Review Article

Benign disorders of the mediastinum: a narrative review

Saad Farooq[1], Sabiha Armin[2], Daniel Ocazionez[3], Rosa M. Estrada-Y-Martin[1], Sujith V. Cherian[1]^

[1]Divisions of Critical Care, Pulmonary and Sleep Medicine, Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center (UTHealth), Houston, TX, USA; [2]Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center (UTHealth), Houston, TX, USA; [3]Department of Diagnostic and Interventional Radiology, McGovern Medical School, The University of Texas Health Science Center (UTHealth), Houston, TX, USA

Contributions: (I) Conception and design: S Farooq, S Armin, RM Estrada-Y-Martin, SV Cherian; (II) Administrative support: SV Cherian, D Ocazionez, RM Estrada-Y-Martin; (III) Provision of study materials or patients: D Ocazionez, RM Estrada-Y-Martin, SV Cherian; (IV) Collection and assembly of data: S Farooq, S Armin, SV Cherian; (V) Data analysis and interpretation: S Farooq, SV Cherian, RM Estrada-Y-Martin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Sujith V. Cherian, MD, FCCP. Divisions of Critical Care, Pulmonary and Sleep Medicine, Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center (UTHealth), 6431 Fannin Street, Houston, TX 77030, USA. Email: sujithvcherian@gmail.com; sujith.v.cherian@uth.tmc.edu.

Background and Objective: There are several benign processes that affect the mediastinum with considerable morbidity that may range from reactive entities to neoplastic disorders. This review article will focus on non-neoplastic benign mediastinal diseases which include large vessel vasculitis such as Takayasu and giant cell arteritis, mediastinal granulomas, fibrosing mediastinitis and mediastinal infections. These diseases can cause significant morbidity and mortality; therefore, we aim to familiarize readers with the pathophysiology, epidemiology and diagnosis of these mediastinal diseases and provide an update on the treatment options available.

Methods: We searched various databases such as PubMed and Google Scholar from August 2023 until January 2024 for the various benign mediastinal disorders we wanted to discuss. Relevant articles that were written in English were shortlisted and used to help write this narrative review.

Key Content and Findings: We will briefly discuss the anatomy of the mediastinum along with some of the more common benign mediastinal disorders. We will discuss epidemiology, etiology, clinical features, and treatment. Relevant laboratory, and imaging findings important to make the diagnosis will be included as well.

Conclusions: Prompt diagnosis of these diseases is of the utmost importance as delay in care may be associated with increased mortality. Our article aims to provide an up-to-date review and summarize the current literature regarding these diseases.

Keywords: Mediastinum; vasculitis; infection; mediastinitis

Received: 23 March 2024; Accepted: 11 August 2024; Published online: 25 September 2024.
doi: 10.21037/med-24-14
View this article at: https://dx.doi.org/10.21037/med-24-14

Introduction

The mediastinum is the central part of the thoracic cavity bounded by the sternum anteriorly, the pleurae laterally and the thoracic vertebral spine posteriorly. It contains several vital structures including the pericardium, heart, aorta, trachea, esophagus, and the thoracic duct which may all be affected by different diseases (1,2). For the purposes of this article, we focus on causes of mediastinitis, granulomas and

^ ORCID: 0000-0003-0177-9979.

Table 1 The search strategy summary

Items	Specification
Date of search	08-2023 till 01-2024
Databases and other sources searched	PubMed, Google Scholar
Search terms used	Mediastinitis; benign mediastinal disorders vasculitis
Timeframe	1980–2023
Inclusion criteria	English only
Selection process	Independently. All selected articles were reviewed by all authors

vasculitides that involve the structures in the mediastinum.

The main blood vessels contained within the mediastinum include the aorta, superior and inferior vena cava, and pulmonary arteries (1). Involvement of these vessels often occurs due to vasculitides which results in inflammation of the vessel wall and may cause perfusion to vital structures. Giant cell and Takayasu arteritis (TA) are the main vasculitides affecting large vessels. While some of these processes are not clinically apparent and may be found incidentally on imaging, others are found when patients present with symptoms secondary to mass effect. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-14/rc).

Methods

We conducted a comprehensive literature review of relevant articles on databases such as PubMed and Google Scholar that were written in English. The literature review was conducted from August 2023 until January 2024. The articles were shortlisted by the authors and used to help write this review (*Table 1*).

Vasculitides

Takayasu and giant cell arteritis (GCA)

TA and GCA are both large vessel vasculitides that can affect the aorta and its major branches. Inflammation can lead to loss of vascular wall integrity and cause bleeding, ischemia, and thrombosis (3).

TA was first described in 1908 by a Japanese ophthalmologist (4). It is also described as a pulse-less disease due to the absence of radial pulse in some patients. It is the most common vasculitis to affect the aorta in patients under the age of 50 years. The inflammation may be limited to a particular part of the vessel, or it may be diffuse (4). Other arteries that may be involved include the coronaries, pulmonary and renal arteries which can lead to vascular aneurysms, thrombosis, wall rupture, dissection, and obstruction of the vascular lumen (5).

GCA (also called Hortons disease) is the most common primary systemic vasculitis which can affect both extra or intra-cranial vessels (6). The similarities between these two large vessel vasculitides have led some to question whether they represent varying phenotypes within the same spectrum of disease (7).

Epidemiology

TA is predominantly seen in young women of reproductive age and mainly in Asian countries such as Japan. It is nine times more common in females than males (8). Although data on incidence in the United States (US) is limited, it is estimated to effect 0.9 people per million but there is considerable heterogeneity between different populations (9).

On the other hand, GCA affects older population, usually more than 50 years of age. Peak incidence is typically in the 7th decade of life. Northern Europeans and women are more commonly affected. In the US, GCA is the most frequent primary vasculitis with an incidence of 18/100,000 in one study (10).

