A 46-year-old woman presenting with anterior mediastinal mass and superior vena cava obstruction syndrome

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Mucormycosis can rarely lead to an anterior mediastinal mass and a high index of suspicion is necessary so that intervention can be carried out at an early stage. https://bit.ly/4aUuqvc

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A 46-year-old non-diabetic woman, with a history of hypothyroidism and bronchial asthma, presented with persistent chest and upper back pain for 5–6 days with radiation to the neck region. Chest pain was neither related to exertion, nor associated with any sympathetic response. She also had a history of dry cough over the previous 3–4 months. There was no associated history of fever, weight loss, anorexia or any other systemic symptoms. She was a homemaker, never travelled out of the city, and did not have any specific hobbies or interests. She did not keep any pets. There was no damp in the house and no occupational exposures. Her asthma was mild with no previous hospital admissions related to asthma exacerbations and she was using a rescue short-acting bronchodilator only. Her only daily prescription medicine was replacement thyroxine. There was no history of severe acute respiratory syndrome coronavirus 2 infection. Other than hypothyroidism and bronchial asthma she had no other known comorbidities.

On examination, she was overweight with a height of 160 cm and a weight of 71.6 kg. There was no pallor, lymphadenopathy, pedal oedema or clubbing. The patient's vital signs included a body temperature of 98.3°F (36.8°C), blood pressure of 110/70 mmHg, and she was not tachypnoeic or tachycardic; her oxygen saturation was 99% on room air. On admission, her random blood glucose level was 114 $mg \cdot dL^{-1}$, which was within the normal range. She had no episodes of dysglycaemia during her course of illness. Jugular venous pressure was raised at 10 cmH_2O with engorged and non-pulsatile neck veins. On respiratory system examination, her breathing was unlaboured; auscultation revealed decreased air entry in the basal right hemithorax. No inspiratory or expiratory wheeze or stridor was noted. Heart sounds were normal with no additional sounds. Abdominal examination did not reveal any abnormality. Cranial nerves, sensory and motor examination findings were also normal. Electrocardiography and Troponin-I were normal.

The final blood investigation panel is shown in table 1. Her chest radiograph showed widened mediastinum with no parenchymal abnormality. A contrast enhanced computed tomography (CECT) scan of the thorax was carried out. Sputum and bronchoalveolar lavage cultures were not sent as there were no parenchymal lung lesions.

Task 1
What does the CECT scan of the thorax (figure 1) reveal?
Go to Answers >>

Task 2
What is the differential diagnosis of the CECT scan abnormality in this patient?
Go to Answers >>

A CT-guided Tru-cut biopsy was carried out for histological confirmation. However, histopathology was inconclusive showing only areas of marked fibrosis, hyalinisation and focal areas of necrosis. The possibility of sampling error was considered, therefore, a fluorodeoxyglucose (FDG) positron emission tomography (PET) scan was undertaken to identify areas suitable for biopsy. The PET scan showed an FDG avid ill-defined soft tissue density mass involving the entire mediastinum with areas of extensive necrosis in the centre and hyper-enhancing non-necrotic solid components in the superior and inferior aspect (figure 2). However, the patient had difficulty lying flat and to ensure a good size sample, a limited thoracotomy was performed and the biopsy was taken from the superior aspect of the mass.

Task 3

What are the causes of mediastinal granulomatous disease?

Go to Answers >>

Task 4

What is the diagnosis?

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Histopathology from the repeat biopsy showed areas of hyalinisation and marked fibrosis and necrotic foci (figure 3). In addition, there were several multinucleated giant cells and ill-defined granulomas with moderate lymphoplasmacytic infiltration. Granulomatous mediastinal disease was considered based on the histopathology report.

Fungal infection was considered one of the differential diagnoses based on the histopathology report. Periodic acid–Schiff and Grocott methenamine silver (GMS) staining revealed many branched septate slightly thickened fungal hyphae suggestive of mucor. There was no evidence of histoplasmosis or aspergillosis, Gene Xpert from the tissue was negative for *M. tuberculosis*. Fungal culture was not sent initially as there was no suspicion of fungal disease; therefore, species and genus identification could not be carried out due to the lack of fresh tissue. However, the presence of granulomatous fibrosing mediastinitis prompted us to send for fungal studies. The patient was started on intravenous liposomal amphotericin B considering a diagnosis of mucormycosis. However, she succumbed to infection and multiorgan failure.

