

# Case Report

## Sclerosing mediastinitis in the differential diagnosis of mediastinal tumors\*

DAVI WEN WEI KANG<sup>1</sup>, MAURO CANZIAN<sup>2</sup>, RICARDO BEYRUTI<sup>3</sup>, FÁBIO BISCEGLI JATENE<sup>4</sup>

### ABSTRACT

Sclerosing mediastinitis is a rare disorder characterized by an extensive fibrotic reaction involving the mediastinum. Due to the compression or invasion of mediastinal structures, the disorder mimics neoplasia. We present three cases of superior vena cava syndrome in which sclerosing mediastinitis was confirmed. The pathophysiological process is related to enlarged mediastinal lymph nodes, fibroblast proliferation and collagen deposition. The main causes of sclerosing mediastinitis are histoplasmosis and tuberculosis, both of which are prevalent in Brazil. It is difficult to make an accurate histopathological diagnosis using minimally invasive methods, and there is no effective treatment for this condition. In order to make a definitive diagnosis and resolve the aerodigestive tract obstruction, exploratory surgery is indicated.

**Keywords:** Mediastinitis/physiopathology; Mediastinum; Pulmonary fibrosis; Mediastinal neoplasms; Diagnosis, differential; Case reports [Publication type].

---

\*Study carried out in the Department of Thoracic Surgery of the Universidade de São Paulo (USP, University of São Paulo) School of Medicine Hospital das Clínicas, São Paulo (SP), Brazil

1. Medical resident in Thoracic Surgery at the Instituto do Coração (InCor, Heart Institute) of the Faculdade de Medicina da Universidade de São Paulo (FMUSP, University of São Paulo School of Medicine), São Paulo, São Paulo, Brazil

2. Attending physician in the Pathology Department of the Instituto do Coração (InCor, Heart Institute) of the Faculdade de Medicina da Universidade de São Paulo (FMUSP, University of São Paulo School of Medicine), São Paulo, São Paulo, Brazil.

3. Attending physician in the Department of Thoracic Surgery of the Instituto do Coração (InCor, Heart Institute) of the Faculdade de Medicina da Universidade de São Paulo (FMUSP, University of São Paulo School of Medicine), São Paulo, São Paulo, Brazil.

4. Professor and Director of the Department of Thoracic Surgery of the Instituto do Coração (InCor, Heart Institute) of the Faculdade de Medicina da Universidade de São Paulo (FMUSP, University of São Paulo School of Medicine), São Paulo, São Paulo, Brazil.

Correspondence to: Davi Wen Wei Kang. Rua Prof. Aristides de Macedo, 77 apto.731,

Vila Mariana - CEP: 04106-080, São Paulo, SP, Brasil. Tel.: 55 11 5579-2345. E-mail: daviwwkang@ig.com.br

Submitted: 14 June 2004. Accepted, after review: 15 May 2005.-

## INTRODUCTION

Sclerosing mediastinitis is a clinical pathological entity characterized by an extensive fibrotic reaction that involves the mediastinum, with little evidence of active inflammation, and leads to compression, entrapment or invasion of mediastinal structures. There are several terms that are used as synonyms in the literature, all of which refer to the same physiopathological process: sclerosing mediastinitis, mediastinal granulomatosis, mediastinal adenitis, mediastinal collagenosis, and fibrosing mediastinitis.

Sclerosing mediastinitis affects individuals of all ages, presenting a higher incidence among individuals between 40 and 60 years of age, and is the third leading cause of superior vena cava syndrome. In general, the etiology of sclerosing mediastinitis is uncertain or idiopathic. Often, the etiologic agents isolated are fungi or mycobacteria, among which the most common are *Histoplasma capsulatum* (in the USA, especially in the central region) and the tuberculosis bacillus (in Brazil and in other countries). Other causes include: actinomycosis, syphilis, infection with *Aspergillus flavus* or *Wuchereria bancrofti*, as well as coccidioidomycosis, zygomycosis, nocardiosis, sarcoidosis, silicosis, trauma and use of methysergide.<sup>(1-3)</sup>

It is usually difficult to make an accurate diagnosis of this rare condition using minimally invasive methods, and exploratory surgery is often needed in order to make a definitive diagnosis.<sup>(1)</sup>

Herein, we describe three cases of sclerosing mediastinitis that were similar in their presentation and were diagnosed using median sternotomy. Physiopathological aspects, clinical profiles and available treatments are discussed.

