Pulmonary cavitation in a diabetic patient: TB or not TB

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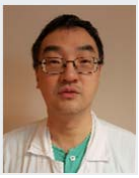

Case History

Mr CCY M/71, he was smoker and had history of diabetes mellitus. He complained of on and off cough for 2 months in 8/2015. There was no hemoptysis. He complained of exertional shortness of breath with exercise tolerance of 3 flights of stairs. There was no fever or night sweat.

He was referred from chest clinic to Kowloon Hospital for further care. Chest x-ray showed right upper cavitating shadow (fig 1). Blood result showed HbA1c 11, white cell count 9.3 and creatinine level of 112. Insulin was started for better glycemic control.

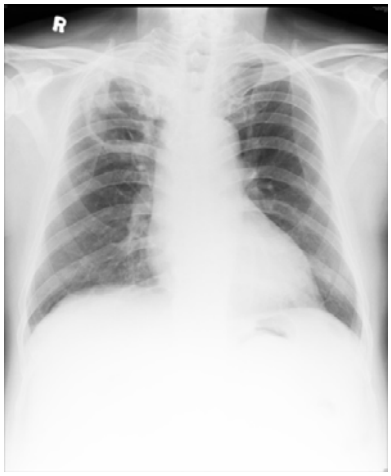

Figure 1. CXR on presentation

He was treated with empirical Rocephin but there was no radiological response. Bronchoscopy was arranged and it showed swollen right upper lobe bronchi and whitish lesion. The bronchial biopsy turned out to be chronic inflammation with mucormycosis. Among the inflammatory exudate covering the bronchial mucosa, non-septate wide-angled branching hyphae with admixed spores are demonstrated by PASD stain (Fig 2).No intra-vascular fungal invasion is noted. Computed tomogram of the chest was done and it showed 5.3 x5.3x 5.4 cm cavitation lesion with air-fluid level in right upper lobe of lung. Adjacent patchy consolidations seen at the apex and posterior aspect of the cavity (Fig 3)

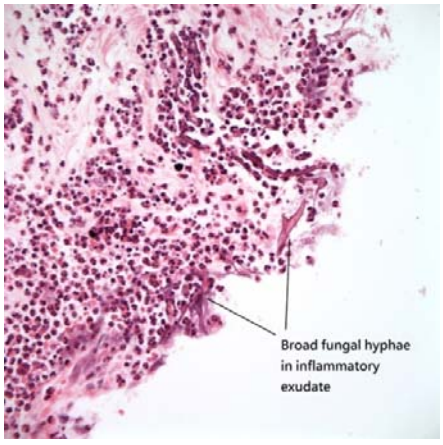

Figure 2. Histology of bronchial biopsy

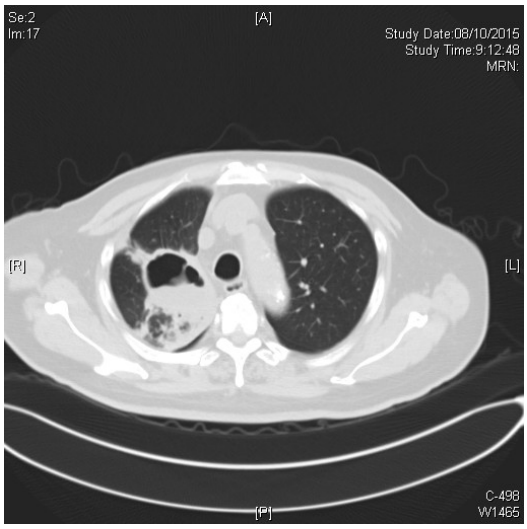

Figure 3. CT scan on presentation

He was treated with posaconazole with intravenous amphotericin B as bridging therapy. However this patient suffered from deterioration of renal function after amphotericin B with creatinine rising from 140 to 318. Thus amphotericin B was given for only 5 days. The renal function improved after stopping amphotericin B. The patient tolerated posaconazole well with only transient elevation of liver enzyme.

Follow-up chest X-ray showed progressive radiological improvement. The latest chest x-ray showed residual fibrotic shadow after nine months of posaconazole (Fig 4). Follow up computed tomogram of the chest also showed much smaller right upper cavitating air-filled shadow (Fig 5). Screening computed tomogram of brain and sinus were also done and were unremarkable. Clinically the patient had minimal chest symptoms with occasional cough only.