Discussion

Mucormycosis is caused by fungi belonging to the order *Mucorales*. Humans acquire the infection predominantly by inhalation of sporangiospores, and occasionally by ingestion of contaminated food or traumatic inoculation [1]. 11 genera and ∼27 species under *Mucorales* are associated with human infections. *Rhizopus arrhizus* is the most common agent causing mucormycosis worldwide, followed by *Lichtheimia*, *Apophysomyces*, *Rhizomucor*, *Mucor* and *Cunninghamella* species [1]. They are ubiquitous in nature and are found on decaying vegetation and in the soil. Their morphology of broad, aseptate or sparsely septate ribbon-like hyphae is very distinct, which allows for a presumptive identification from clinical specimens.

TABLE 1 Results of the blood investigation panel

Investigation	Result	Reference range
Haemoglobin (g·dL^{-1})	9.0	Male: 13–18; female: 11.5–16.5
Total leukocyte count (per mm^3)	13 500	4000–11 000
Differential leukocyte count (%)		
Neutrophils	92	40–60
Lymphocytes	4	20–40
Monocytes	2	2–8
Eosinophils	2	2–8
Platelet count (per mm^3)	170 000	150 000–450 000
Serum urea (mg·dL^{-1})	33	5–20
Serum creatinine (mg·dL^{-1})	0.35	Male: 0.74–1.35; female: 0.59–1.04
Calcium (mg·dL^{-1})	8.18	8.6–10
Corrected calcium (mg·dL^{-1})	8.54	8.6–10
C-reactive protein (mg·L^{-1})	186.4	0–5
Random blood glucose (mg·dL^{-1})	114	110–140
Antinuclear antibody (ANA) Hep2 line	Negative	

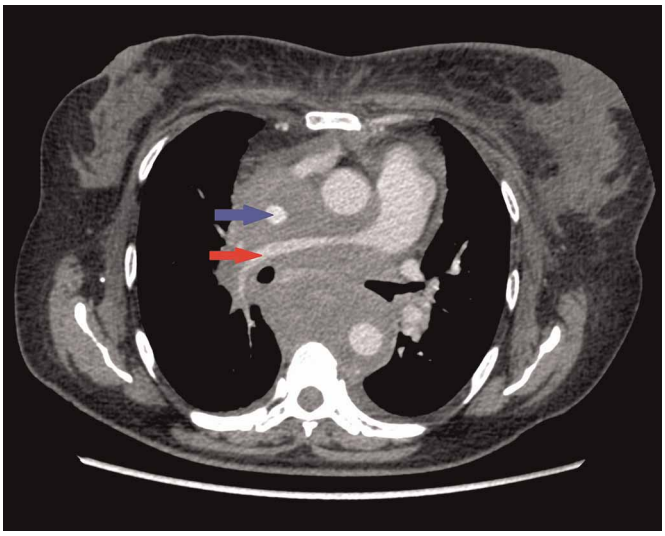

FIGURE 1 Contrast enhanced computed tomography scan of the thorax. The blue arrow indicates the superior vena cava, the red arrow indicates the right pulmonary artery.

The exact burden of mucormycosis is not known, as it is rare in developed countries [1]. However, a change in the epidemiology of mucormycosis has been observed in recent years with a rise in the incidence of the disease, new causative agents and a susceptible population. The rise has been observed globally, but it is significant in Asian countries mainly due to the rising population with diabetes mellitus [1, 2]. New risk groups have emerged that include post-tuberculosis, patients with chronic kidney disease, following a stay in an intensive care unit and severe COVID-19 infection, especially in developing countries. In developed countries, the rise in the incidence of mucormycosis is related to intense immunosuppression in haematological malignancies and transplant recipients [1–4].