## CASE REPORTS

### Case 1

A 43-year-old, previously healthy, female sought treatment after experiencing progressive facial and cervical edema for a month. The patient had also developed edema of her right arm ten days prior. Concomitantly with this profile, the patient presented some episodes of fever and weight loss, without anorexia. Physical examination revealed turgescence of the jugular veins (anterior and external), palpable fibroelastic mass in the suprasternal region, as well as enlargement of the axillary and supraclavicular lymph

nodes. At another health care facility, the patient had been submitted to left supraclavicular lymph node biopsy and was diagnosed with reactive lymphohistiocytic hyperplasia. The patient was referred to the University of São Paulo School of Medicine Hospital das Clínicas for diagnostic clarification in August of 2000. A computed tomography scan of the chest revealed an anterior mediastinal tumor involving the superior vena cava. The patient was submitted to right axillary lymph node biopsy, the result of which was reactive lymphoid hyperplasia. Due to this finding, the patient was again submitted to biopsy through mediastinoscopy, which revealed fibrous connective tissue with focal lymphoid infiltrate and anthracosis, without neoplastic cells. Since there was still suspicion of neoplasia, the patient was finally submitted to median sternotomy. The macroscopic findings included significantly enlarged mediastinal lymph nodes as well as fibrosis of the superior vena cava and left brachiocephalic vein. Those veins were resected, and the postoperative evolution was favorable. A month later, an echocardiogram revealed pericardial effusion with signs of restriction of the right ventricle. The patient was then submitted to anterior pericardiectomy, and the evolution was favorable. Anatomopathological examination revealed fibrosis of the adventitia of the superior vena cava, as well as organizing thrombosis, reactive lymphoid hyperplasia, chronic pericarditis with a pronounced fibrotic component, and foreign-body type gigantocellular immune response. After a three-year follow-up period, the patient remained asymptomatic.

### Case 2

A 58-year-old female, a heavy smoker with chronic obstructive pulmonary disease and hypothyroidism secondary to Hashimoto's thyroiditis, presented with edema and redness of the face for a year. The patient was diagnosed with superior vena cava syndrome. Consequently, she was submitted to computed tomography and magnetic resonance angiography of the chest. The results of those tests revealed increased fat density in the anterior mediastinum and stenosis of the superior vena cava. In September 2002, the patient was submitted to median sternotomy and a graft from the superior vena cava and innominate vein to the right atrium was performed (using 8-mm Dacron and 6-mm PTFE stents). The postoperative evolution was favorable, although the anatomopathological examination

revealed significant fibrosis in the superior vena cava. After having remained asymptomatic for a year, this patient began to present superior vena cava syndrome once again. At that time, magnetic resonance imaging revealed stenosis of the superior vena cava prosthesis. This was resolved through dilation using hemodynamic methods. To date, the patient remains asymptomatic.

**Case 3**

A 35-year-old previously healthy male presented with headache accompanied by cervical and facial edema for seven years, the symptoms having been incapacitating for the last two years. The working diagnosis was superior vena cava syndrome, and the patient was submitted to computed tomography of the chest, which revealed a mass in the anterior mediastinum, with a calcified center, invading the superior vena cava (Figure 1). In December of 2001, the patient was submitted to video-assisted thoracoscopy and a biopsy of the mass was carried out. The results of the frozen biopsy examination were inconclusive. A definitive, reviewed anatomopathological examination revealed dense adipose connective tissue infiltrated by atypical cells. Based on the immunohistochemical test results, the differential diagnosis between infiltrative neoplasia and entrapped reactive mesothelium was inconclusive. One year later, radiotherapy was unsuccessful, and there was an enlargement of the lesion as well as formation of significant collateral circulation revealed by a computed tomography scan of the chest. The

patient was subsequently submitted to median sternotomy, during which significant sclerosis and fibrosis of the mediastinum were found. Subsequently, the left brachiocephalic vein was grafted to the right atrium using an 8-mm PTFE stent (Figure 2). In the postoperative period, the patient presented signs and symptoms of congestive heart failure, which were controlled using classic measures. The patient was discharged while still being treated with warfarin and has been in outpatient follow-up treatment for two months, his symptoms being well compensated. Anatomopathological examination revealed sclerosing mediastinitis. (Figure 3)