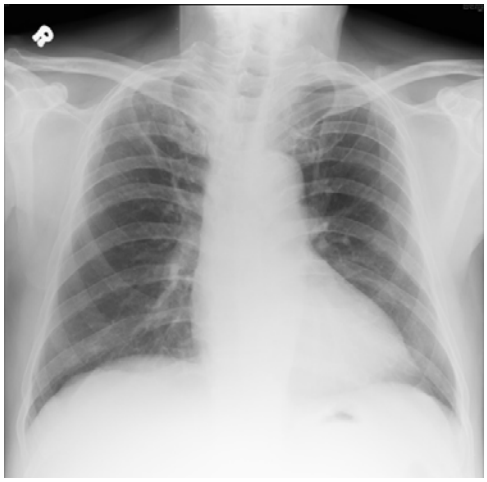

Figure 4. CXR after 9 months of posaconazole

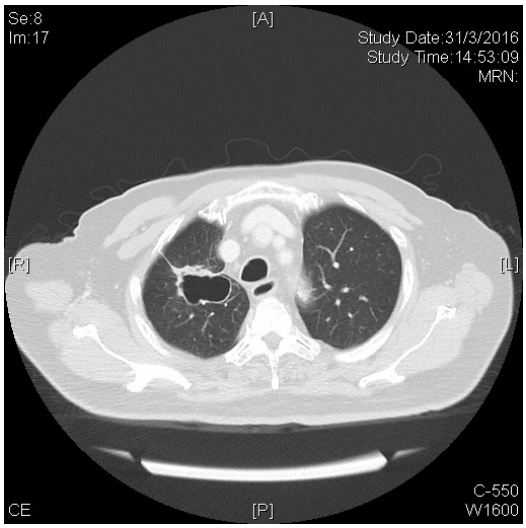

Figure 5. Follow up CT scan

Discussion

Mucormycosis is aggressive, angioinvasive, and potentially life-threatening fungal infection due to molds within the Mucorales order. The common risk factors are hematological malignancies, post sold organ transplantation, use of immunosuppressive agents and poorly

controlled diabetes. The incidence is increasing as increase in at-risk population.[1]

Pulmonary mucormycosis is transmitted via inhalation of fungal spores which are trapped in sinus or distal airways. Under the favorable conditions the spores can germinate and proliferate. Hyperglycemia, acidosis and steroid impair the alveolar macrophages and phagocytic functions and decreasing host defense against Mucorales. Mucorales are vasotrophic. Angioinvasion and thrombosis cause extensive tissue necrosis limiting immune response.[2,4]

The clinical features of pulmonary mucormycosis include prolonged high fever which is nonresponsive to empiric board spectrum antibiotics, other symptoms are cough, dyspnea and pleuritic chest pain. Progression may be rapid and invasion of vessels by the mould may lead to hemoptysis. Endobronchial lesions are also reported and may cause airway obstruction and massive hemoptysis. Concurrent rhino-sinusitis may be present. Physical findings may be minimal or absent. The mortality rate can be as high as 76% for pulmonary mucormycosis.[2,4]

High degree of suspicion is required for making diagnosis of pulmonary mucormycosis in patients with poorly controlled diabetes, hematological malignancy, post-transplant and those on immunotherapy. Imaging should be done early to assess the extent of the disease. High resolution computed tomogram of the thorax showed variable findings. They include nodules, cavitary lesions, consolidation, infiltrates or lymphadenopathy. The nodules may show halo or reverse halo signs.

Endoscopy should be done for visualization of the sinuses. Serum markers such as galactomannan and 1,3-beta-D-glutan are not useful for mucormycosis. Bronchoscopy with bronchoalveolar lavage should be performed when possible. Computed tomogram guided percutaneous biopsy is proposed if bronchoscopy is non-diagnostic. Surgical lung biopsy is an option when the lesions are not accessible to percutaneous biopsy.[4]

Definitive diagnosis requires the demonstration of the organisms in affected tissue. The histological examination show the organism appear as thin-walled, broad, ribbon-like hyphae with few septations and right-angle branching. Invasion of blood vessels, necrosis, hemorrhage and thrombosis of vessel may be visible.[2]

Prompt treatment of mucormycosis is necessary is necessary. Surgery is considered as case by case basis. The rationale is to debride as mush non-vital tissue as possible as penetration of anti-fungal drug is poor.

