SCLEROSING LESIONS OF THE MEDIASTINUM

Mark R. Wick, MD
Division of Surgical Pathology
University of Virginia Health System
Charlottesville, VA, USA

SCLEROSING MEDIASTINITIS

- A slowly-evolving tumefactive fibroinflammatory process in the anterior & middle mediastinum that may present as a discrete mass or an infiltrative lesion that entraps great vessels, thymus, and lung tissue
- May be associated with signs & symptoms of superior vena cava syndrome

SCLEROSING MEDIASTINITIS: Other Clinical Data

- Most often seen in Caucasian females (F:M ratio 3:1) below the age of 30 yrs.
- Roughly 40% of patients are asymptomatic and have the condition detected radiographically
- The remainder present with cough, short of breath, chest pain, wheezing, dysphagia, or hemoptysis
- Diffuse effacement of mediastinal architecture may be seen radiographically, or a discrete mass can be present with or without calcifications
- Compression of pulmonary artery branches may cause secondary pulmonary infarction
SYNONYMS FOR SCLEROSING MEDIASTINITIS

- Fibrosing mediastinitis
- Idiopathic fibrosclerosing disease of the mediastinum
- Granulomatous mediastinitis
- Post-infectious mediastinal fibrosis
- Oulmont’s disease

Potential Etiological Factors for Fibrosing Mediastinitis

Fungal Infections
- Histoplasmosis
- Aspergillosis
- Zygomycosis
- Cryptococcosis

Mycobacterial Infections
- Tuberculosis
- Non-tuberculous

Other Bacterial Infections
- Nocardiosis
- Actinomycosis

Autoimmune Conditions
- Behcet syndrome
- IgG4-related fibrosclerosing disease
- Sarcoidosis
- Rheumatic Fever
- Prior Trauma
- Selected Drugs (Methysergide)
- Idiopathic
WHAT IS THE RELATIONSHIP BETWEEN SCLEROSING MEDIASTINITIS & IgG4-RELATED FIBROSCLEROSIS?

• This question is still being examined, but the best hypothesis is that all forms of sclerosing mediastinitis represent a type IV hypersensitivity response that shares similar histologic manifestations, regardless of the inciting factor(s).

• The four principal subsets of the disease are:
  - Infection-related (20-25%)
  - IgG4-related (~30%)
  - Autoimmune disease [e.g., Sjögren syndrome, primary sclerosing cholangitis, primary biliary cirrhosis, inflammatory bowel disease] (~20%)
  - Idiopathic (25-30%)

*Histopathologic Overlap between Fibrosing Mediastinitis and IgG4-Related Disease.*

Abstract

Fibrosing mediastinitis (FM) and IgG4-related disease (IgG4-RD) are two fibroinflammatory disorders with potentially overlapping clinical and imaging presentations. Involvement of the mediastinal structures, including the lung, pleura, heart, pericardium, esophagus, and tracheobronchial tree, can be seen in both FM and IgG4-RD. This study investigates the histopathologic and clinical features of 30 patients with fibrosing mediastinitis (11 men, 19 women; mean age 50 years) and 30 patients with IgG4-related disease (16 men, 14 women; mean age 55 years) to determine the overlap between the two conditions. The presence of diagnostic numbers of florid infiltrating IgG4-positive plasma cells was seen in a number of additional cases with similar clinical symptoms and imaging findings. The overlap of histologic features between FM and IgG4-RD suggests a shared immunologic basis for these disorders. Further studies are needed to determine the clinical significance of this histopathologic overlap.
SCLEROSING MEDIASTINITIS: Outcomes

- Most cases pursue a slowly-evolving, self-limited course that may last for several years
- Administration of antifungal or antimycobacterial drugs empirically does not appear to alter outcomes
- Symptomatic patients may benefit from placement of vascular stents, balloon angioplasty, or surgical reconstructive procedures
- Only ~3% of patients die of cardiorespiratory failure

Because of the potential simulation of sclerosing mediastinitis by other fibrosing conditions, the former diagnosis is one of ultimate exclusion and close correlation with clinical findings

FIBROSING NEOPLASMS THAT MAY SIMULATE SCLEROSING MEDIASTINITIS IN SMALL BIOPSIES

- "Obliterative subtotal sclerosis"-type Hodgkin lymphoma
- Sclerosing non-Hodgkin lymphoma (large-cell type)
- Sclerosing seminoma
- Desmoplastic mesothelioma presenting in the mediastinum
- Sclerotic ("ancient") thymoma
- Sclerosing thymic carcinoid
- Sclerosing paraganglioma
- Calcifying fibrous pseudotumor
- Solitary fibrous tumor
- Peripheral nerve sheath tumors
- Selected metastatic carcinomas
"Obliterative Subtotal Sclerosis"-Type Hodgkin Lymphoma (HL)

- This terminology was used by Rappaport in the 2nd series AFIP fascicle on hematopoietic tumors in 1966, to refer to a subtype of nodular sclerosis HL cases in which a densely-fibrotic stroma dominated the microscopic image of the lesion.
- The OSS variant of HL is not well-recognized by general pathologists, but several publications have described its ability to imitate non-neoplastic fibrosclerosing conditions such as Oulmont's and Ormond's diseases in the mediastinum and retroperitoneum.