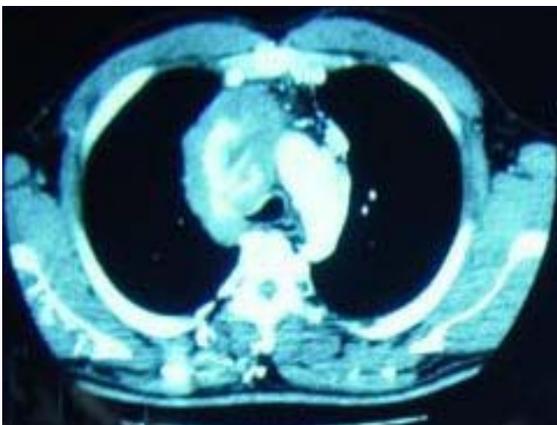


Figure 1 - Computed tomography of the chest: calcified mass in the anterior mediastinum with superior vena cava syndrome and extensive collateral circulation in the chest wall (Case 3)

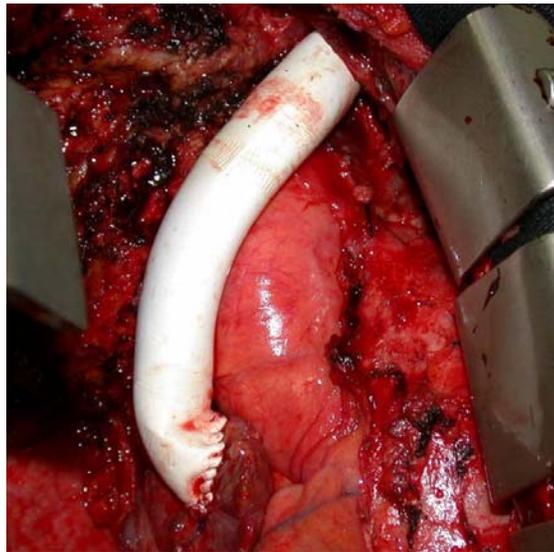


Figure 2 - PTFE stent grafting the left brachiocephalic venous stem to the right atrium (intraoperative - Case 3)

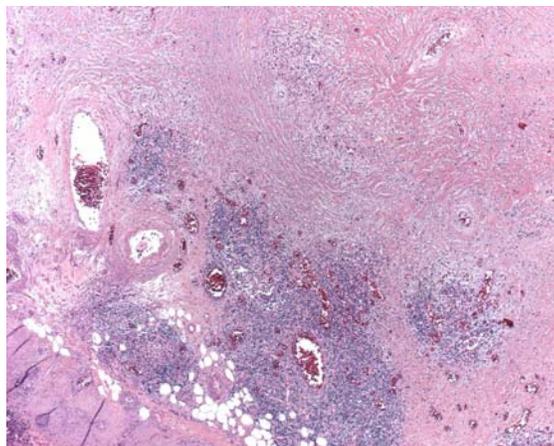


Figure 3 - Inflamed lymph node conglomerates and intense collagen deposition with few fibroblastic cells (magnification, x25 - Case 3)

## DISCUSSION

The physiopathological process of sclerosing mediastinitis and its biological behavior are still controversial. It is believed that pulmonary infection is accompanied by enlarged hilar and mediastinal lymph nodes, which can become lymph node conglomerates and inflamed masses. Subsequently, the inflammatory process would result in scarring and capsular fibrosis. This fibrosing process, in the long term, might produce dense calcifications or might progress, leading to compression of adjacent structures. Some authors, however, support the hypothesis that sclerosing mediastinitis is the result of a late hypersensitivity reaction. The continuous release of inflammatory or antigen material by cellular elements that constitute the process would stimulate fibroblastic activity in the more peripheral zones, leading to the formation and uncontrolled deposition of collagen, taking on a hilar and paucicellular aspect.<sup>(1)</sup> Mediastinal sclerosis might even be accompanied by retroperitoneal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, orbital pseudotumor or keloids. Therefore, it is believed that there is a genetic predisposition associated with the HLA-A2 system, leading to an altered immune response.<sup>(1,4)</sup>

