable with a blood pressure of 120/70 mmHg, neither tachycardic nor tachypnoeic; oxygen saturation was 97% on room air. Chest examination revealed normal breath sounds without any wheeze or crackles. A chest radiograph was done. Due to the chest radiograph abnormality, high-resolution computed tomography (HRCT) of the thorax was performed.

Task 1

What does the chest radiograph show (figure 1)?

Go to Answers >>

Task 2

What does the HRCT of the thorax reveal (figure 2)?

Go to Answers >>

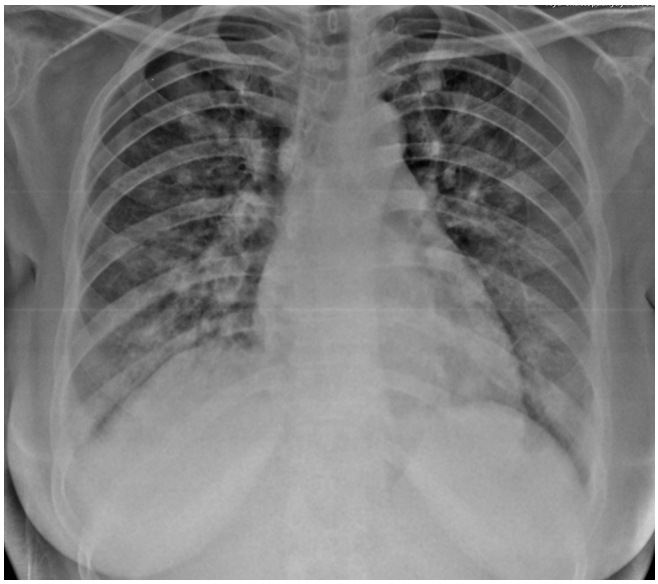

FIGURE 1 Chest radiograph.

Task 3

What is the differential diagnosis of the HRCT scan abnormality in this patient?

Go to Answers >>

The chest radiograph changes were stable over a few weeks since first noted, with stable symptoms. HRCT of the thorax revealed bilateral multifocal ground glass opacity and consolidation in combination, relatively sparing the periphery, along with small bilateral symmetrical pleural effusion. Bilateral multifocal airspace opacity was also present (figure 2). A contrast-enhanced computed tomography scan of the whole

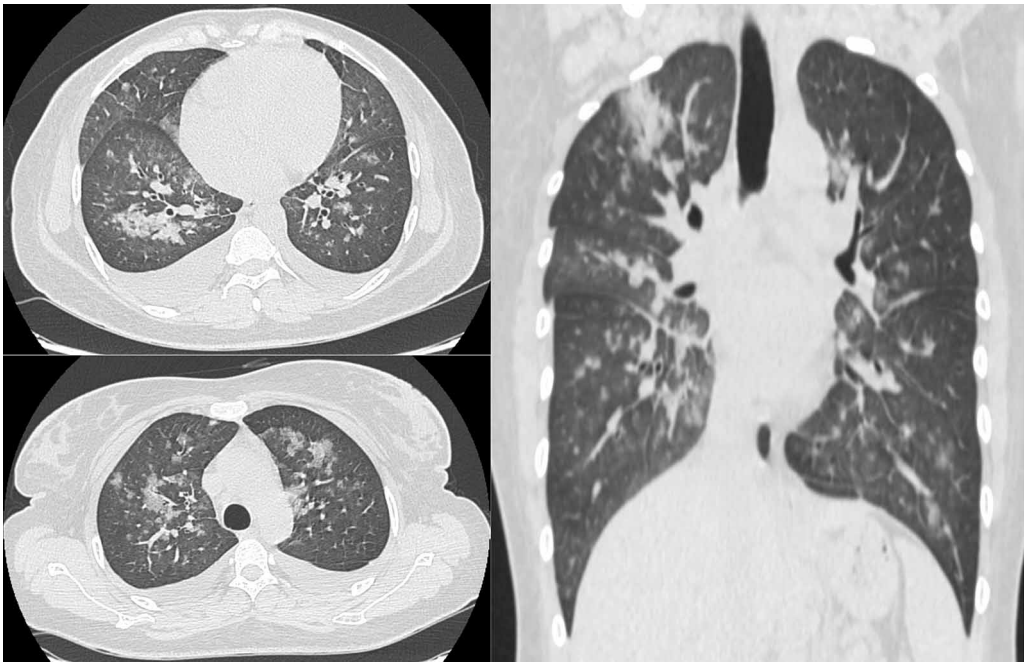

FIGURE 2 HRCT of the thorax.