---

Subheadings

**Hodgkin's disease masquerading as sclerosing mediastinitis.**

Fleming RB, Espino M, Allen P, Miranda J, Toledano FM.

Abstract

Cases in which fibrotic variants of Hodgkin's disease have been confused with sclerosing mediastinitis have rarely been reported. Sclerosing mediastinitis typically involves the superior mediastinum, and is most commonly due to tuberculosis. We describe the case of a patient who came to us with fever, a mixed anemia, and a posterior mediastinal mass that pathologic examination appeared to be due to idiopathic sclerosing mediastinitis. Only inclusion of a biopsy specimen from a local cervical node, after two porta hepatis mass was found, revealed the correct diagnosis of Hodgkin's disease of the nodular sclerosing type. With the correct diagnosis, early intervention and appropriate therapy resulted in clinical cure.
LARGE-CELL NON-HODGKIN LYMPHOMA OF THE THYMIC REGION, SCLEROSING B-CELL TYPE

- Recognized in the late 1970s & early 1980s as a distinctive intrathoracic neoplasm that could be associated with the superior vena cava syndrome
- Now well-characterized as a B-cell proliferation that is centered in the thymus, with singular cytogenetic & molecular characteristics
SCLEROSING SEMINOMA OF THE MEDIASTINUM

- A rare variant of seminoma, previously reported only in the testis; the speaker also has observed 3 such cases in the anterior mediastinum
- Tumor cells are scant in number and obscured by stromal fibrosis and chronic inflammation
- Immunostains for PLAP, CD117, OCT ¾, and SALL4 are usually necessary to document the presence of neoplastic germ cells in such tumors

Clinical, pathological and genetic features of primary mediastinal large B-cell lymphomas and mediastinal gray zone lymphomas in children.

Abstract

Background Primary mediastinal large B-cell lymphoma is a rare lymphoma accounting for more than 3% of all B-cell lymphomas in children and adolescents. However, patients in this young age group with this lymphoma have the shortest overall survival of patients with any B-cell lymphoma under current standard chemotherapy protocols. Lymphomas with features intermediate between primary mediastinal large B-cell lymphoma and classical Hodgkin’s lymphoma (mediastinal gray zone lymphomas) have been acknowledged in the latest World Health Organization classification. Recent studies suggest that mediastinal gray zone lymphomas have an aggressive clinical course whereas patients, at least adult ones, with primary mediastinal large B-cell lymphoma might respond very well to chemotherapy in combination with anti-CD20 antibody.

DESIGN AND METHODS: We aimed to evaluate whether biological differences exist or not for consensually defined mediastinal gray zone lymphomas might explain the relatively poor outcome of pediatric patients with apparent primary mediastinal large B-cell lymphoma. We therefore, performed a retrospective histopathological, immunohistochemical and interphase cytogenetic analysis of 52 pediatric lymphomas.

RESULTS: The childhood primary mediastinal large B-cell lymphomas (n=42) showed a similar pattern of histology, immunophenotype and genetic changes at frequencies and landmarks in adult cases, as determined from published data. We identified only four so far unrecognized cases of mediastinal gray zone lymphoma among 52 lymphomas registered in previous trials. Conclusion Mediastinal gray zone lymphomas is very rare in children and adolescents. It does, therefore, seem unlikely that these lymphomas account for the unsatisfactory clinical results with current therapy protocols in pediatric patients. These data have major implications for the design of future treatment protocols for mediastinal lymphomas in children and adolescents.
DESMOPLASTIC MESOTHELIOMA OF THE MEDIASTINUM (DMM)

- An uncommon histologic variant of an uncommon neoplasm in an uncommon anatomical location
- DMM may be surprisingly hypocellular, with a predominance of hyalinizing stroma which superficially resembles the histologic appearance of a fibrohyaline (asbestos-related) serosal plaque
- At least modest nuclear atypia and growth into fat are necessary microscopic diagnostic elements
- Neoplastic cells are pankeratin-positive
Desmoplastic malignant mesothelioma masquerading as chronic mediastinitis: a diagnostic dilemma.