Etiology

It is unclear what exactly causes TA and GCA and what the initial triggering event is. Vascular injury occurs primarily by cell mediated mechanisms. A genetic association with human leukocyte antigen (HLA) alleles has been reported and specific HLA alleles may be associated with more severe forms of the disease (11). It is believed that cell-mediated

Table 2 Classification criteria for Takayasu arteritis [modified with permission from the reference (13)]

Takayasu arteritis classification criteria	Points
Clinical criteria	
Arm or leg claudication	2
Reduced pulse in upper extremity	2
Ischemic cardiac pain or angina	2
Female gender	1
Vascular bruit	2
Carotid artery abnormality	2
Difference of ≥20 mmHg in systolic blood pressure	1
Imaging criteria	
Systemic involvement of paired arteries	1
Abdominal aorta involvement with renal and mesenteric artery involvement	3
One arterial territory involved	1
Two territories involved	2
Three arterial territories involved	3

Absolute requirements: (I) age ≤60 years at the time of diagnosis; (II) evidence of vasculitis on imaging. Score ≥5 is needed for the diagnosis of Takayasu arteritis.

mechanisms cause an inflammatory process that involves the aorta and its major branches and lead to vascular damage, fibrosis, and scarring (10).

Under microscopic examination, cytotoxic T lymphocytes which cause vascular injury by releasing various cytokines are observed. The inflammatory pattern is granulomatous and giant cells along with well-formed granulomas containing clusters of activated macrophages may be seen in some patients (5).

Severe adventitial scarring may be seen in TA whereas in GCA inflammation is most severe in the inner media of blood vessels and adventitia is relatively spared. Intimal hyperplasia may be present as well. In GCA, compact granulomas are usually absent whereas giant cells and epithelioid macrophages may be seen. Furthermore, vascular smooth muscle and elastic fibers may be lost due to vasa vasorum involvement (5).

Clinical features and diagnosis

Due to ongoing inflammation, both TA and GCA can cause non-specific symptoms like fatigue, fever, lethargy, weight loss, and hypertension. More specific symptoms are upper extremity or chest pain. Once the damage to the aorta and its major branches occur, weakness and neurological manifestations such as strokes and seizures may be present due to arterial insufficiency (8). In some patients, tenderness around the region of the carotid artery may be seen. However, some patients may be asymptomatic only to be diagnosed on autopsy (5).

On examination, high or discordant blood pressure between limbs, arterial bruits and decreased or absent pulses may alert a clinician to the possibility of this diagnosis. Rashes resembling erythema nodosum or pyoderma gangrenosum may be seen in a few patients.

Clinical symptoms often reflect the end-organ whose perfusion is affected, for example visual impairment may result from involvement of retinal vessels. Other symptoms may include unilateral headache, jaw pain, scalp tenderness, vision loss, and myalgias.

Importantly, GCA is associated with polymyalgia rheumatica (PMR) in 40% to 60% of patients at diagnosis which can cause myalgia of various parts such as shoulder, pelvic, and back muscles; therefore, a diagnosis of GCA should be considered in all patients with PMR (10). TA and GCA diagnosis can be made with the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) criteria which scores the probability of having these vasculitides by using absolute and additional criteria (12,13). For GCA importance is given to laboratory parameters such as elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as well. A score of 5 or greater is needed for diagnosis of TA whereas a score of 6 or greater is needed for GCA (*Tables 2,3*) (12,13).

Laboratory data

There are no specific lab markers that indicate large vessel vasculitides. Acute phase reactants such as ESR, CRP, and interleukin-6 (IL-6) may be elevated which helps support the diagnosis in patients with other features of the disease. Anemia of chronic disease and thrombocytosis may also be seen (12,13).

Imaging

Imaging studies involving computed tomography (CT) angiograms and magnetic resonance imaging (MRI) can help in determining the extent of the disease. Sometimes the diagnosis may be incidentally discovered based on imaging done for some other cause (14). Imaging may show vascular

Table 3 Giant cell Arteritis classification criteria [modified with permission from the reference (12)]

Giant cell arteritis classification criteria	Points
Clinical criteria	
Sudden vision loss	3
Jaw or tongue claudication	2
New temporal headache	2
Shoulder/neck morning stiffness	2
Scalp tenderness	2
Abnormal temporal artery examination	2
Lab, biopsy and imaging criteria	
ESR ≥50 mm/hour or CRP ≥10 mg/liter	3
Halo sign on temporal artery ultrasound or positive temporal artery biopsy	5
Bilateral axillary involvement	2
FDG-PET avid activity throughout the aorta	2

Absolute requirement: age ≥50 years at the time of diagnosis. A score of 6 or greater needed for diagnosis. ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FDG-PET, fluorodeoxyglucose positron emission tomography.

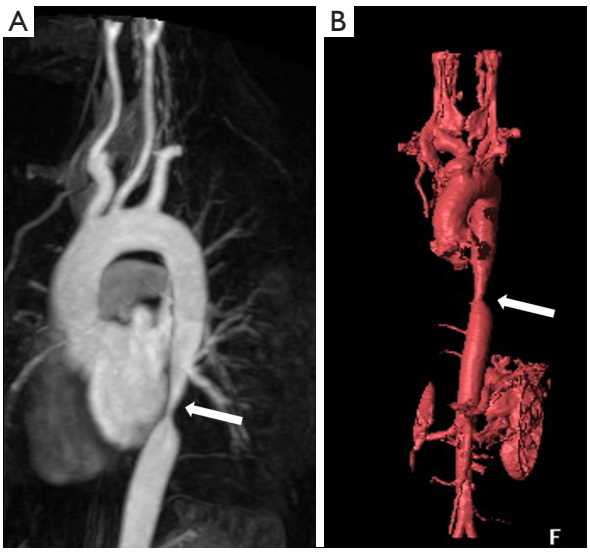

Figure 1 A 27-year-old woman with Takayasu arteritis. (A) Magnetic resonance angiography showing severe narrowing of the descending thoracic aorta (white arrow). (B) 3-dimensional volume-rendered magnetic resonance image showing severe narrowing of the descending thoracic aorta (white arrow).

wall thickening, luminal narrowing and aneurysms (15) (*Figure 1*). Positron emission tomography (PET) scans are also being used to differentiate large vessel vasculitis from clinical mimickers and to monitor disease remission (16).