The clinical profile is caused by the compression, entrapment or invasion of mediastinal structures. The following are the sites that are most often affected: the right paratracheal region (leading to superior vena cava syndrome and compression of the azygous vein); the subcarinal lymph nodes (the lateral extension obstructs the bronchi and the pulmonary artery, the anterior extension obstructs the pulmonary vein, and the posterior extension affects the esophagus); and the right pulmonary hilum. Initial symptoms can include cough, dyspnea, hemoptysis and chest pain.<sup>(1,5)</sup> The principal complication of mediastinal sclerosis is superior vena cava syndrome, which is characterized by venous distention (of the veins of the neck and upper limbs), edema (of the upper extremities, neck and face), onset of collateral circulation (in the chest and back) and facial plethora. This occurred in all of the cases presented herein. When the process has a more prolonged evolution, the symptoms are better compensated by the formation of collateral circulation. The esophagus can be affected, leading to dysphagia, chest pain, traction outpouchings, motility alterations, and significant digestive hemorrhage via varices resulting

from collateral vessels formed by the superior vena cava syndrome. Airway involvement can lead to broncholithiasis, hemoptysis, atelectasis, pleural effusion and obstructive pneumonitis. Recurring laryngeal nerve involvement leads to dysphonia due to paralysis of the vocal chords. Phrenic nerve lesion generates diaphragm paralysis, and stellate ganglion lesion leads to Horner's syndrome. Pericardial involvement can generate constrictive pericarditis and sudden death. Other manifestations include cor pulmonale, pulmonary hypertension, profile suggestive of mitral stenosis (pulmonary vein stenosis) or pulmonary thromboembolism (pulmonary artery stenosis), and aortic stenosis.<sup>(1,5-8)</sup>

The radiographic findings are very unspecific and are indicative of the lack of pathognomonic characteristics of this disease. Chest X-rays usually show widening of the mediastinum (especially on the right side), increased right hilar bronchovascular bundles or enlargement of the right paratracheal area. The anterior and upper regions of the mediastinum are the most often affected. Atelectasis and pneumonitis might also be seen. On computed tomography scans, the most common pattern is that of a localized mass, with attenuation of the soft parts, accompanied by irregular calcifications. The other pattern consists of tissue with diffuse homogeneous attenuation of the soft parts throughout the mediastinum, and this tissue is usually calcified. Either of these patterns can be accompanied by compression or entrapment of the tracheobronchial tree, of the major mediastinal vessels or of the esophagus. Greater pulmonary attenuation, thickening of the interlobular septa and peribronchial distention are seen when there is obstruction of the pulmonary veins. When most of the mass presents no calcifications, there should be greater suspicion of lymphoma or carcinoma. In comparison to magnetic resonance imaging, computed tomography is superior in identifying calcifications (spleen calcification is suggestive of histoplasmosis) and compression of the proximal airways. Magnetic resonance imaging, however, improve the definition of vascular compression. On magnetic resonance imaging, we observed intermediate signal intensity mixed with areas of low signal intensity in the images based on T1- and T2-weighted images. The areas of low signal intensity are attributed to the reactive fibrous tissue, to the presence of calcium amid the fibrosis or to both. Due to hypocellularity and abundant collagen

stroma, mature fibrous tissue usually presents low signal intensity in the T1- and T2-weighted images. However, immature fibrosis contains little collagen, many endothelial cells and many fibroblasts, thereby leading to heterogeneous images with variable signal intensity in the T2-weighted images.<sup>(1,9)</sup> The results of whole-body fluorine-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography scanning correlate with the severity of sclerosing mediastinitis. The greater the signal intensity, the more active is the disease. Such scans can be used for control and follow-up evaluation of patients in order to assess the efficacy of the treatment used.<sup>(10)</sup>

Diagnosis of fibrosing mediastinitis is difficult. Sputum culture is rarely positive. Skin tests are unspecific and, when positive, are only suggestive. Serologic tests for histoplasmosis are positive in less than a third of cases. Bronchoscopy can be useful for diagnosing endobronchial lesions, although endobronchial biopsy or culture rarely allow for diagnosis, which almost always results in the patient being submitted to surgical biopsy. In this case, there are several surgical approaches that can be used: mediastinoscopy, video-assisted thoracoscopy and thoracotomy. In general, the macroscopic description of the lesion during the intraoperative period is hardened ligneous mass (thick, dense fibrous collagenous tissue). Many authors advocate that the indication for biopsy in a suspicion of fibrosing mediastinitis depends on radiological characteristics related to the presence or absence of symptoms. Asymptomatic patients presenting calcified masses can be simply monitored (no biopsy), whereas patients presenting noncalcified masses accompanied by symptoms and compression should undergo biopsy. The principal differential diagnosis would be the nodular sclerosis subtype of Hodgkin's lymphoma.<sup>(11-11)</sup>