Clinical presentation is classified according to the organ involvement. It can be: 1) rhino-cerebral, 2) pulmonary, 3) cutaneous, 4) gastrointestinal or 5) disseminated disease. It is angioinvasive, having a clinical hallmark of tissue necrosis resulting in subsequent thrombosis. The most reported sites of invasive

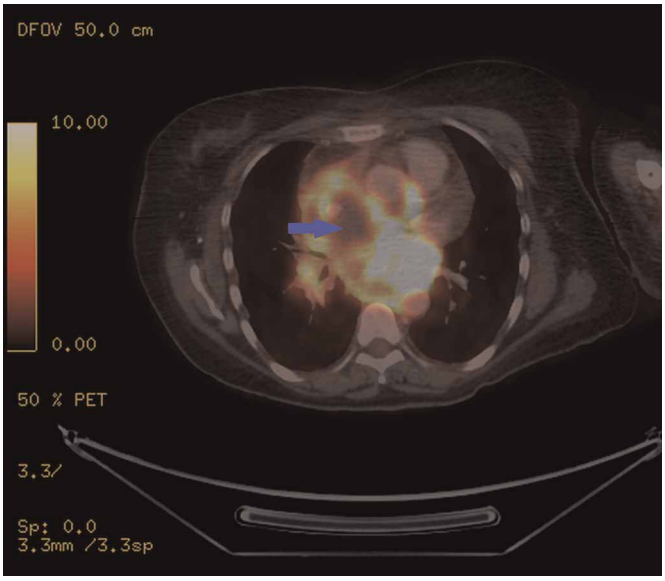

FIGURE 2 Positron emission tomography scan showing fluorodeoxyglucose avid ill-defined soft tissue density mass involving entire mediastinum with areas of extensive necrosis (blue arrow) in the centre and a hyper-enhancing non-necrotic solid component in superior and inferior aspect.

