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Case report

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Sputum smear and GeneXpert negative pulmonary tuberculosis; a diagnostic dilemma in primary tuberculosis

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Abstract

We discuss a case of a 60-year-old man with no known comorbidities who presented with sudden onset severe haemoptysis and chest pain. Sputum and pleural fluid smears for acid fast Bacillus and GeneXpert were repeatedly negative. Pleural fluid cytology demonstrated presence of fungal organisms with hyphae and serum IgE was elevated. The patient developed a haemorrhagic pericardial effusion and cardiac tamponade. Sputum mycobacterial culture after 7 weeks was positive for Mycobacterium tuberculosis. This case highlights the difficulties that may be associated with diagnosis of Pulmonary Tuberculosis (PTB) in the acute clinical setting and the importance of mycobacterial culture, particularly in the presence of negative initial investigations and superadded non-tuberculous infections. Furthermore, it demonstrates the potential clinical course of Mycobacterium tuberculosis (MTB) infection, including development of severe extra-pulmonary complications. Finally, it highlights the importance of the multidisciplinary team in assessing the need to presumptively start anti-TB medication in selected cases.

Introduction

Tuberculosis (TB) remains a significant public health burden, with over 2 billion people worldwide thought to be infected with *Mycobacterium tuberculosis* (MTB) [1]. In order to overcome the global TB epidemic, identification and treatment of individuals, as set forth in the World Health Organisation (WHO) End TB Strategy, are imperative [2]. These targets include prompt testing of key and at risk populations, including those in TB endemic regions such as Ghana. The diagnosis of Pulmonary Tuberculosis (PTB) may be at-times challenging in the acute clinical setting, particularly in early disease, and in situations where there are atypical presenting features or difficulty in obtaining definitive results such as mycobacterial culture, which may take 2 - 6 weeks to be obtained [3]. Moreover, PTB may exist with superadded bacterial, viral or fungal infection, which can lead to a complicated clinical presentation, delayed or incomplete diagnosis and poorer patient outcomes [4]. Although mycobacterial culture remains the diagnostic test with highest sensitivity, its lengthy duration for interpretation makes it less favourable in the acute clinical setting, where more rapid and relatively simple, albeit less sensitive, investigations such as sputum acid fast bacilli (AFB) smear and nucleic acid amplification (NAA) e.g. GeneXpert tests are favoured [5]. Imaging modalities such as Chest X-ray and computerised tomography e present the caCT scan are supportive, though less specific and may demonstrate typical PTB findings such as apical lung opacification and cavitation, as well as help to detect the presence of extra-pulmonary disease [3]. Herein, we present the case of a 60-year old male patient with sputum AFB smear and GeneXpert negative, yet culture positive pulmonary tuberculosis with a superadded fungal pneumonia. This case highlights the challenges that may be associated with diagnosis of PTB when presentation is complicated by superadded infections, and the utility of mycobacterial culture for a definitive diagnosis and management of patients. Furthermore, it demonstrates the disease course and complications including extra-pulmonary infection such as tuberculous pleural effusion and pericarditis, that may be associated with active pulmonary tuberculosis.

Patient and observation

A 60-year-old male reported to the Cape Coast Teaching Hospital in the Central Region of Ghana on account of worsening right sided chest pain, cough and severe haemoptysis of sudden onset, one hour prior to presentation. He was previously well with no known comorbidities. The chest pain was dull, non-radiating, associated with dyspnoea and general malaise, exacerbated by lying in the left lateral decubitus position, and relieved by lying on his right side. There was no history of fever nor night sweats, no contact with persons with chronic cough nor known immunocompromising disease

and no significant weight loss. He had no family and personal history of cancer, and no recent long distance or foreign travel. This was the first episode of such a presentation in his lifetime. Past medical history revealed that the patient had polio when he was 2 months old, otherwise there was nil of note. There was no history of cigarette smoking, however there was an occupational history of working in a 300-year-old building with a ceiling under refurbishment.