TABLE 1 Pulmonary function test results

Parameter	Result	% predicted
Spirometry		
FVC (L)	2.07	64
FEV_1 (L)	1.75	62
FEV_1/FVC	0.845	
D_{LCO}		
D_{LCO} (mL·min^{-1}·mmHg^{-1})	6.7	26
D_{Ladj} (mL·min^{-1}·mmHg^{-1})	6.6	25
D_{LCO}/V_A (K_{CO}) (mL·min^{-1}·mmHg^{-1}·L^{-1})	2.53	44
FRC (L)	1.48	59
TLC (L)	2.81	62

FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lungs for carbon monoxide; D_{Ladj}: D_{LCO} adjusted after bronchodilator; V_A: alveolar volume; K_{CO}: carbon monoxide transfer coefficient; FRC: functional residual capacity; TLC: total lung capacity.

abdomen revealed no significant abnormality. Fibreoptic bronchoscopy revealed no endobronchial pathology. Bronchoalveolar lavage (BAL) was negative for GeneXpert for *Mycobacterium tuberculosis*, *M. tuberculosis* culture, acid-fast bacilli, fungal culture, fungal hyphae, pneumocystis, galactomannan and malignant cells, with negative bacterial culture. The total BAL cell count was 160 per mm^3, with neutrophils of 65% and lymphocytes of 35%. A vasculitis screen including antineutrophil cytoplasmic antibodies (proteinase 3 and myeloperoxidase), complement C3 and C4 and antinuclear antibodies was negative. BAL fluid was not blood stained. No iron staining and periodic acid–Schiff stain was done on the BAL fluid.

Pulmonary function tests showed a mild non-specific ventilatory defect; the results are shown in table 1. The final blood investigations panel is shown in table 2.

Task 4

What is the diagnosis?

Go to Answers >>

TABLE 2 Final blood investigations panel

Investigation	Result	Reference range
Haemoglobin (g·dL^{-1})	6.9	Male: 13–18 Female: 11.5–16.5
Total leukocyte count (per mm^3)	8200	4000–11 000
Differential leukocyte count (%)		
Neutrophils	65	40–60
Lymphocytes	33	20–40
Monocytes	1	2–8
Eosinophils	1	2–8
Platelet count (per µL)	485 000	150 000–450 000
Blood urea nitrogen (mg·dL^{-1})	51	6–24
Serum urea (mg·dL^{-1})	48	5–20
Serum creatinine (mg·dL^{-1})	5.7	Male: 0.74–1.35 Female: 0.59–1.04
Calcium (mg·dL^{-1})	9.31	9–10.5
Corrected calcium (mg·dL^{-1})	10.9	9–10.5
Phosphorus (mg·dL^{-1})	3.36	3.4–4.5
Alkaline phosphatase (IU·L^{-1})	172	44–147
Albumin (g·dL^{-1})	2.0	3.5–5.5
Parathormone (pg·mL^{-1})	209	10–55

Discussion

Our patient had bilateral metastatic calcification secondary to ESRD. Parenchymal pulmonary calcifications may be classified into two types: dystrophic and metastatic. Dystrophic calcification is due to the deposition of crystalline hydroxyapatite calcium salt in areas of damaged lung tissues, which is usually secondary to any post-inflammatory process, *e.g.* tuberculosis. The serum levels of calcium and phosphate are usually normal in these situations. Conversely, metastatic pulmonary calcification (MPC) is associated with high serum levels of calcium and phosphate, causing the deposition of calcium salts in the alveolar epithelial basement membrane over a span of time inside the lung parenchyma [6–8]. Although rare, this metabolic lung disorder is often associated with ESRD. Besides being seen in patients with ESRD on dialysis, MPC can be found in primary hyperparathyroidism, granulomatous diseases like sarcoidosis, milk-alkali syndrome, parathyroid carcinoma or any malignancies like multiple myeloma and lymphoma [9].