EULAR recommends MRI as the initial diagnostic modality to investigate mural inflammation or stenosis in patients with suspected TA, with PET and CT scans as alternative imaging modalities if MRI is not promptly available (17). PET scan is particularly useful in patients with non-specific symptoms as it helps rule out alternative diagnoses. Ultrasound is of limited utility in assessment of thoracic aorta (17). Conventional angiography used to be the gold standard for diagnosis but is not recommended now due to availability of more advanced imaging techniques and the invasive nature of the procedure. EULAR recommends that in cases where diagnosis cannot be confirmed via clinical history, laboratory tests and imaging, additional tests (biopsy) and further imaging should be obtained to confirm the diagnosis. Importantly, treatment should not be delayed while waiting to obtain imaging studies if the large vessel vasculitis is suspected as the consequences of untreated vasculitis may cause irreversible damage (17).

For GCA, EULAR recommends ultrasound of temporal or axillary arteries for predominantly intracranial suspected GCA whereas ACR recommends an initial long segment (>1 cm) unilateral temporal artery biopsy. ACR recommends contralateral biopsy in cases of negative initial biopsy or if symptoms are not unilateral. Treatment with-corticosteroids should be initiated as soon as the diagnosis is suspected and a biopsy should be obtained within 2 weeks of starting steroids (13,18). Temporal artery biopsy is recommended over performing ultrasound or MRI to aid in diagnosis but in patients with newly diagnosed GCA, it is recommended to obtain non-invasive imaging to assess for large vessel involvement (18).

Treatment

Corticosteroids form the backbone of treatment for large vessel vasculitides. For TA, EULAR recommends starting 40–60 mg/day of prednisone or equivalent and once disease is controlled, taper to 15–20 mg/day over 2–3 months (19). Tocilizumab and methotrexate may be used as adjuncts in select cases (19). Occasionally, for life or organ threatening disease pulse dose steroids (500–1,000 mg IV) may be used for the first few days and then tapered to oral prednisone. Steroids sparing agents are commonly used and include methotrexate, azathioprine, and mycophenolate; however, there is no good quality data to favor one over the other (20).

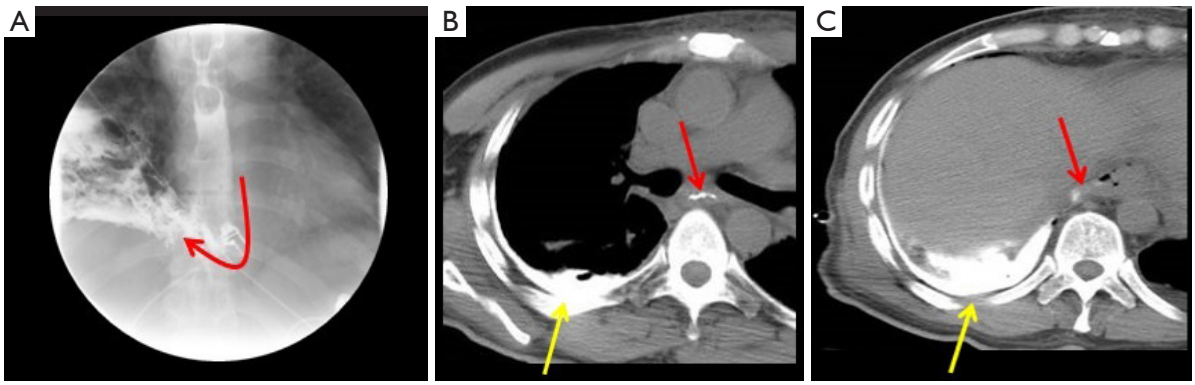

Figure 2 A 50-year-old man with esophageal rupture. (A) Fluoroscopic image showing a defect in the left esophageal wall with the red arrow pointing towards contrast tracking into the right pleural space. (B) Axial views of chest CT scan showing contrast in the esophagus (red arrow) and extravasation into the right pleural space (yellow arrow). (C) Axial views of chest CT scan showing contrast in esophagus (red arrow) and extravasation into the right pleural space (yellow arrow). CT, computed tomography.

ACR also recommends starting tocilizumab in addition to corticosteroids in patients with newly diagnosed GCA whereas EULAR recommends it in selected patients only (18,19).

For existing vascular stenosis, endovascular and other surgical procedures may be used to help relieve vascular narrowing and reduce symptoms. Regular follow-ups and imaging studies are needed to ensure that there is no ongoing subclinical vasculitis.

The optimum duration of treatment is not defined by ACR whereas EULAR recommends to slowly taper steroids over 2–3 months once the disease is controlled. Neither society recommends the addition of antiplatelets or anticoagulants unless other indications for their use exist (18,19).

Mediastinitis

Mediastinitis refers to infection within the connective tissue of the mediastinum. It may occur in the form of (I) acute mediastinitis due to descending necrotizing infection or esophageal rupture and (II) post-surgical mediastinitis (PSM) or chronic mediastinitis as (I) mediastinal granulomas (MG) and (II) fibrosing mediastinitis (FM) (21). Due to involvement of several vital structures within the mediastinum, prompt diagnosis and management is of paramount importance.

Acute mediastinitis

Acute mediastinitis is an infectious process typically caused by bacteria. These infections can spread rapidly and cause significant morbidity and mortality. They may result from direct contamination, post-surgery, lymphangitic or hematogenous spread, extension from the head and neck or extension from nearby structures such as lung, pericardium, or esophagus (22). While in the past, most cases of mediastinitis were due to esophageal rupture or extension of infections from the head and neck, currently, most cases of mediastinitis are post-surgical.

Esophageal perforation (Boerhaave's syndrome) is commonly due to forceful retching or vomiting and can cause acute mediastinitis (*Figure 2*). Esophageal perforation may also be iatrogenic, for example during endoscopy or failed surgical anastomosis, trauma, or from foreign body ingestion. The underlying esophagus is usually normal although some patients may have esophagitis or preexisting ulcers. Mortality is 21% to 50 % and any delay in recognition and treatment increases mortality risk substantially (23).

Descending necrotizing mediastinitis (DNM) is an infection which starts from above the mediastinum and then descends towards the mediastinum (*Figure 3*) (24). Sources include dental and tonsillar abscess, epiglottitis, and neck infections, which can spread through the facial planes and track downward into the mediastinum. DNM is often polymicrobial with both aerobic and anaerobic bacteria involved. In a report of 17 patients with DNM, all patients required surgery along with antibiotics. Mortality rates are variable and range from 6% to 40% with more recent studies suggesting a lower mortality rate than observed in prior studies (22,25).