On examination, the patient was in acute respiratory distress with a respiratory rate of 28 cycles per minute and a peripheral oxygen saturation of 85% on room air. He was afebrile (35.5^{o}C), anicteric, not pale, acyanotic and had no evidence of finger clubbing. There were diffuse areas of skin depigmentation of maximum size 3mm x 2mm on the upper limbs (Figure 1) and the trunk suggestive of a fungal skin infection. Auscultation of the chest identified bronchial breath sounds with reduced intensity and coarse crackles in all lung zones of the right hemithorax. Findings were normal on the left side. The heart rate was 99bpm and the blood pressure was 160/110mmHg, with no other significant findings on cardiovascular examination at presentation. Neurological exam revealed hypotonia, areflexia and power of 2/5 in the polio-affected right lower limb, but otherwise normal findings. The differential diagnoses were: pulmonary tuberculosis; lung cancer; diffuse alveolar haemorrhage; and bacterial or COVID-19 pneumonia. Following initial resuscitation, the patient was started on IV Amoxicillin + Clavulanic acid for bacterial pneumonia, as per hospital protocol, whilst we awaited investigation results to confirm or exclude the differential diagnoses.

A summary of the patient´s full blood count results is shown in Table 1 below, with evidence of leucocytosis with neutrophilia during the course of admission. Viral serologies for HIV, Hepatitis B and C were negative. Real-time polymerase chain reaction (PCR) for SARS-CoV-2 was negative. Chest X-ray demonstrated diffuse heterogenous opacification in the right lung, predominantly in the middle and upper zones and moderate right pleural effusion. Within 2 days of admission, he developed a stony dull percussion note in the right lower lung zone, with repeat CXR showing a hydropneumothorax (Figure 2). A contrast enhanced chest CT scan (Figure 3) demonstrated right lung field consolidation with air bronchograms, bronchiectasis, hydropneumothorax likely due to bronchopleural fistula, and compressive atelectasis, with differential diagnosis of complicated PTB and atypical pneumonia. No masses or hilar lymph nodes were seen. Sputum for bacterial culture yielded no bacterial growth after 7 days and Ziel Nielssen stain for acid-fast bacilli, as well as GeneXpert for MTB which were collected following resolution of haemoptysis were repeatedly negative. Pleural fluid adenosine deaminase (ADA) was 15.7 IU/L, with total protein of 13g/L which was not suggestive of an exudative effusion. Serum IgE was elevated by more than two times the upper limit of normal, 218 KU/L (0.0 - 100.0 KU/L). Pleural aspirate and sputum for cytopathology demonstrated presence of mixed inflammatory infiltrates and desquamated epithelial cells interspersed by fungal organisms with hyphae (Figure 4). Fungal cultures yielded no growth of organisms, and *Aspergillus fumigatus* IgG was negative.

The possibility of bronchoscopy with bronchoalveolar lavage or a CT guided lung biopsy were considered, however the patient´s peripheral oxygen saturation was not adequate and the decision was made to begin antifungal therapy with a view to perform these once the patient was more clinically stable. Though the clinical suspicion for TB remained, owing to the high endemicity in the country, laboratory data had as yet not supported the diagnosis, and sputum culture for MTB was still pending, so a working diagnosis of Fungal Pneumonia DDx PTB was made. He was therefore treated with IV Caspofungin for a total of 22 days, and discontinued when sputum smears became negative for fungal elements. The patient developed bipedal pitting oedema and smooth tender hepatomegaly during the course of

admission, therefore Cor pulmonale secondary to severe pneumonia was diagnosed, and this was evidenced by right ventricular enlargement on transthoracic echocardiography. Notably at this stage, there was no evidence of a pericardial effusion. Approximately 3,145mL of initially serosanguinous and then serous fluid, together with air was drained over a 15-day period via tube thoracostomy. Upon chest-tube removal, there still remained pockets of loculated effusion (Figure 5). Due to the prolonged hospital admission and the patients desire to be discharged, plans were made to perform ultrasound guided aspiration of the remaining effusion estimated by ultrasound (USG) to be 250 ml, after discharge. He underwent chest physiotherapy and incentive spirometry to improve lung function whilst on admission and after discharge.

On day 37, the patient was discharged home for weekly follow up at the respiratory clinic, however one week after discharge, he began to experience worsening breathlessness on minimal exertion, chest pain and recurrent cough. He was re-admitted with urgent work-up. A subcostal ultrasound and trans-thoracic echo showed a massive pericardial effusion with cardiac tamponade (Figure 6), and an urgent pericardiocentesis was performed. Pericardial fluid, which was initially bloody and later sanguineous, yielded no significant findings on microscopy, bacterial and fungal cultures, ADA nor GeneXpert, with cytology reporting the presence of inflammatory cells. With the commonest cause of pericarditis in our setting being tuberculosis, particularly when the effusion is haemorrhagic, a clinical decision was made to start the patient on first line anti-TB medication and an oral corticosteroid, whilst we awaited mycobacterial culture results. Following initiation of first line anti-TB medication, culture for MTB returned a positive result, 7 weeks after initial presentation, with line-probe assay reporting sensitivity to both rifampicin and isoniazid. The patient was therefore maintained on medication and follow up visits continued at the TB clinic, where he reported improvement of his breathlessness and resolution of his cough.