European confederation of medical mycology and European Society for Clinical Microbiology

and Infectious Diseases suggest amphotericin b as first line anti-fungal treatment for mucormycosis. Posaconazole can be considered as salvage therapy.

The lipid amphotericin B is preferred as it is less nephrotoxic. The suggested dose is 5mg/kg. The duration of treatment should be determined on individual basis and adjusted according to underlying condition. But it must be as least 6 to 8 weeks or reversal of immunosuppression. Two series use posaconazole as salvage therapy showed good results with over 60% of survival. Posaconazloe is an oral drug and should be taken with fatty food in increase the absorption. The recommended dose is 200mg four times daily as salvage treatment.

Fluconazole and voriconazole have no activity against Mucorales. Isavuconazole has partial activity against different strains of Mucorales. It can be employed as salvage therapy.[3]

Correction of underlying disease like better glycaemic control, tapering of steroid and immunosuppressive agents and use of granulocyte growth factor in case of neutropenia are recommended. Other adjuncts like use of hyperbaric oxygen or iron chelation therapy are not substantiated by data.

The take home message is to consider mucormycosis in susceptible patient like the presented as with poorly controlled diabetes. Early investigation and treatment are mandatory as it is life threatening. Combined surgical and medical treatment should be considered if poor response to anti-fungal treatment.

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INTERVENTIONAL PULMONOLOGY CORNER

Porsche or Maserati – EBUS or EUS?

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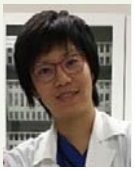