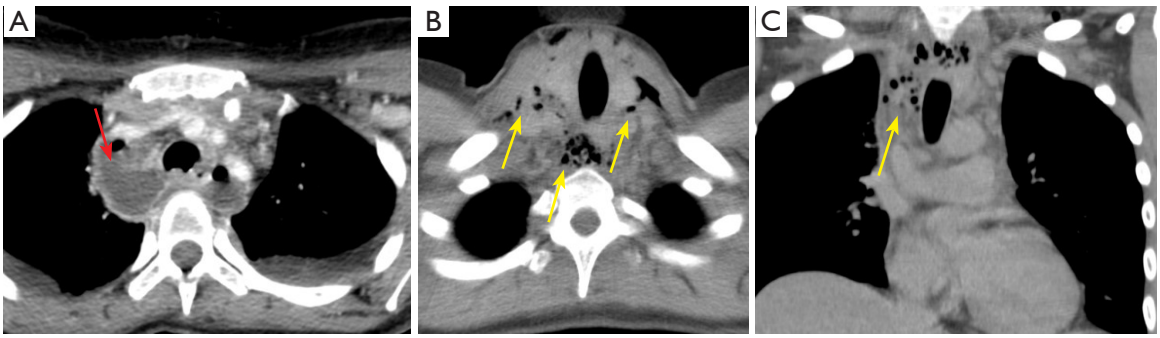

Figure 3 A 60-year-old man with odontogenic infection who developed neck and mediastinal infection as seen by foci of gas. (A) Axial view chest CT scan showing upper mediastinal involvement and rim-enhancing fluid collections (red arrow). (B) Axial view chest CT scan showing multiple foci of gas because of infection in the neck (yellow arrows). (C) Coronal view chest CT scan showing gas in the mediastinum (yellow arrow). CT, computed tomography.

Epidemiology

Risk factors for DNM include immunodeficiency, smoking, alcohol use, use of glucocorticoids diabetes and poor dentition. Men and women appear equally affected and mean age of presentation is around 50 years (25).

Esophageal perforation is rare with an incidence of 3.1/million per year. The majority is iatrogenic whereas the rest are spontaneous or due to foreign body ingestion (26). Spontaneous rupture is associated with the poorest survival (27).

Clinical features

Patients may present with signs and symptoms of infection such as fever, chills, night sweats and more acute presentation may be due to septic shock. In esophageal perforation, patients may have dysphagia, odynophagia, severe chest pain and may have a preceding history of retching and/or vomiting. On exam, crepitus due to subcutaneous emphysema may be present (28).

Clinical features for DNM were established by Estrera *et al.* and include clinical manifestation of severe infection, characteristic imaging, evidence of necrotizing mediastinitis on surgery and/or autopsy or both and establishment of relationship between an oropharyngeal or cervical infection and development of DNM (29).

Lab markers

Acute inflammatory markers such as ESR, CRP, procalcitonin and white cell count will be raised but are non-specific. Blood cultures should also be obtained. Some patients may have evidence of disseminated intravascular coagulation (DIC) (25).

Imaging

CT scan with contrast is often the modality of choice for acute mediastinitis. Widening of mediastinum, mediastinal fluid collection, extraluminal gas bubbles, increased fat attenuation, lymphadenopathy all support the diagnosis (30).

Findings suggestive of esophageal perforation on chest imaging include esophageal wall thickening, free peritoneal air or subcutaneous emphysema, pleural effusions, pneumothorax or hydropneumothorax, widened mediastinum and pneumomediastinum. A contrast esophagogram establishes the location and extent of the rupture but false negative may occur in up to 10% of cases (27).

Treatment

Management of mediastinitis depends on the underlying cause. Often patients require intensive care unit (ICU) level of care as they may be in septic shock. Airway compromise should also be anticipated and plan to manage airway should be discussed with the anesthesia team, particularly in cases of DNM. Antibiotics with additional anerobic coverage are indicated in all patients. Surgical debridement in surgical candidates is often indicated. For DNM, surgical drainage of the deep neck infection along with mediastinal drainage should be performed as soon as possible (31).

In cases of esophageal perforation, it is important to avoid all oral intake. Total parenteral nutrition is often initiated along with proton pump inhibitors and possible addition of antifungals. Endoscopic techniques are also being increasingly used, especially in patients who are not candidates for open surgery (32).

PSM

PSM can manifest in two primary forms: superficial, which involves the skin and subcutaneous tissue (occurring above the fascial line), and deep, affecting the sternum, ribs, and retrosternal tissues (occurring below the fascial line). A key diagnostic indicator is the presence of subcutaneous emphysema, which is detectable through imaging techniques (33).

Postoperative infections, particularly following cardiothoracic or esophageal procedures, have become the most common etiology associated with mediastinitis. PSM carries an alarmingly high mortality rate, estimated between 14% and 47%, and is associated with numerous challenges, including the need for repeated surgical interventions, prolonged stays in intensive care units, extended hospitalization, and the potential development of other postsurgical complications (33-35). These complications can encompass pericarditis, sepsis, multiorgan failure, airway obstruction, and bleeding diathesis, underscoring the urgency of a multidisciplinary approach to its management.

Pathogenesis

The precise pathogenesis of PSM remains a subject of ongoing research, but several factors are believed to contribute such as sternal separation or instability arising from chest wall issues such as obesity, underlying obstructive lung diseases, or poor wound healing. Additionally, preoperative colonization and the migration of bacteria from other body sites into the mediastinal space play a role, as do the specific procedural and surgical techniques employed. In obese patients, the greater presence of adipose tissue provides a potential environment for microbial growth, while issues related to antibiotic dosage adjustments may arise in patients with larger volumes of distribution. Patients with underlying chronic obstructive pulmonary disease (COPD) face an increased risk of PSM, primarily due to mechanical stress on the sternum resulting from frequent coughing, which can lead to sternal instability and dehiscence. Postoperative respiratory complications and prolonged mechanical ventilation further compound this risk (34,35).