Discussion

This case highlights the difficulties that may be associated with diagnosis of PTB, particularly in the presence of negative initial investigations and superadded non-tuberculous infections. Moreover, it demonstrates the potential clinical course including development of severe extra-pulmonary complications. Rapid diagnosis of PTB in the acute clinical setting in developing countries such as Ghana often relies on identification of AFB on sputum spear microscopy, or detection of mycobacterial DNA using nucleic acid amplification tests such as GeneXpert [6]. It is however known that the sensitivity of sputum AFB smear remains at roughly 50%, and that the sensitivity of Gene-Xpert decreases significantly with smear-negative sputum samples [7]. Thus, it is possible that without a strong clinical suspicion, cases of PTB may remain undiagnosed, and consequently contribute to the burden of disease via community spread. In fact, it is reported that up to 15% of GeneXpert negative PTB cases may remain undiagnosed if mycobacterial culture is not performed [6]. In patients who develop tuberculous pleural effusions, diagnosis of MTB infection includes demonstration of the bacteria via pleural fluid AFB smear or culture, as well as pleural biopsy. However, more commonly, diagnosis may be inferred by a high ADA or lymphocytosis of the pleural fluid. In areas of high TB endemicity including West African countries like Ghana, an elevated ADA is considered as confirmatory for a tuberculous pleural effusion, and a level below 40U/L has a high negative predictive value [8]. The low ADA in this patient was therefore notable.

With numerous first-line investigations failing to support a diagnosis of TB, and additional imaging inconclusive in this patient, the clinical picture was further challenged by the evidence of fungal elements on pleural fluid cytology. Superadded pulmonary infections are known to delay the

diagnosis of PTB [4], since clinicians may be more inclined to treat a disease they have definitive evidence of. That being said, the presence of a fungal pneumonia in this patient could be seen as a further clue to the existence of MTB infection, since it is known that a significant risk factor for the presence of superadded fungal infection is pre-existing lung disease, such as the cavitating lesions seen in PTB [9]. The true prevalence co-infection of PTB and fungal infections such as Aspergillosis is poorly documented in Africa. Following development of a bloody pericardial effusion, the clinical decision to presumptively treat for MTB infection was made. Although the echo did not show fibrinous strands typically seen on the visceral pericardium in TB pericarditis, the clinical sequelae supported this diagnosis. Moreover, TB pericarditis is known to be the principal cause of pericardial effusion in sub-Saharan Africa [10]. Mycobacterial culture eventually confirmed our diagnosis. Until culture results were received, there had been no detection of MTB in any samples obtained. The importance and utility of mycobacterial culture as gold standard in the diagnosis of MTB infection can therefore not be understated.

Conclusion

Once there is a high index of suspicion for MTB infection, and in the presence of negative rapid tests, it is imperative for clinicians to pursue culture, irrespective of the prolonged duration before interpretation. Finally, in the presence of mounting evidence for a diagnosis of TB, and whilst awaiting mycobacterial culture, discussion with the multidisciplinary team including a clinical microbiologist, internist, radiologist and pathologist to decide on a case by case basis, which patients can be presumptively initiated on TB treatment, even without identification of MTB in specimen, should be pursued.

Competing interests

The authors declare no competing interests.

Authors' contributions

Author YAN wrote the first draft of the manuscript. Authors YAN, RKA and AGB were responsible for the literature review. Authors RKA, AGB, KUA, BBJ, EA and YAA were responsible for reviewing and editing the manuscript. All authors were involved in the care of the patient, and read and approved the final manuscript.