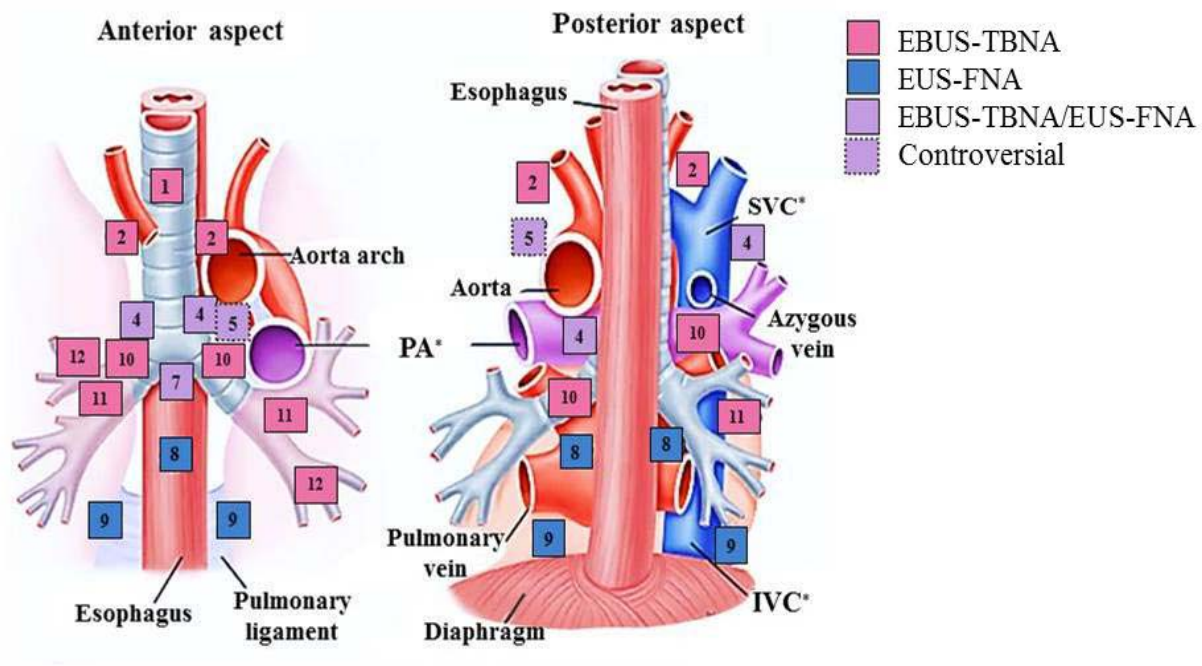
Introduction

The diagnosis and staging of lung carcinoma have contributed a significant portion of local respiratory physician's workload. In the past, the mediastinal staging relied on imaging including computer tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and recently PET-CT. However, even in a case with confirmed lung malignancy, mediastinal lymph nodes (LN) enlargement can be due to reasons other than metastasis (reactive lymph node, infection including tuberculosis, etc.). In our local traditional practice, invasive mediastinal staging i.e. mediastinoscopy is usually reserved for otherwise good surgical candidate with equivocal imaging results. Nowadays, evidence shows that CT scanning for identifying mediastinal LN metastasis has a low sensitivity 51% (95% CI, 47–54%) and specificity 85% (95% CI, 84–88%). Therefore, CT scan is not adequate for mediastinal staging. The sensitivity and specificity of PET scanning for identifying mediastinal metastasis is 74% (95% CI, 69–79%) and 85% (95% CI, 82–88%) respectively (1); hence, the latest ACCP guidelines requires all abnormal imaging findings to have cytological or histological confirmation (2). Over the last decade, endoscopic needle aspiration technique has gained popularity with its comparable sensitivity and specificity while saving patient to undergo a general anesthesia for mediastinoscopy. A pooled analysis of twelve studies using Endobronchial ultrasound (EBUS) for mediastinal staging showed a weighted sensitivity of 93% (range, 79–99%) and a false-negative rate of 9% (range, 1–37%). The specificity is 100 % (3). EBUS is now recommended over surgical staging as a best first test (2).

Different types of endoscopic ultrasound

Endoscopic ultrasonography is the combination of endoscopy and ultrasonography. Two passages are available for physicians to assess the mediastinum- trachea and esophagus. The first available endoscopic ultrasound is the esophageal ultrasound (EUS) which was developed in the 1980s. It is now an integral part of the evaluation for gastrointestinal

malignancies. Since the esophagus is located at the left-posterior of trachea, part of the mediastinum is assessable by EUS. EUS can assess the posterior and the inferior mediastinum (station 7, 8, 9) and left adrenal gland. EUS also allow us to visualize station 4L, 5 and 6. Trans-aortic EUS fine needle aspirations of LNs have been performed in specialized centers. For patients with persistent cough or poor lung reserve which render EBUS technically difficult, EUS is usually better tolerated in these patients.



The application of endobronchial ultrasound (EBUS) was first described in 1992. The current widely available linear EBUS scope is actually a miniature of the EUS scope. EBUS can assess the superior and anterior mediastinum (station 2R, 2L, 4R, 4L, 7, 10R, 10L, 11R, 11L) and centrally located tumours.

Although the EBUS scope is evolved from the EUS scope, there are minor differences in how to perform the procedures and their specifications.

Table 1. Comparison of specification of EBUS vs. EUS scope

	EBUS scope ^	EUS scope *
Field of view	80°	100°
Direction of view	Forward oblique 35°	Forward oblique 55°
Depth of field	2-50mm	3-100mm
Working length	600mm	1250mm
Distal end outer diameter	6.9mm	14.6mm
Channel inner diameter	2.2mm	3.7mm
Angulation range	Up 120°, Down 90°	Up 130°, Down 90°, Rt 90°, Lt 90°

^ Olympus BF-UC260FW

*Olympus GF-UCT 180

Table 2. Differences in procedure of EBUS vs. EUS

	EBUS	EUS
Patient position	Supine	Left lateral
Sedation	Higher dose	Lower dose
Route	Transbronchial	Transesophageal
Needle size (gauge)	21, 22, 25	19, 20, 22, 25, Histology possible^
Suction (cmH2O)	5-15	Variable, half way*

^ 19G, Tru-cut, Quick core

*Pull the stylet half way out, no suction applied

EUS by Respiratory physician

For the respiratory physician who has no prior gastroendoscopy experience, the hurdle to learn EUS will be the unfamiliar esophageal sonographic anatomy. When performing EUS, the endoscopists can only rely on US imagines for orientation. In patient undergoes workup for lung malignancy, a complete EUS evaluation starts by identifying the left adrenal from the stomach. The endoscope is then retracted stepwise in the following sequence –

1) Left adrenal gland
2) Celiac axis
3) Liver
4) Vena cava
5) Right atrium
6) Left atrium
7) Pulmonary artery
8) Arch of Aorta.