Epidemiology

Despite its relatively low overall incidence, ranging from 0.4% to 7% across most medical institutions, PSM is a life-threatening complication (36). The development of both superficial and deep mediastinitis is influenced by various risk factors, encompassing patient-related and surgical technical factors. Patient-related risk factors include older age (age >65 years), obesity (defined as >20% of ideal body weight or body mass index >30 kg/m^2), a history of smoking, diabetes mellitus, chronic infection, chronic obstructive lung disease, the presence of ventricular assist devices, preoperative hemodynamic instability, preoperative renal failure necessitating hemodialysis, sepsis, multiple transfusions (>4 units), prolonged postoperative ventilation, and perioperative immunosuppression (37-39). Surgical technical factors related to PSM include emergency surgery, bilateral internal mammary artery use, prolonged operating room time (>200 minutes), excessive use of electrocautery, and median sternotomy incision.

Microbiology

As is often the case for surgical site infections, most cases of PSM stem from a patient's endogenous flora. Among the culprits for postoperative mediastinitis, Gram-positive *Staphylococcus* (*S.*) species are the most common, with methicillin-sensitive *S. aureus* (MSSA) being prevalent in cases where preoperative nasal MSSA colonization exists (40). Conversely, postoperative mediastinitis involving methicillin-resistant *S. aureus* (MRSA) appears to be linked to nosocomial transmission (40). In a study evaluating intensive care units admissions of 316 patients of PSM in a 10-year period, the most common micro-organisms isolated were MSSA (45%), MRSA (16%), Gram-negative bacilli (17%), coagulase-negative staphylococci (13%) and streptococci (5%) (41). Rarely other micro-organisms associated with PSM include fungi and mycobacteria including *Mycobacterium tuberculosis* (42-44).

Clinical features and diagnosis

Diagnosing PSM poses challenges as it is often difficult to clinically distinguish between superficial and deep sternal wound infections. Diagnosis typically relies on a combination of factors, including clinical history, radiographic features, serologic markers for infection, and microbiologic culture growth. Patients may exhibit signs of superficial or deep PSM for up to a year after surgery, although most cases arise within 30 days postoperatively (33,34). The Centers for Disease Control and Prevention define mediastinitis by the presence of one or more of the following criteria: (I) isolation of microorganisms from mediastinal tissue or fluid culture; (II) evidence of mediastinitis upon gross anatomic or histopathologic examination; or (III) the presence of chest pain, sternal

instability, or fever (>38 ℃), accompanied by purulent drainage from the mediastinum or mediastinal widening on chest imaging (36). Common physical examination findings associated with PSM include wound dehiscence, wound discharge, and sternal instability, particularly when accompanied by fever (41).

Laboratory data

Laboratory tests may reveal leukocytosis, thrombocytosis, electrolyte imbalances, elevated lactic acid levels, increased ESRs, elevated CRP levels, and positive blood cultures. However, no single test is sufficiently sensitive or specific for diagnosing PSM. Given the strong association between PSM and bacterial infections, blood cultures should always be obtained in addition to surgical wound-based culture collections (45,46).

Imaging

Chest radiography may reveal pleural effusions, pneumomediastinum, mediastinal widening, displacement of suture wires, and air-fluid levels (preferably observed on lateral films), suggestive of PSM. However, it is essential to note that these radiographic signs can also be present in cases of postoperative edema, lymphadenopathy, and hemorrhage. For more accurate diagnosis CT and MRI are preferred over radiography or nuclear imaging due to their higher sensitivity and specificity (47). These modalities are particularly valuable for detecting air-fluid levels several weeks after surgery and assessing the depth of dehiscence and infection. CT scans are the preferred choice for evaluating suspected mediastinitis, especially in patients 14 days post-operatively with fever and leukocytosis but without evident signs of infection or sternal wound drainage. CT findings indicative of PSM may include increased attenuation of mediastinal fat, pleural effusions, sternal dehiscence, localized mediastinal fluid collections, and free gas bubbles. However, less than 50% of PSM cases exhibit mediastinal lymphadenopathy, pericardial effusions, lung infiltrates, or mediastinal fistula on CT scans. It is worth noting that obtaining an MRI for PSM diagnosis can be limited by artifact issues caused by sternal wires and the presence of metallic devices in postoperative patients, especially those requiring prolonged mechanical ventilation (30,47,48).

Management of PSM

The treatment of PSM primarily involves early surgical debridement and sternal irrigation, along with culture-directed antibiotic therapy and prolonged antibiotic treatment. Many different surgical strategies have been described including primary closure, revision with open dressings and sternal reconstruction with muscle flaps (either pectoralis major or rectus abdominis or omental flaps). Vacuum assisted closure with application of negative pressure facilitates drainage and tissue granulation which help with wound healing (33,49). The optimal surgical approach however remains unknown, and approach varies depending on operator and institutional experience and expertise. The focus rather should be on prevention which should include a collective approach including preoperative screening for microbes, administration of prophylactic antibiotics, preoperative skin preparation, avoiding wound contamination, proper surgical technique and optimizing conditions for wound healing and correcting hyperglycemia (50-52).

Regarding antimicrobial therapy, it typically extends from 4 to 6 weeks for most patients and can extend to months for those requiring sternal resection and flap use. Initial empiric therapy involves broad-spectrum coverage against both Gram-positive cocci and Gram-negative bacilli. In cases where MRSA is a concern, intravenous vancomycin, and a third-generation cephalosporin, such as ceftazidime or cefotaxime, or alternatives like fluoroquinolones or aminoglycosides may be appropriate choices (53). However, the treatment regimen should be adjusted based on local antibiograms and the results of blood and mediastinal wound cultures.

MG and FM

MG may appear as a mass in the mediastinum and can result from a variety of etiologies. Histoplasmosis is the most common etiology in the US whereas other causes include tuberculosis (TB), sarcoidosis, other fungal infections, actinomyces and syphilis. These organisms may also cause mediastinal adenitis (2,54). MGs are clusters of necrotic lymph nodes which are filled with semi liquid necrotic debris and surrounded by a thin capsule due to the host cellular immunity attempt to contain possible infection (54).