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Tables and figures

Table 1: summary of full blood count (FBC) results

Figure 1: diffuse depigmentation of skin on left forearm

Figure 2: (A,B) posteroanterior chest X-ray taken on day 0 (left) showing diffuse patchy opacification in right lung and moderate right pleural effusion and dextroscoliosis; and day 2 (right) showing massive hydropneumothorax on the same side and mediastinal shift to the left

Figure 3: (A,B,C) three in a series of axial and corona CT scans of the chest, mediastinal and lung windows. It shows a large right hydropneumothorax with multiple pockets of air suggestive of bronchopleural fistula or abscess. The entire right lung shows dense consolidation with air bronchograms. The mediastinum and trachea are central. No obviously enlarged lymph nodes. The visualised left lung is clear

Figure 4: (A,B,C,D) smears of conventional pap stained sputum magnification X40 and X100 showing mixed inflammatory infiltrate predominantly eosinophils (above). Images below show hyphae with septae and acute angle branching as well as conidia suggestive of *Aspergillus* species

Figure 5: (A,B) posteroanterior and lateral chest X-ray following removal of chest tube with loculated pleural effusions in right hemithorax

Figure 6: subcostal sonogram demonstrating large pericardial effusion

References

1. Dheda K, Barry CE 3rd, Maartens G. Tuberculosis. Lancet. 2016;387(10024): 1211-26. **PubMed**
2. Raviglione Mario. GT Director, Global strategy and targets for tuberculosis prevention, care and control after 2015. World Health Organization, Geneva. 2013. **Google Scholar**
3. Ryu, Yon Ju. Diagnosis of pulmonary tuberculosis: recent advances and diagnostic algorithms. Tuberculosis and respiratory diseases. 2015;78(2): 64-71. **PubMed**| **Google Scholar**
4. AArora AA, Krishnaswamy UM, Moideen RP, Padmaja MS. Tubercular and bacterial coinfection: a case series. Lung India: Official Organ of Indian Chest Society. 2015;32(2): 172-174. **PubMed**| **Google Scholar**
5. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E *et al*. Official American thoracic society/infectious diseases society of america/centers for disease control and prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clinical Infectious Diseases. 2017;64(2): e1-e33. **PubMed**| **Google Scholar**
6. Jafari C, Olaru ID, Daduna F, Ernst M, Heyckendorf J, Lange C *et al*. Rapid diagnosis of pulmonary tuberculosis by combined molecular and immunological methods. The European Respiratory Journal. 2018;51(5): 1702189. **PubMed**| **Google Scholar**
7. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N.Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2014 Jan 21;2014(1): CD009593. **PubMed**| **Google Scholar**
8. Vorster MJ, Allwood BW, Diacon AH, Koegelenberg CF. Tuberculous pleural effusions: advances and controversies. Journal of thoracic disease. 2015;7(6): 981-991. **PubMed**| **Google Scholar**
9. Hosseini M, Shakerimoghaddam A, Ghazalibina M, Khaledi A. Aspergillus coinfection among patients with pulmonary tuberculosis in Asia and Africa countries; a systematic review and meta-analysis of cross-sectional studies. Microbial Pathogenesis. 2020;141: 104018. **PubMed**| **Google Scholar**
10. Sagristà-Sauleda Jaume, Axel Sarrias Mercé, Jordi Soler-Soler. Diagnosis and management of pericardial effusion. World Journal of Cardiology. 2011;3(5): 135-143. **PubMed**

Table 1: summary of full blood count (FBC) results					
FBC Parameter	**Day 1**	**Day 6**	**Day 11**	**Day 17**	**Range**
WBC ($X10^3$/uL)	4.7	14.8	16.5	12.1	4-10
Neutrophils	3.9	12.0	13.9	9.5	2-7
Eosinophils	0.00	0.03	0.03	0.04	0.0-0.3
Lymphocytes	0.7	1.3	1.42	1.3	0.8-4.0
RBC ($x10^6$/uL)	4.8	4.8	3.7	2.7	4.5-6.5
Hb (g/dL)	14.0	13.6	10.1	7.6	13.0-18.0
Haematocrit (%)	46.7	42.3	31.2	25.3	39.8-54
MCV (fL)	96.7	89.1	87.6	93.0	80-97
MCH (pg)	29.0	28.6	28.4	27.9	26-34
MCHC (g/dL)	30.0	32.2	32.4	30.0	32-36
Platelets (x103/uL)	149	185	556	414	150-400