In contrast to EBUS, circular movement of the EUS scope is required to visualize all mediastinal nodes that can be detected from the esophagus. EUS-FNAC is then performed in the identical way as EBUS-TBNA. However, the necessity of applying suction in EUS is still a debatable object. Some endoscopists prefer to withdraw the stylet half way out after puncture instead of applying suction. Due to the absence of cartilage rings, performing EUS-FNAC is relatively easier than EBUS-TBNA. EBUS and EUS for lung lesions share similar complications including pneumothorax, pneumomediastinum, bleeding and Haemothorax.

Combined EBUS/EUS

Combination of EUS-FNAC and EBUS-TBNA are required to have complete assessment of the whole mediastinum, this combination is regarded as an appealing alternative for mediastinoscopy (5). Wallace et al reported a sensitivity of 93% (95% CI, 81–99%), and a negative predicted value of 97% (95% CI, 91–99%) for combining EUS-FNA with EBUS-TBNA in a population with a prevalence of mediastinal metastases of 30%. Moreover, they reported that the combination of EUS-FNA and EBUS-TBNA was better than either alone (6). In Hone Kong, due to the limitation of resources, combined EBUS/EUS is rarely performed for staging of lung cancer. This combination is time, expertise and cost demanding. Patients also need to undergo two endoscopies.

EUS-B (EUS using EBUS Scope)

Recent researches are exploring the use of single EBUS bronchoscope (EUS-B) to perform EBUS plus EUS in a single session. When using the smaller EBUS scope entering the collapsible esophagus, respiratory physician will likely encounter several technical difficulties. It is because the EBUS scope is smaller and hence less stiff then EUS scope. EBUS scope has a narrower angulation range and it also provides less clear US image. All these limitations will lead to the EUS-B biopsy sampling more challenging. EBUS scope is shorter so it cannot reach the stomach, therefore, EUS-B cannot visualize and sample the left adrenal gland.

Local experience – EUS for mediastinal lesion in United Christian Hospital

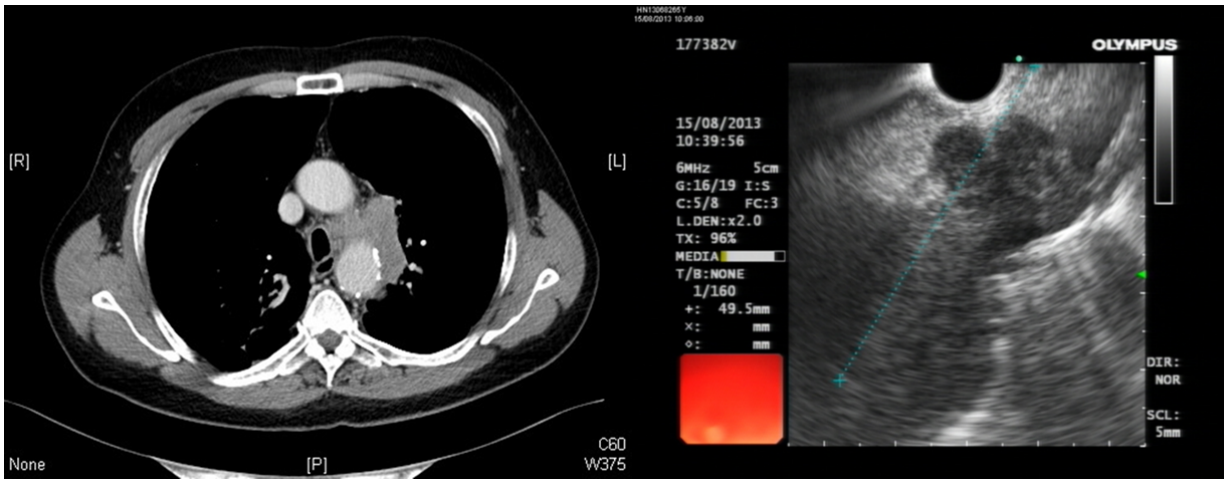
In our hospital, we have set up a combined endoscopic session by gastroenterologist and respiratory physicians for mediastinal lesion since 2013. For patients with lesion reachable by either conduit, EBUS or EUS would be arranged according to availability. Anterior located mediastinal lesions would be channeled to EBUS whereas EUS would be arranged to patients with poor lung reserve or with lesion in vicinity of esophagus. The EUS were jointly performed by at least one endoscopist from each sub-specialty. Esophageal ultrasounds using the

linear EUS scope (Olympus GF-UCT 180) were performed with patient lying in left lateral position under conscious sedation. Typically a lower dose of sedation (3mg diazemul and 15mg pethidine) would be required. Over the past four years, we have performed more than 80 case of EUS-FNAC for mediastinal lesions. For the initial 50 cases, EUS was the first investigation in more than half of the cases. The diagnostic yield in our initial series was 85%. FNAC had revealed malignancy in 63% of cases with majority (79.4%) were non-small cell carcinoma. EUS was aborted in two cases due to inaccessible lesion and significant bleeding tendency. Concerning complication, one patient was admitted for a small pneumothorax which resolved conservatively (7).