FM is characterized by an excessive, progressive fibrotic reaction which often compresses nearby structures such as the esophagus and mediastinal vascular structures such as pulmonary artery, pulmonary veins, superior vena cava (SVC) (55). In the US, FM is almost always due to an idiosyncratic response to histoplasma exposure, though the initial infection may not always be apparent (56). Other rare causes include TB, other fungal infections such as

aspergillosis, sarcoidosis, silicosis, immunoglobulin G4 (IgG4) related disease, prior mediastinal radiation, or autoimmune diseases (55).

Epidemiology

Histoplasma is endemic in the Ohio and Mississippi river valleys. Although, many persons are histoplasma seropositive, MG and FM do not develop in most patients (56). As mentioned previously other infections that may cause MG and FM like fungi, syphilis, actinomyces and TB are also present in the US. There is a lack of data on the exact incidence and prevalence of MG and FM and further epidemiological studies are needed. FM is extremely rare, the largest study on FM just described 94 patients over a 9-year period (57).

Etiology

It is not known why certain individuals are predisposed to granuloma formation or FM. Initial infection is often subclinical, and granulomas can form in the affected organ which may eventually necrose and calcify. Occasionally, the involved lymph node can enlarge and coalesce to form granulomas (54).

FM may result from leakage of fungal antigens which can lead to a progressive hypersensitivity response. Certain genotypes may increase the odds of developing FM over granulomas for example, HLA-A2 is associated with more than a 3-fold increase in risk of developing FM (58). It is thought that TB may cause FM in a similar way but mechanisms for other causes of FM are yet unknown. While MG and FM have been speculated as continuums of the same disease; there remains no evidence that this is indeed the case.

The causes of MG and FM may be different outside the US. In a French study 31 patients with FM and pulmonary hypertension were evaluated. Thirteen patients had FM due to sarcoid, 9 due to TB, 2 had prior radiation and 3 had idiopathic FM (59). Interestingly, no patient was thought to have had prior histoplasmosis, likely due to low incidence of histoplasmosis in France.

Clinical features and diagnosis

Patients with MG are often asymptomatic and may have an incidentally discovered mass on imaging performed for other reasons. Patients may have a remote history of histoplasmosis. If the granulomas become large, they can compress adjacent structures and causes symptoms, for example SVC syndrome, dysphagia, odynophagia, cough, pneumonia, or hemoptysis. A fistula may develop between the granuloma and neighboring structure and lead to symptoms as well (54).

FM causes symptoms due to compression of neighboring structures. Symptoms are often progressive over a few years as the growth of fibrous tissue is usually slow at around 1 mm/year (55). SVC syndrome, pulmonary artery or vein obstruction, airway compression and esophageal compression may occur. Obstruction of pulmonary artery or vein may also lead to pulmonary hypertension (59).

If imaging is not characteristic, a biopsy is indicated to rule out any other causes of a mediastinal mass such as lung cancer or lymphoma. However, most patients with malignancies have a more rapid clinical course and calcifications are absent. If the lesion is accessible, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can be performed to obtain tissue samples.

Imaging

Chest CT should be done in patients suspected of having a granuloma and it may show a well-defined mass with some scattered or diffuse calcifications. There may be other signs of prior histoplasma infection such as calcifications in the lymph nodes, spleen, and/or liver. A history of residence in a histoplasma or TB endemic region may be present.

Circumferential compression of structure with a dense infiltrate which often traverses fat planes is more typical of FM whereas lymphadenopathy and lack of calcifications raise concern for adenitis (*Figure 4*) (2). Contrast enhancement is variable. This process is typically unilateral although it can be bilateral as well. Other features seen in FM include mediastinal widening, lymphadenopathy, atelectasis, and pleural effusion. Imaging features are characteristic enough to suggest the diagnosis in the right clinical context (56). PET scans are often non-specific and not routinely performed.

Laboratory data

Histoplasma antigen testing and serologic tests should be performed. If other infections such as TB, aspergillus or sarcoidosis is suspected, testing for them should be performed as well.

Treatment

Asymptomatic patients with classic history and imaging findings can be monitored by serial CT scans. The frequency of imaging is not well established but may

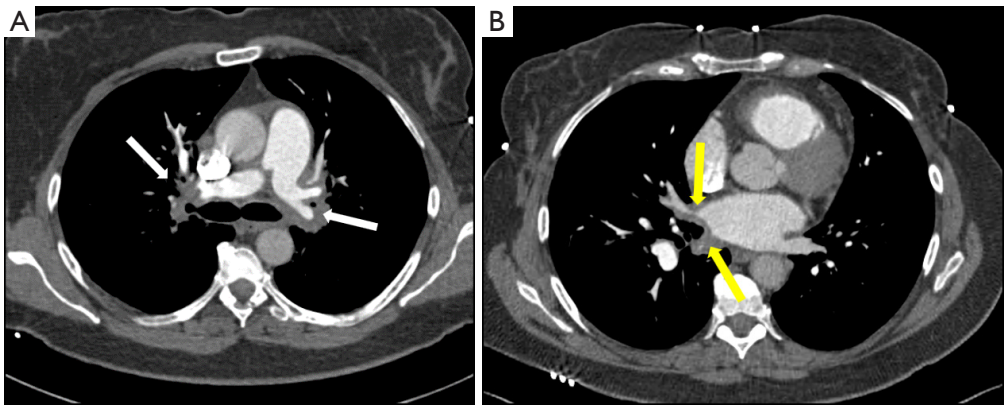

Figure 4 A 60-year-old woman with a known history of fibrosing mediastinitis. (A) Axial view chest CT scan showing diffuse mediastinal soft tissue thickening around the pulmonary artery (white arrows). (B) Axial view chest CT scan showing diffuse mediastinal soft tissue thickening around the pulmonary veins (yellow arrows). CT, computed tomography.

be obtained at 6-month intervals initially and spaced out to yearly scans afterwards. Surgical excision may be recommended if the mass grows. In some patients, MG may resolve spontaneously without any specific treatment. In symptomatic patients the definitive therapy is surgical excision with the removal of the free wall. Sometimes, it may not be possible to completely excise the granuloma as the free wall may be adherent to critical mediastinal structure (54). Infectious Disease Society of America (IDSA) guidelines does not recommend treatment for MG due to histoplasmosis. However, in symptomatic patients itraconazole may be used (60).