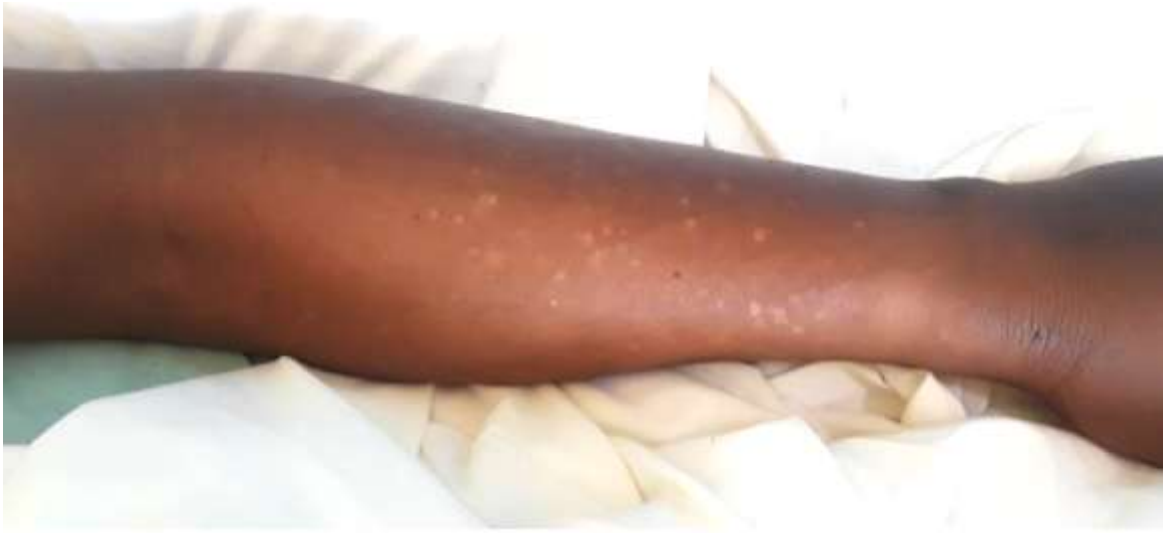
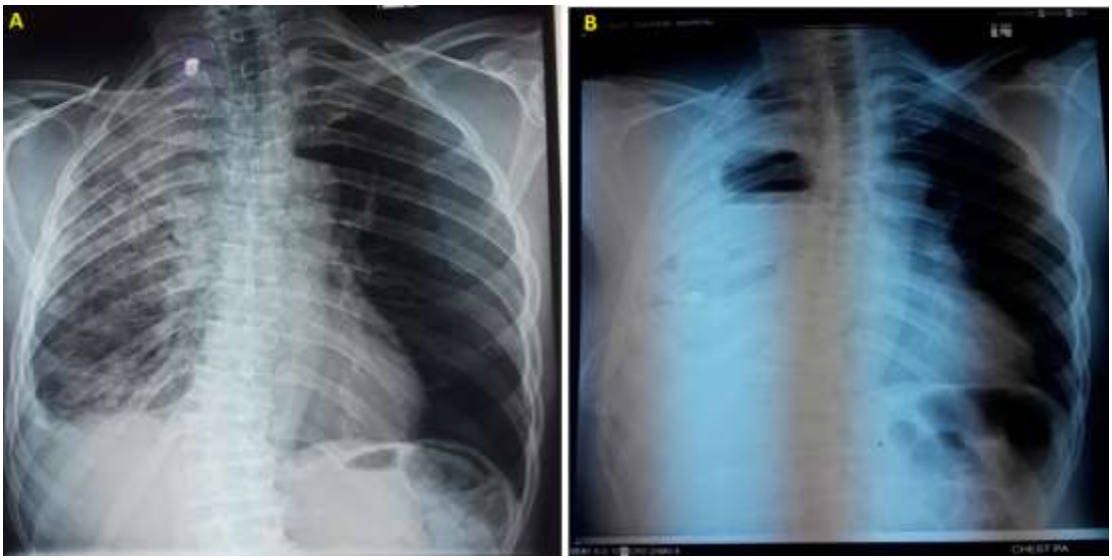