Case 1 – 56 year old male with known very severe COPD

CT showed matted mediastinal LN encases the aortic arch, AP window and left upper zone paravertebral region.

Bronchoscopy abandoned at vocal cord level due to severe respiratory distress and persistent cough



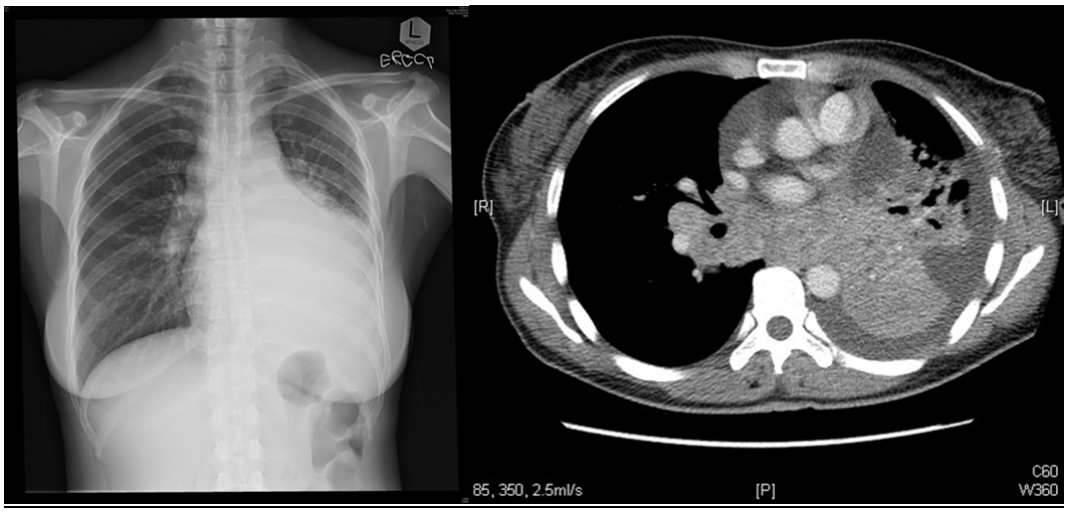
Patient tolerated EUS well without significant desaturation

EUS showed a huge homogenous mass lesion encasing aortic arch and a few small LN at subcarinal area. FNAC performed with 19G needle, Cytology - Consistent with Small cell carcinoma

Case 2- 48 year old female with chronic cough for 3 months

Bronchoscopy - Carina widen with extrinsic compression and narrowing of left main bronchus

BAL, pleural fluid, and biopsy were all negative for malignancy.



Echo showed 2cm pericardial effusion with tapenade hence pericardial drain inserted

Pericardial fluid no malignant cell seen.

EUS guided FNAC to left lung mass – Squamous cell carcinoma

Conclusion

Endoscopic ultrasonography is the combination of endoscopy and ultrasonography. Linear endoscopic ultrasound allows direct visualization when we perform needle aspiration. The recent advances in EBUS provide a less invasive but yet adequate assessment of the mediastinum. The combination of EBUS/EUS further allows a complete assessment of the mediastinum. EUS or EBUS-B performing by respiratory physician is technically more demanding but allows continuity of care and saving patient to undergo two endoscopies. It will be cruel to ask a car lover to choose between Porsche and Maserati, it will be best to own both of them.

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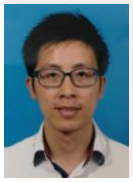
THORACIC RADIOLOGY CORNER

A potentially life threatening complication of pharyngitis



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History

A young female enjoying good past health, was admitted to the medical ward with fever, and headache for a few days. There was no cough or sputum. She was hypotensive with markedly elevated neutrophils on blood tests. Blood culture and other septic workup were unrevealing.