There are four major possible predisposing factors that may contribute to MPC in dialysis patients. First, it has been postulated that chronic acidosis in the inter-dialytic interval can leach calcium from bone, leading to its deposition in soft tissue during post-dialysis alkalosis. Secondly, intermittent alkalosis favours deposition of calcium salts by increasing the activity of alkaline phosphatase, which catalyses the release of phosphates thereby leading to calcium-phosphate deposition. Thirdly, secondary hyperparathyroidism in CKD tends to cause bone resorption and intracellular hypercalcaemia. Parathormone, vitamin D and uraemia act like sensitising agents and promote calcification. Finally, low glomerular filtration rate can cause hyperphosphataemia and an elevated calcium-phosphorus product. Haemodialysis for chronic renal insufficiency seems to be the leading benign cause that may precipitate to pulmonary calcifications. The lung is particularly susceptible to metastatic calcification as the pH of blood in the lung is more alkalotic compared with other organs because of the active carbon dioxide removal process at the lung apex and upper lobe as compared to other lung regions [10]. MPC can be present even with normal levels of calcium, magnesium and phosphate [11].

Conventionally, patients with MPC are asymptomatic; sometimes symptoms can be mild dyspnoea, rarely acute respiratory distress. Pulmonary function testing shows a restrictive lung pattern, which corresponds to MPC in lungs [7, 11]. Pulmonary artery pressures do not have any relation to MPC [12]. Chest radiographs are generally normal with occasional presence of confluent or patchy airspace opacities, discrete calcified nodules or diffuse interstitial process. HRCT of the thorax is more sensitive, exhibiting calcification in approximately 60% of cases [13]. Usually, multiple poorly defined centrilobular nodules, diffuse or patchy areas of ground-glass opacities or consolidation may be present. The diagnosis of MPC can be made by characteristic high-attenuation signals in combination with pulmonary and vascular calcification. The relative stability and central distribution of these pulmonary infiltrates, despite treatment, helps in differentiating MPC from pulmonary oedema or infection and goes against organising pneumonia [6]. Radionuclide imaging (with technetium-99m dicarboxypropane diphosphonate (Tc-99m DPD)) is reckoned as the most sensitive technique for early detection of MPC. A study by Rajkovača *et al.* [14] suggests that scintigraphy with Tc-99m DPD in patients with chronic renal failure undergoing long-term haemodialysis, alongside a reduced pulmonary function test, helps in early detection of pulmonary calcification.

Rarely, there might be dense bilateral consolidation without calcification; however, density of opacities might not be high enough to suggest calcification. Differential diagnosis should always include infection, as these patients are usually immunosuppressed [8]. The density of opacities is not sufficiently high to suggest calcification in most of the reported cases and might need high-kilovoltage and low-contrast techniques for detection [15–17].

Our patient was relatively asymptomatic with abnormal chest imaging, corresponding to what has been published in the literature. Pulmonary function tests revealed a mild restrictive defect with severe reduction in the gas transfer indices. No technetium studies were done as the facility was not available in the centre. The HRCT scan of thorax features, particularly the presence of consolidation, was not typical of non-specific interstitial pneumonia. Lung biopsy would have established the diagnosis, as calcification is often intracellular and might not be apparent on the HRCT scan. However, because of the low transfer factor, the patient was a high-risk case for surgical lung biopsy. A transbronchial biopsy would not have been useful because of the small size of the sample and crush artefacts. No iron staining was done on the BAL fluid as there was no history of haemoptysis, the BAL fluid was clear and there was no suspicion of pulmonary haemosiderosis. No periodic acid–Schiff stain was done, as the physical appearance and cellular profile were against pulmonary alveolar proteinosis. Moreover, the patient had minimal dyspnoea with no history of fever or weight loss. There was no clinical suggestion of fluid overload or heart failure.

Patients with MPC are rarely symptomatic; in symptomatic patients the treatment goal is to normalise the calcium and phosphate levels, which often helps in alleviating the symptoms. Biphosphonates,

calcimimetics, parathyroidectomy and increase in the frequency of dialysis have shown success in some patients. Renal transplantation in renal failure patients is another option, but worsening of MPC has also been reported despite successful transplantation [1, 6].

Answer 1

The chest radiograph showed bilateral infiltrates with relative sparing of the lung periphery.