Figure 1: diffuse depigmentation of skin on left forearm



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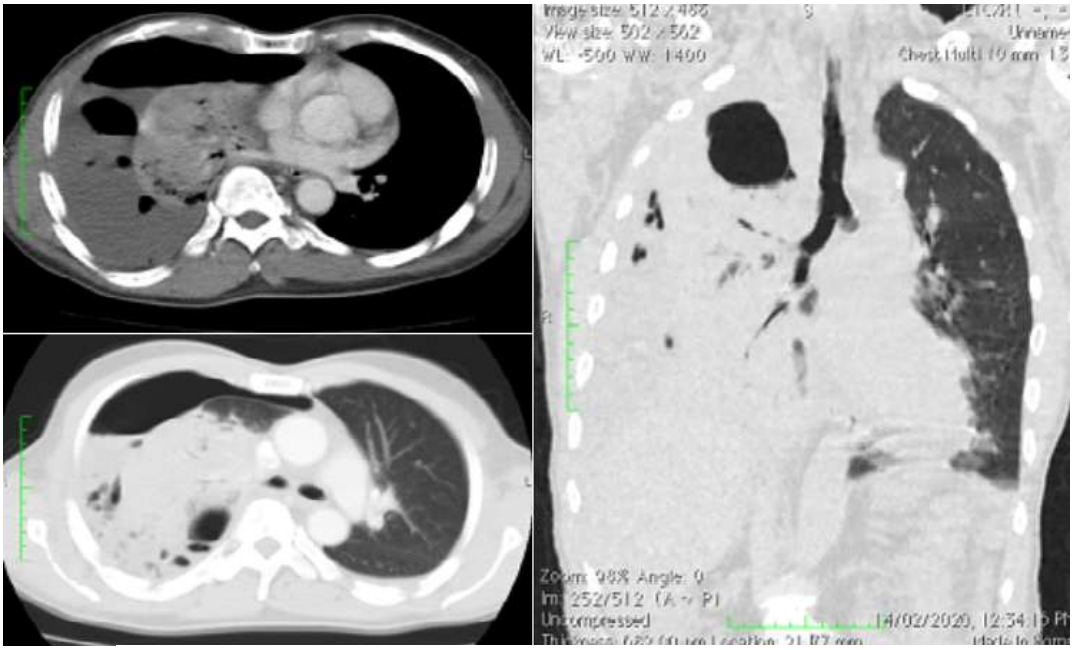

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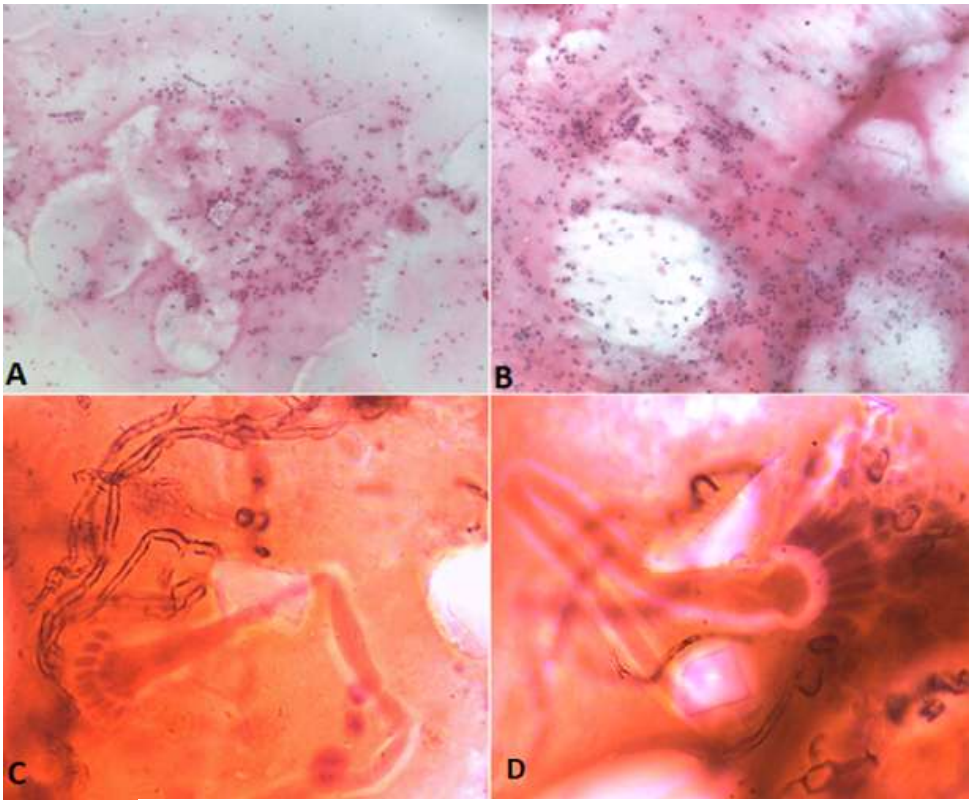