Serial CXR showed multi-lobar consolidation affecting bilateral lungs, with some areas suspicious of cavitation. Transthoracic echocardiogram did not show any valvular lesions. CT thorax demonstrated multiple cavitary lesions involving all the lung lobes (FIGURE), with thick irregular walls, fluid contents and peri-focal consolidative changes compatible with infective lesions. She revealed some sore throat and neck pain before the admission on detailed history taking. Doppler ultrasound of the neck showed markedly narrowed lumen with dampened flow signal in the left internal jugular vein suspicious of venous thrombosis. It was confirmed on contrast CT venogram. The patient responded well to prolonged course of intravenous antibiotic.

Fusobacterium necrophorum, a normal flora in throat, is the classical bacteria involved in Lemierre's syndrome. The bacteria cause thrombophlebitis of veins in the head and neck regions and septic emboli to the lungs.

Lemierre's syndrome is a rare complication of pharyngitis which could be life threatening. High index of suspicion is pivotal.

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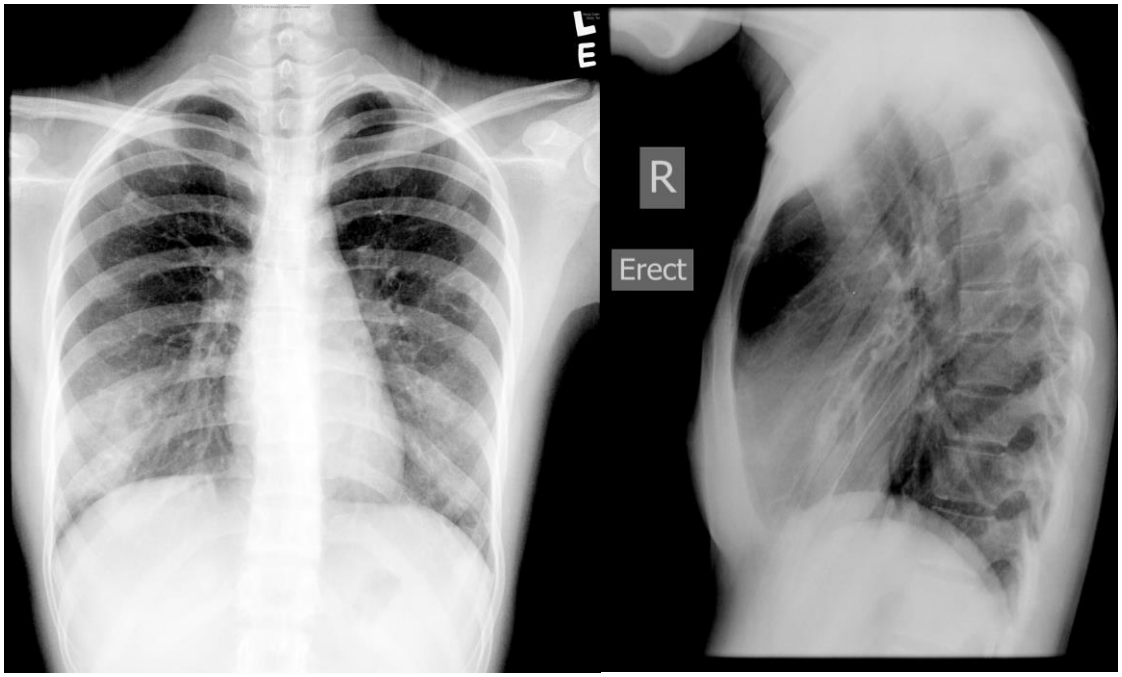

Fig. 1 CXR revealed multiple areas of consolidation in the bilateral lung fields with no zonal predominance. There were cavitatory changes in RUL and RML consolidation.