We can divide the treatment for sclerosing mediastinitis into clinical and surgical, the latter usually being reserved for anatomical complications. The clinical treatment is highly controversial. Reports of the empirical use of ketoconazole, fluconazole and amphotericin B, as well as of combinations of the three, have demonstrated conflicting results. It is believed that the use of antifungal agents should be considered only after the microbiological diagnosis has been made (through culture of the mass, positive serologic tests or both). The use of corticosteroids and immunosuppressants (azathioprine) has also

produced highly controversial results. There have been isolated reports that the use of tamoxifen results in general improvement.<sup>(1-3,11)</sup> Surgical resection is rarely feasible due to the degree of invasion and entrapment of the mediastinal structures.

There are, however, palliative surgical procedures that can alleviate the anatomical complications due to obstruction or compression. Grafting of the superior vena cava grafts using autogenous spiral saphenous vein, autogenous superficial femoral vein or stents (PTFE or GoreTex®) is the treatment of choice for superior vena cava syndrome of benign etiology.<sup>(12)</sup> Reconstruction with autogenous spiral saphenous vein achieves excellent clinical results and a perviousness index of 80% in the long run.<sup>(12)</sup> The superficial femoral vein makes a good graft, but has been less frequently used due to the occurrence of thrombosis and distal venous vascular insufficiency at the donor site.<sup>(12)</sup> The use of prosthetic materials, as compared to autogenous grafts, presents a shorter patency period and worse clinical results. Among such materials, PTFE stents are the best, reaching a perviousness index of up to 100% within a year.<sup>(12)</sup> The use of endovascular interventions with percutaneous transluminal angioplasty, stent placement or both was, until recently, accepted only as treatment for superior vena cava syndrome secondary to malignancy since these patients had decreased life expectancy. Such interventions were also used to remove obstructions from thrombosed grafts.<sup>(12-13)</sup> In view of the good results that have been obtained and the improvement in the quality of the catheters and stents, endovascular interventions for the treatment of superior vena cava syndrome of benign etiology have more extensively studied in recent years. Initial success rates ranging from 90% to 100% have been reported in the literature, with grafts remaining patent in more than 85% of cases during a one-year follow-up period.<sup>(12)</sup> The long-term durability of this intervention has yet to be established. The following are the principal types of stents: self-expanding (Gianturco and Wallstent) and balloon-expandable (Palmaz). These stents are rapidly covered by a neointima while their fibers are engulfed by the intima and layers of fibrous connective tissue.<sup>(13)</sup> Anticoagulation therapy is necessary when prosthetic grafts and stents are used. However, varying treatment regimens have been reported in the literature.<sup>(13-14)</sup>

Patients presenting tracheobronchial invasion might require lung resection (lobectomy,

pneumonectomy, bronchial sleeve resection or carinal resection) or even intraluminal prostheses. Many authors suggest resection of the mediastinal granulomas in order to prevent the progression to fibrosing mediastinitis since the latter presents high surgical morbidity/mortality rates and is usually nonresectable.

The cases of mediastinal fibrosis subjected to surgical intervention at our facility are indicative of the difficulty in making the diagnosis of the lesion since, even when using video-assisted surgery, samples are typically obtained only from the periphery of the lesion. Since it is an extremely rare disease, it rarely comes to mind in the differential diagnosis of principal anterosuperior mediastinum tumors such as lymphomas, thymomas and thyroid goiters. When surgical access was attempted, it was not possible to make a complete resection in any of our cases due to the degree of invasion of the fibrosis. In agreement with findings in the international literature, all patients presented superior vena cava syndrome, which constitutes the principal complication of this process, and two of them were submitted to venous diversion using synthetic prostheses. These patients received full anticoagulation in order to prevent thrombosis. However, in case 2, this did not prevent the fibrosing process from causing stenosis in the grafts. That patient was submitted to catheterization and dilation of the prosthesis, resulting in improvement in the facial and cervical edema. In case 1, due to the extensive collateral circulation, there was compensation of the superior vena cava syndrome. Over the course of three and a half years of follow-up evaluation after the incomplete resection of the mass, the patient remained asymptomatic and did not develop any new compressive symptoms. This case leads us to believe that fibrosis resection might promote a decrease in the stimulus for proliferation of the sclerosing tissue.