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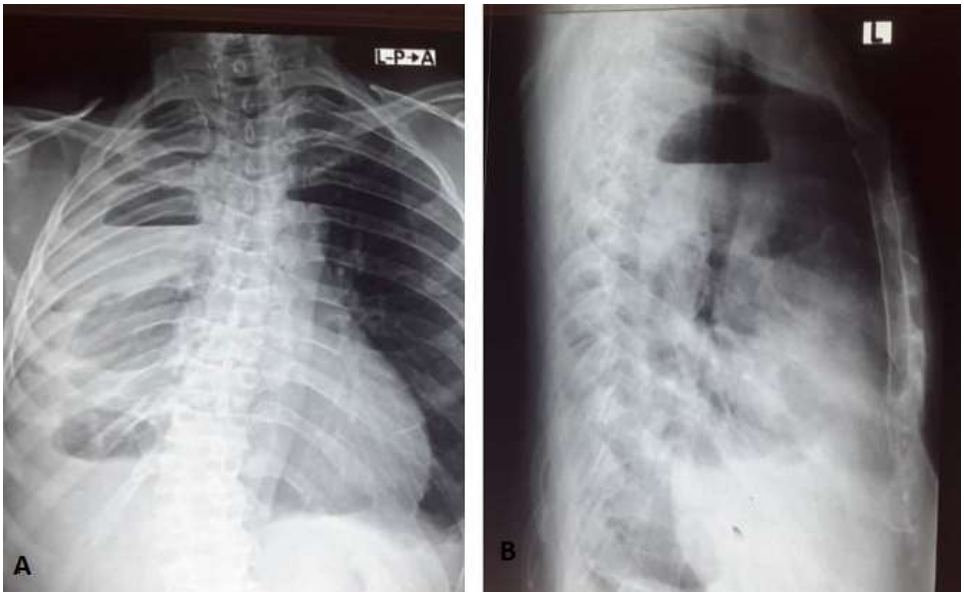

Figure 5: (A,B) posteroanterior and lateral chest X-ray following removal of chest tube with loculated pleural effusions in right hemithorax

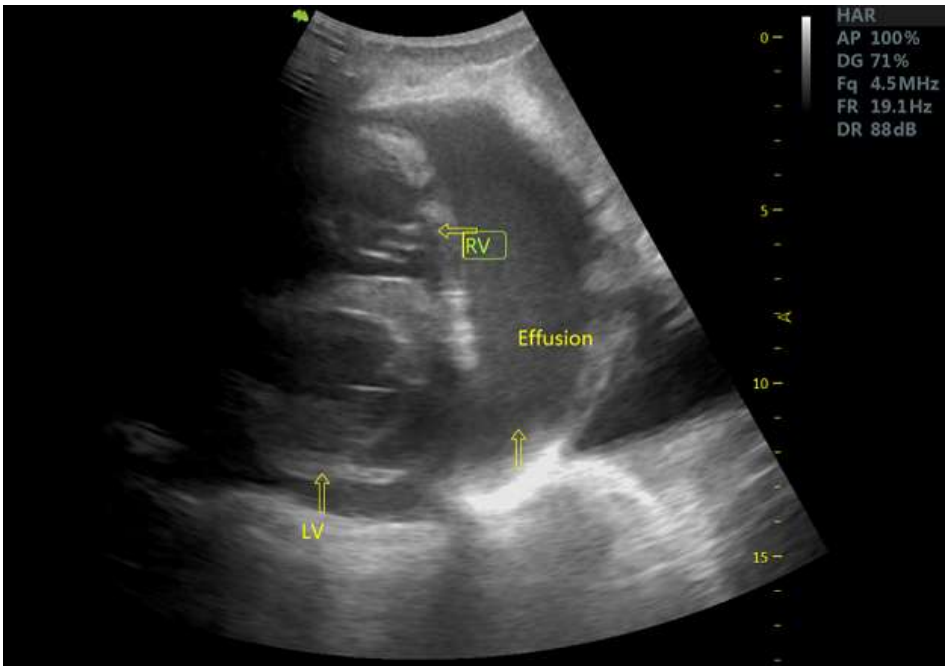

Figure 6: subcostal sonogram demonstrating large pericardial effusion