<< Go to Task 1

Answer 2

HRCT of the thorax revealed bilateral multifocal ground-glass opacity and consolidation in combination, relatively sparing the periphery, along with small bilateral symmetrical pleural effusion.

<< Go to Task 2

Answer 3

The scan abnormality may be due to the following important causes of bilateral ground-glass opacities on HRCT [5]:

- Infections: bacterial, *Pneumocystis jirovecii*, viral pneumonia
- Vasculitis
- Diffuse alveolar haemorrhage
- Non-specific interstitial pneumonia
- Desquamative interstitial pneumonia
- Organising pneumonia
- Eosinophilic pneumonia
- Pulmonary alveolar proteinosis
- Pulmonary oedema
- Malignancy
- Drug induced (*e.g.* amiodarone)

<< Go to Task 3

Answer 4

The diagnosis was metastatic pulmonary calcification secondary to ESRD.

<< Go to Task 4

Consent: Informed consent taken.

Conflict of interest: The authors have nothing to disclose.

References

1 Inamdar AA, Pulinthanathu R. Metastatic pulmonary calcification with coexisting non-specific interstitial pneumonia: a rare case report and literature review. *Cureus* 2019; 11: e4183.
2 Ferkol T, Schraufnagel D. The global burden of respiratory disease. *Ann Am Thorac Soc* 2014; 11: 404–406.
3 Pierson DJ. Respiratory considerations in the patient with renal failure. *Respir Care* 2006; 51: 413–422.
4 Yılmaz S, Yildirim Y, Yilmaz Z, *et al.* Pulmonary function in patients with end-stage renal disease: effects of hemodialysis and fluid overload. *Med Sci Monit* 2016; 22: 2779–2784.
5 Ghosh M, Chakraborty S, Bhattacharya A, *et al.* A 22-year-old patient presenting with seizures and migratory pulmonary infiltrates. *Breathe* 2014; 10: 249–256.
6 Belém LC, Zanetti G, Souza AS Jr, *et al.* Metastatic pulmonary calcification: state-of-the-art review focused on imaging findings. *Respir Med* 2014; 108: 668–676.
7 Kauntia R, Bhargava V, Gupta P, *et al.* Pulmonary calcifications: is it an entity in the new world dialysis patient? *Indian J Nephrol* 2019; 29: 128–131.
8 Bendayan D, Barziv Y, Kramer MR. Pulmonary calcifications: a review. *Respir Med* 2000; 94: 190–193.
9 Chan ED, Morales DV, Welsh CH, *et al.* Calcium deposition with or without bone formation in the lung. *Am J Respir Crit Care Med* 2002; 165: 1654–1669.
10 Romagnoli M, Mourad G, Serre I, *et al.* Diffuse pulmonary calcinosis without calcium metabolism abnormalities in a renal transplant recipient. *Eur Respir J* 1997; 10: 958–960.

11 Conger JD, Hammond WS, Alfrey AC, *et al.* Pulmonary calcification in chronic dialysis patients. Clinical and pathologic studies. *Ann Intern Med* 1975; 83: 330–336.

12 Yigla M, Keidar Z, Safadi I, *et al.* Pulmonary calcification in hemodialysis patients: correlation with pulmonary artery pressure values. *Kidney Int* 2004; 66: 806–810.

13 Hartman TE, Müller NL, Primack SL, *et al.* Metastatic pulmonary calcification in patients with hypercalcemia: findings on chest radiographs and CT scans. *AJR Am J Roentgenol* 1994; 162: 799–802.

14 Rajkovača Z, Kovačević P, Jakovljević B, *et al.* Detection of pulmonary calcification in haemodialised patients by whole-body scintigraphy and the impact of the calcification to parameters of spirometry. *Bosn J Basic Med Sci* 2010; 10: 303–306.

15 Breitz HB, Sirotta PS, Nelp WB, *et al.* Progressive pulmonary calcification complicating successful renal transplantation. *Am Rev Respir Dis* 1987; 136: 1480–1482.

16 Kaltreider HB, Baum GL, Bogaty G, *et al.* So-called “metastatic” calcification of the lung. *Am J Med* 1969; 46: 188–196.

17 Marchiori E, Müller NL, Souza AS Jr, *et al.* Unusual manifestations of metastatic pulmonary calcification: high-resolution CT and pathological findings. *J Thorac Imaging* 2005; 20: 66–70.