For FM, there is no evidence that antifungals or glucocorticoids improve symptoms. There may be some benefit by using rituximab although, further studies are needed to see if it is truly beneficial (54). IDSA only recommends itraconazole if findings cannot differentiate between MG and FM (60). For vascular and airway stenosis, stents may be used to relieve obstruction although, durability of airway stents for FM is poor (54).

Conclusions

There are several causes of benign mediastinal pathologies, which include but are not limited to masses, cystic lesions, benign neoplasms, vasculitis, and infections—of which a few have been reviewed within this article. While some of these entities are discovered incidentally, others are diagnosed when patients present with symptoms secondary to pressure effect on several vital structures within the mediastinum. Furthermore, infections pose an important benign cause due to the several catastrophic consequences associated with them if not diagnosed or managed in time. We hope our article will enable readers to recognize these mediastinal disorders and initiate prompt treatment. Further research is needed on several of these pathologies to improve diagnostic ability and treatment options.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-24-14/rc

Peer Review File: Available at https://med.amegroups.com/article/view/10.21037/med-24-14/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-24-14/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Stoddard N, Heil JR, Lowery DR. Anatomy, Thorax, Mediastinum. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Sep 6]. Available online: http://www.ncbi.nlm.nih.gov/books/NBK539819/
2. Liu T, Gao L, Xie S, et al. Clinical and imaging spectrum of tuberculosis-associated fibrosing mediastinitis. Clin Respir J 2018;12:1974-80.
3. Cid MC, Font C, Coll-Vinent B, et al. Large vessel vasculitides. Curr Opin Rheumatol 1998;10:18-28.
4. Sugiyama K, Ijiri S, Tagawa S, et al. Takayasu disease on the centenary of its discovery. Jpn J Ophthalmol 2009;53:81-91.
5. Stone JR, Bruneval P, Angelini A, et al. Consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology: I. Inflammatory diseases. Cardiovasc Pathol 2015;24:267-78.
6. Savage CO, Harper L, Cockwell P, et al, Howie AJ. ABC of arterial and vascular disease: vasculitis. BMJ 2000;320:1325-8.
7. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Takayasu arteritis and giant cell arteritis: a spectrum within the same disease? Medicine (Baltimore) 2009;88:221-6.
8. Trinidad B, Surmachevska N, Lala V. Takayasu Arteritis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Aug 13]. Available online: http://www.ncbi.nlm.nih.gov/books/NBK459127/
9. Alnabwani D, Patel P, Kata P, et al. The Epidemiology and Clinical Manifestations of Takayasu Arteritis: A Descriptive Study of Case Reports. Cureus 2021;13:e17998.
10. Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. N Engl J Med 2003;349:160-9.
11. Saruhan-Direskeneli G, Hughes T, Aksu K, et al. Identification of multiple genetic susceptibility loci in Takayasu arteritis. Am J Hum Genet 2013;93:298-305.
12. Ponte C, Grayson PC, Robson JC, et al. 2022 American College of Rheumatology/EULAR Classification Criteria for Giant Cell Arteritis. Arthritis Rheumatol 2022;74:1881-9.
13. Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/EULAR Classification Criteria for Takayasu Arteritis. Arthritis Rheumatol 2022;74:1872-80.
14. Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review. J Clin Pathol 2002;55:481-6.
15. Aghayev A. Multimodality Imaging of Large-Vessel Vasculitis, From the AJR Special Series on Inflammation. AJR Am J Roentgenol 2022;218:213-22.
16. Grayson PC, Alehashemi S, Bagheri AA, et al. 18 F-Fluorodeoxyglucose-Positron Emission Tomography As an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients With Large Vessel Vasculitis. Arthritis Rheumatol 2018;70:439-49.
17. Dejaco C, Ramiro S, Duftner C, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis 2018;77:636-43.
18. Maz M, Chung SA, Abril A, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Care Res (Hoboken) 2021;73:1071-87.
19. Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19-30.
20. Somashekar A, Leung YT. Updates in the diagnosis and management of Takayasu's arteritis. Postgrad Med 2023;135:14-21.
21. Stewart BD, VandenBussche CJ, Leon ME. Benign lesions of the mediastinum: A review with emphasis on cytology and small biopsy specimens. Semin Diagn Pathol 2020;37:199-210.
22. Kocher GJ, Hoksch B, Caversaccio M, et al. Diffuse descending necrotizing mediastinitis: surgical therapy and outcome in a single-centre series. Eur J Cardiothorac Surg 2012;42:e66-72.
23. Larsen K, Skov Jensen B, Axelsen F. Perforation and rupture of the esophagus. Scand J Thorac Cardiovasc Surg 1983;17:311-6.
24. Freeman RK, Vallières E, Verrier ED, et al. Descending necrotizing mediastinitis: An analysis of the effects of serial surgical debridement on patient mortality. J Thorac Cardiovasc Surg 2000;119:260-7.
25. Pastene B, Cassir N, Tankel J, et al. Mediastinitis in the intensive care unit patient: a narrative review. Clin