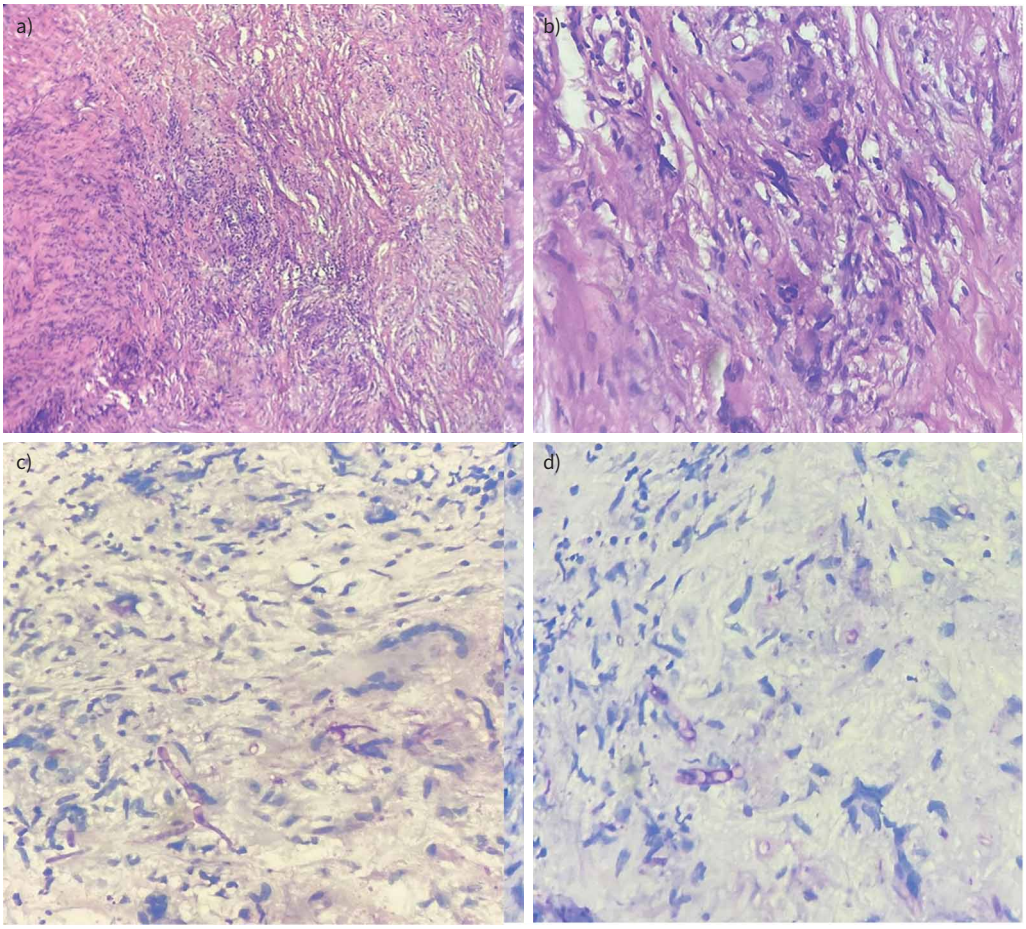

FIGURE 3 Histopathology of tissue obtained by lung biopsy. a) Areas of marked fibrosis, hyalinisation, and focal areas of necrosis (haematoxylin and eosin (HE), 100×); b) several multinucleated giant cells and ill-defined granulomas with moderate lymphoplasmacytic infiltration (HE, 400×). c, d) Many branched septate slightly thickened fungal hyphae suggestive of mucor (Periodic acid–Schiff and Grocott methenamine silver, respectively, 400×).

mucormycosis have been the sinuses (39%), lungs (24%) and skin (19%) [3–5]. Very rarely, mucormycosis can present as a mediastinal mass and should be included in the differential diagnosis along with Hodgkin disease, non-Hodgkin lymphoma, neuroblastoma, germ cell tumour, teratoma, thymomas and very rarely chronic fibrosing mediastinitis, also termed as sclerosing mediastinitis [6].

Our case is a rare presentation of fibrosing/sclerosing mediastinitis due to mucor. Histopathologically it showed an invasive proliferation of the fibrous tissue within the mediastinum.

Fibrosing mediastinitis is most commonly seen between age 13 and 65 years with a strong preponderance for young females [7]. Two major subtypes have been described in the literature, granulomatous and non-granulomatous. In the granulomatous type, the most common aetiologies are tuberculosis and histoplasmosis [8]; other causes include blastomycosis, aspergillosis, cryptococcosis, mucormycosis and granulomatous diseases like sarcoidosis [9]. Non-granulomatous fibrosing mediastinitis is considered an idiopathic reaction to autoimmune disorders (*e.g.* Bechet disease, rheumatoid arthritis and systemic lupus erythematosus), drugs (*e.g.* methysergide) and radiation; other causes include adenocarcinoma of the lung and Hodgkin disease. It is frequently associated with other fibrosing conditions such as retroperitoneal fibrosis, primary sclerosing cholangitis and orbital pseudotumours [8]. Fibrosing/sclerosing mediastinitis can often present with mediastinal masses and symptoms are due to compression of the vital mediastinal structures [8]. In four case series, the commonest symptoms noted were cough followed by dyspnoea; other symptoms included chest pain, haemoptysis, fever and superior vena cava (SVC) syndrome [10–13].

Given that all the above mediastinal masses can present with similar symptoms and similar imaging appearances, histopathology forms an important and essential tool for confirmation of diagnosis [6].

Radiologically two distinct subtypes are mentioned in literature. In the first, a soft tissue mass is localised with the presence of dense and stippled calcification; a pattern more frequently seen in the granulomatous type. The second subtype is of diffuse and infiltrative nature involving different compartments of the mediastinum. Calcification is generally not seen in this pattern [8].

Our case shows a diffuse infiltrative soft tissue mass; however, granulomas were present on the histopathology, and as mentioned earlier, the GMS stain was positive for mucor. The other aetiologies of the granulomatous subtype (*e.g.* tuberculosis, aspergillosis, cryptococcosis, sarcoidosis) were mostly excluded, including any other autoimmune disease. Malignant cells were not detected from the sample and there was no history of prior radiation.