Clinical treatment remains controversial due to the fact that there have been few reports and that those have shown conflicting results. Due to the anatomical complications, surgical treatment continues to be the principal option although its long-term results are still unknown. In the future, the treatment might have to be based on the study of the abnormal inflammatory and fibroproliferative response of the individuals affected.

Fibrosing mediastinitis is a rare disorder that must be borne in mind in the differential diagnosis of anterosuperior mediastinum masses, especially when

several attempts at diagnosis have been unsuccessful. The principal complication is superior vena cava syndrome, and, due to the hypocellularity of the process, an etiologic diagnosis is rarely made. Clinical treatment is usually empirical and has produced unconvincing results. Surgical treatment is the best option to alleviate the symptoms, although its long-term results are still being investigated.

## REFERENCES

1. Parish J, Rosenow EC 3rd. Mediastinal granuloma and mediastinal fibrosis. *Semin Respir Crit Care Med.* 2002; 23(2):135-43.
2. Robertson BD, Bautista MA, Russell TS, Naclerio AL, Porisch ME, Sorrells DL, et al. Fibrosing mediastinitis secondary to zygomycosis in a twenty-two-month-old child. *Pediatr Infect Dis J.* 2002;21(5):441-2.
3. Parish JM, Marschke Jr RF, Dines DE, Lee RF. Etiologic considerations in superior vena cava syndrome. *Mayo Clin Proc.* 1981;56(7):407-13.
4. Comings D, Skubi K, Van Eys J, Motulsky A. Familial multifocal fibrosclerosis. Findings suggesting that retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, and pseudotumor of the orbit may be different manifestations of a single disease. *Ann Intern Med.* 1967;66(5):884-92.
5. Mathisen DJ, Grillo HC. Clinical manifestation of mediastinal fibrosis and histoplasmosis. *Ann Thorac Surg.* 1992;54(6):1053-7; discussion 1057-8.
6. Shorr A, Bennett S, Mair E, Lane J, Lyon R, Fitzpatrick T. Airway and vascular complications of fibrosing mediastinitis [abstract]. *Chest.* 2000;118(4 Suppl):2915-25.
7. Wright C. Surgical management of mediastinal tumors and fibrosis. *Semin Resp Crit Care Med.* 1999;20(5): 473-81.
8. St Krasopoulos G, Ibrahim M, Venn G. Sclerosing mediastinitis with aortic valve regurgitation and aortic root dilatation. *J R Soc Med.* 2000;93(2):83.
9. Rodriguez E, Soler R, Pombo F, Requejo I, Montero C. Fibrosing mediastinitis: CT and MR findings. *Clin Radiol.* 1998;53(12):907-10.
10. Imran M, Kubota K, Yoshioka S, Yamada S, Sato T, Fukuda H, et al. Sclerosing mediastinitis: findings on fluorine-18 fluorodeoxyglucose positron emission tomography. *Clin Nucl Med.* 1999;24(5):305-8.
11. Elmaghraby Z, Blom D, Lee D, Trayner E, Hendra K. Idiopathic fibrosing mediastinitis (IFM) diagnosed by CT-guided needle biopsy and treated with tamoxifen and corticosteroids. *Chest.* 2001;120(4):354S.
12. Kalra M, Gloviczki P, Andrews JC, Cherry KJ Jr, Bower TC, Panneton JM, et al. Open surgical and endovascular treatment of superior vena cava syndrome caused by nonmalignant disease. *J Vasc Surg.* 2003;38(2):215-23.
13. Hochrein J, Bashore TM, O'Laughlin MP, Harrison JK. Percutaneous stenting of superior vena cava syndrome: a case report and review of the literature. *Am J Med.* 1998;104(1):78-84.
14. Doty JR, Flores JH, Doty DB. Superior vena cava obstruction: bypass using spiral vein graft. *Ann Thorac Surg.* 1999;67(4):1111-6.