Microbiol Infect 2020;26:26-34.
26. Vidarsdottir H, Blondal S, Alfredsson H, et al. Oesophageal perforations in Iceland: a whole population study on incidence, aetiology and surgical outcome. Thorac Cardiovasc Surg 2010;58:476-80.
27. Bladergroen MR, Lowe JE, Postlethwait RW. Diagnosis and recommended management of esophageal perforation and rupture. Ann Thorac Surg 1986;42:235-9.
28. Pate JW, Walker WA, Cole FH Jr, et al. Spontaneous rupture of the esophagus: a 30-year experience. Ann Thorac Surg 1989;47:689-92.
29. Estrera AS, Landay MJ, Grisham JM, et al. Descending necrotizing mediastinitis. Surg Gynecol Obstet 1983;157:545-52.
30. Exarhos DN, Malagari K, Tsatalou EG, et al. Acute mediastinitis: spectrum of computed tomography findings. Eur Radiol 2005;15:1569-74.
31. Marty-Ane CH, Alauzen M, Alric P, et al. Descending necrotizing mediastinitis. Advantage of mediastinal drainage with thoracotomy. J Thorac Cardiovasc Surg 1994;107:55-61.
32. Barakat MT, Girotra M, Banerjee S. (Re)building the Wall: Recurrent Boerhaave Syndrome Managed by Over-the-Scope Clip and Covered Metallic Stent Placement. Dig Dis Sci 2018;63:1139-42.
33. El Oakley RM, Wright JE. Postoperative mediastinitis: classification and management. Ann Thorac Surg 1996;61:1030-6.
34. Goh SSC. Post-sternotomy mediastinitis in the modern era. J Card Surg 2017;32:556-66.
35. Ridderstolpe L, Gill H, Granfeldt H, et al. Superficial and deep sternal wound complications: incidence, risk factors and mortality. Eur J Cardiothorac Surg 2001;20:1168-75.
36. Abu-Omar Y, Kocher GJ, Bosco P, et al. European Association for Cardio-Thoracic Surgery expert consensus statement on the prevention and management of mediastinitis. Eur J Cardiothorac Surg 2017;51:10-29.
37. Wouters R, Wellens F, Vanermen H, et al. Sternitis and mediastinitis after coronary artery bypass grafting. Analysis of risk factors. Tex Heart Inst J 1994;21:183-8.
38. Baskett RJ, MacDougall CE, Ross DB. Is mediastinitis a preventable complication? A 10-year review. Ann Thorac Surg 1999;67:462-5.
39. Rehman SM, Elzain O, Mitchell J, et al. Risk factors for mediastinitis following cardiac surgery: the importance of managing obesity. J Hosp Infect 2014;88:96-102.
40. San Juan R, Chaves F, López Gude MJ, et al. Staphylococcus aureus poststernotomy mediastinitis: description of two distinct acquisition pathways with different potential preventive approaches. J Thorac Cardiovasc Surg 2007;134:670-6. Erratum in: J Thorac Cardiovasc Surg 2008;136:542.
41. Trouillet JL, Vuagnat A, Combes A, et al. Acute poststernotomy mediastinitis managed with debridement and closed-drainage aspiration: factors associated with death in the intensive care unit. J Thorac Cardiovasc Surg 2005;129:518-24.
42. Pertowski CA, Baron RC, Lasker BA, et al. Nosocomial outbreak of Candida albicans sternal wound infections following cardiac surgery traced to a scrub nurse. J Infect Dis 1995;172:817-22.
43. Baker AW, Lewis SS, Alexander BD, et al. Two-Phase Hospital-Associated Outbreak of Mycobacterium abscessus: Investigation and Mitigation. Clin Infect Dis 2017;64:902-11.
44. Wang TK, Wong CF, Au WK, et al. Mycobacterium tuberculosis sternal wound infection after open heart surgery: a case report and review of the literature. Diagn Microbiol Infect Dis 2007;58:245-9.
45. Chan M, Yusuf E, Giulieri S, et al. A retrospective study of deep sternal wound infections: clinical and microbiological characteristics, treatment, and risk factors for complications. Diagn Microbiol Infect Dis 2016;84:261-5.
46. Fowler VG Jr, Kaye KS, Simel DL, et al. Staphylococcus aureus bacteremia after median sternotomy: clinical utility of blood culture results in the identification of postoperative mediastinitis. Circulation 2003;108:73-8.
47. Gur E, Stern D, Weiss J, et al. Clinical-radiological evaluation of poststernotomy wound infection. Plast Reconstr Surg 1998;101:348-55.
48. Akman C, Kantarci F, Cetinkaya S. Imaging in mediastinitis: a systematic review based on aetiology. Clin Radiol 2004;59:573-85.
49. Pan T, Li K, Fan FD, et al. Vacuum-assisted closure vs. bilateral pectoralis major muscle flaps for deep sternal wounds infection. J Thorac Dis 2020;12:866-75.
50. Lin J, Jimenez CA. Acute mediastinitis, mediastinal granuloma, and chronic fibrosing mediastinitis: A review. Semin Diagn Pathol 2022;39:113-9.
51. Engelman R, Shahian D, Shemin R, et al. The Society of Thoracic Surgeons practice guideline series: Antibiotic prophylaxis in cardiac surgery, part II: Antibiotic choice. Ann Thorac Surg 2007;83:1569-76.
52. Chello C, Lusini M, Nenna A, et al. Deep Sternal Wound Infection (DSWI) and Mediastinitis After Cardiac Surgery: Current Approaches and Future Trends in Prevention and

Management. Surg Technol Int 2020;36:212-6.
53. Bouza E, de Alarcón A, Fariñas MC, et al. Prevention, Diagnosis and Management of Post-Surgical Mediastinitis in Adults Consensus Guidelines of the Spanish Society of Cardiovascular Infections (SEICAV), the Spanish Society of Thoracic and Cardiovascular Surgery (SECTCV) and the Biomedical Research Centre Network for Respiratory Diseases (CIBERES). J Clin Med 2021;10:5566.
54. Hage CA, Azar MM, Bahr N, et al. Histoplasmosis: Up-to-Date Evidence-Based Approach to Diagnosis and Management. Semin Respir Crit Care Med 2015;36:729-45.
55. Rossi SE, McAdams HP, Rosado-de-Christenson ML, et al. Fibrosing mediastinitis. Radiographics 2001;21:737-57.
56. McNeeley MF, Chung JH, Bhalla S, et al. Imaging of granulomatous fibrosing mediastinitis. AJR Am J Roentgenol 2012;199:319-27.
57. Garrett HE Jr, Roper CL. Surgical intervention in histoplasmosis. Ann Thorac Surg 1986;42:711-22.
58. Peebles RS, Carpenter CT, Dupont WD, et al. Mediastinal fibrosis is associated with human leukocyte antigen-A2. Chest 2000;117:482-5.
59. Seferian A, Steriade A, Jaïs X, et al. Pulmonary Hypertension Complicating Fibrosing Mediastinitis. Medicine (Baltimore) 2015;94:e1800.
60. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 2007;45:807-25.

doi: 10.21037/med-24-14
Cite this article as: Farooq S, Armin S, Ocazionez D, Estrada-Y-Martin RM, Cherian SV. Benign disorders of the mediastinum: a narrative review. Mediastinum 2024;8:46.