Despite extensive investigation, we were unable to detect any predisposing factor for mucor in our case. This appears to be quite unusual, however, we cite another case report where mucormycosis occurred in an immunocompetent individual [4]. Interestingly, there was a conspicuous absence of any lung parenchymal lesion (namely consolidations, masses, nodules or any pleural effusion) from the mucor, nor any distant foci of infection. It is an important lesson that although rare, fungal studies should be sent from the biopsy sample even if there is no suggestive lung parenchymal pathology. We could have missed the diagnosis if fungal stains were not done. However, as mentioned, there was very little suspicion of fungal disease in an otherwise immunocompetent individual, and therefore, fungal cultures were not sent.

Diagnosis involves the identification of organisms in tissue by histopathology and culture confirmation. However, culture often yields no growth, and histopathological identification of an organism may hold the key to diagnosis. PCR may be useful for identifying the causative species when histopathology is positive but cultures are negative [6]. Culture of the organism from body fluids is successful in fewer than 20% of cases. While there have been several studies showing the value of serum or plasma PCR tests, their utility in clinical practice is unclear, and their commercial availability remains limited. A negative test cannot rule out mucormycosis. In addition to traditional culture techniques and PCR with sequencing, matrix-assisted laser desorption ionisation-time of flight (MALDI-TOF) mass spectrometry can be used to identify the causative species from culture specimens [6]. In our case, the diagnosis was established by biopsy; however, as fungal culture was not sent, genus identification was not possible. Our centre did not have MALDI-TOF mass spectrometry available for definitive confirmation.

Our case is not the first to be reported. Vyas *et al*. [4] reported a similar case of mediastinal mass with SVC obstruction syndrome in an immunocompetent patient with both the lungs and mediastinum involved. A case of mucormycosis induced anterior mediastinal abscess has been reported by Moorthy *et al*. [14], where aggressive surgery along with an antifungal was the mainstay of management. There are a few case reports of mediastinal mucormycosis in patients with underlying risk factors like uncontrolled diabetes and chronic granulomatous disease [15]. Mediastinal mucormycosis is rare and forms the subject matter of several case reports [4, 5, 14, 15].

Management usually comprises a combination of surgical debridement, antifungal therapy, and elimination of predisposing factors [16]. Early initiation of antifungal therapy improves outcomes [17]. Liposomal amphotericin B is the drug of choice for initial therapy [18]. Pulmonary mucormycosis has mortality rates as high as 87%, while in mediastinal involvement the mortality rate is >80%. Widely disseminated mucormycosis carries a mortality rate of 90–100% [16, 19]. Delayed diagnosis and/or late presentation of mucormycosis has a very poor prognosis with limited surgical options [20]. As medical treatment alone is often unsuccessful in pulmonary and mediastinal mucormycosis, it becomes imperative to have an early diagnosis with histological confirmation and initiate treatment to improve mortality [15].

Answer 1

The CECT scan of the thorax showed a huge mediastinal mass measuring 14×10.3×11.7 cm, encasing the trachea, bilateral bronchi, pulmonary vessels, oesophagus, all great vessels and their branches, with infiltration into the right atrium. It did not reveal any parenchymal lesion or congenital pulmonary abnormality.

<< Go to Task 1

Answer 2

Differential diagnoses are:

- Lymphoma (Hodgkin and non-Hodgkin)
- Thymic neoplasms
- Germ cell tumours
- Neuroblastoma and other neurogenic tumours
- Granulomatous diseases like tuberculosis
- Histoplasmosis
- Lung carcinoma

<< Go to Task 2

Answer 3

Causes of mediastinal granulomatous disease:

- Bacterial: *Mycobacterium tuberculosis*, *Actinomyces* and *Nocardia*, *Treponema*
- Fungal: *Histoplasma*, *Cryptococcus, Blastomyces*, *Aspergillus*
- Parasitic: *Wuchereria*
- Sarcoidosis
- Silicosis
- Berylliosis
- Drug induced: methysergide
- Hypersensitivity pneumonitis
- Amyloidosis
- Idiopathic mediastinal granuloma
- Idiopathic fibrosing mediastinitis
- Mediastinal irradiation
- Immunoglobulin G4 related
- Granulomatosis with polyangiitis

<< Go to Task 3

Answer 4

Sclerosing mediastinitis secondary to mucormycosis.

<< Go to Task 4

Conflict of interest: The authors have nothing to disclose.

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