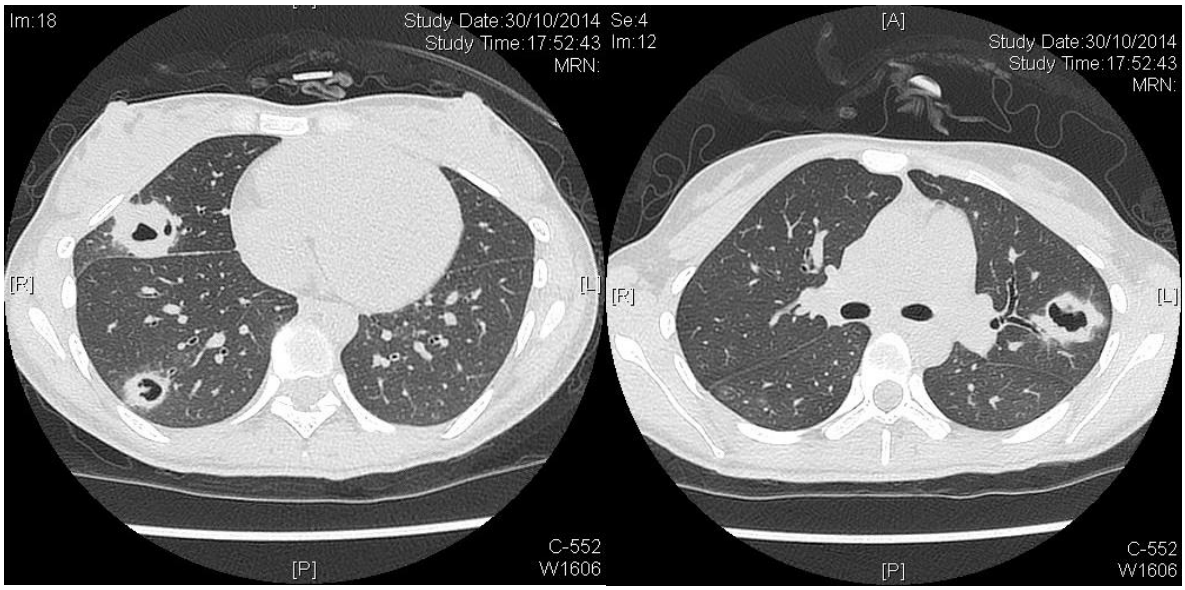

Fig.2 CT thorax demonstrated cavitary lesions of variable sizes involving all the lung lobes with fluid levels for the one at RUL.

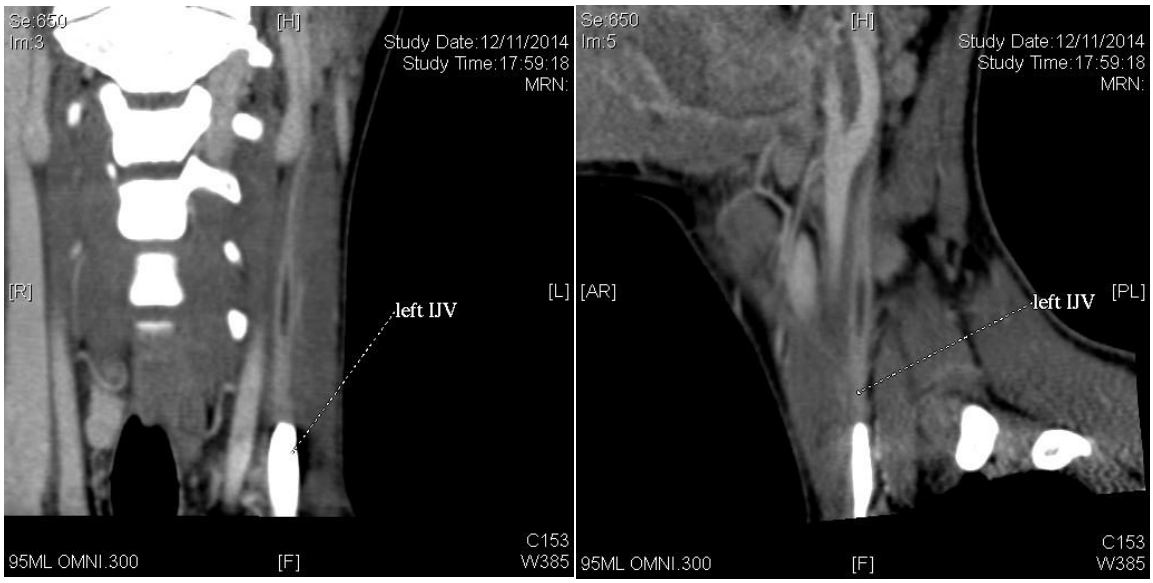

Fig.3 CT venogram in an oblique sagittal view showed presence of filling defect in the mid left internal jugular vein, confirming jugular venous thrombosis.