Abstract
A 50-year-old woman presented with dyspnea, chest discomfort, and left vocal cord paralysis that developed 2 months after a flu-like illness. Radiographic examination showed prominence of mediastinal soft tissues, and on thoracentesis, pleural effusion was aspirated. Thoracotomy and biopsy samples taken from the sciotic areas showed densely hyalinized fibrotic tissue. Necrotizing granulomas containing aggregates of epithelioid cells and multinucleated giant cells were present within mediastinal lymph nodes. Based on these findings, a diagnosis of desmoplastic mediastinitis was made. During the next year, her patient's respiratory function deteriorated, and biopsy samples taken during a second thoracotomy 3 years later were again interpreted as chronic mediastinitis. In the patient's postoperative recovery, the sciotic areas involving the mediastinum were decomposed of a mixture of dense fibrous and granulation tissue. The final diagnosis was based on histological desmoplastic malignant mesothelioma. We report it here because of its unusual clinical presentation, which mimicked chronic mediastinitis.
"ANCIENT" (SCLEROTIC) THYMOMA

- An unusual thymoma variant reported by Moran & Suster in 2004
- Only 10% of patients had myasthenia gravis; the remainder presented with nondescript signs & symptoms or were entirely asymptomatic
- Densely-fibrotic stroma accounted for 85% to 90% of the tumor masses in each case
- Thorough sampling was necessary to document the presence of epithelial neoplastic cell groups
Extensive sclerosis in neuroendocrine carcinomas of the lung was described by Kalhor et al. in 2010; the speaker has encountered 2 primary thymic neoplasms with similar changes.

Dense stromal fibrosis may obscure the diagnosis in small biopsies and also interfere with grading of the tumors.

Lesional cells are immunoreactive for pankeratin, as well as markers of neuroendocrine differentiation.

Marked sclerosis does not appear to affect behavior or prognosis.

Primary sclerosing neuroendocrine carcinomas of the lung: A clinicopathologic and immunohistochemical study of 10 cases.

Natalie H. Tazelaar & Meier, CA.

Abstract

We describe 10 cases of primary well-differentiated neuroendocrine carcinomas (carcinoid tumors) of the lung with extensive sclerotic changes. The patients were 6 women and 4 men, ages 37 to 88 years. Clinically, patients had symptoms of bronchial obstruction such as cough, dyspnea, and chest pain. Surgical resection of the tumors was accomplished in all the cases. Histologically, all tumors corresponded to the well-differentiated type; however, in 4 cases, lymph node metastases were present. Immunohistochemically, all tumors showed positive staining for neuroendocrine markers, including chromogranin, synaptophysin, C50, and broad-spectrum keratins. Follow-up information showed that all patients were alive after a period ranging from 1 to 5 years. The cases presented highlight an important feature of neuroendocrine carcinomas of the lung not previously addressed, one that may pose a problem not only in the diagnosis but also in the grading of these neoplasms.
SCLEROSING PARAGANGLIOMAS

- Described by Plaza & colleagues in 2006
- A pathologic variant of paraganglioma that tends to be overrepresented in middle-aged women
- Can be encountered in both the anterior and posterior mediastinal compartments
- Dominated by mature fibrous stroma, compressing tumor cell groups into irregular, pseudo-infiltrative profiles that can be confused with those of an invasive carcinoma or thymoma
- Non-immunoreactive for pankeratin
Bromine paraganglioma: a report of 18 cases of an unusual variant of neuroendocrine tumor that may be mistaken for an aggressive malignant neoplasm.

**Abstract**

Most cases of this distinctive variant of paraganglioma were characterized by extensive collagen deposition resulting in a pattern of growth that resembled an invasive malignant neoplasm. The tumors were located in the umbilical body region, paranganglioma region, and mesentery. Tumor size ranged from 2 to 6 cm in greatest diameter. Grossly, the tumors were described as a rubbery firm, tan-red, and well-delineated areas of interest. Microscopic aldehyde showed nests of tumor cells separated by broad bands of fibrous tissue. The tumor cells ranged from round to polygonal with abundant cytoplasmic granules resembling epithelial with well-defined cytoplasmic. Nuclear chromatin was present and moderately cellular the typical appearance of the primary cell population in 17 cases. Mitoses were sparse (1 to 5 per 10 HPF), and there was no evidence of necrosis in any of the cases. Most of the tumor had a well-defined boundary and were present in 2 of 3 cases, respectively. The most striking histologic feature was the presence of irregular cords and bands of mitotic fibrous tissue that compartmentalized the lesions into irregular nests, lobules, or cords of tumor cells, imparting them with a distinctive appearance. All the tumors showed positive immunostaining for chromogranin, synaptophysin, and neuronal-specific enolase. S-100 protein stains identified a sustentacular cell network; vimentin (AB1662) was negative in all cases. Clinical follow-up (14 cases, ranging from 2 months to 3 years (mean follow-up 6.5 years) showed evidence of local recurrence in 2 cases and the development of a separate tumor in the contralateral nuch in 1 case. The remainder of the patients were free of recurrence or metastasis following simple local excision. Because of the potential risks, a diagnosis of an invasive malignant neoplasm was initially considered in the majority of cases. Bromine paraganglioma should be included in the differential diagnosis of neuroendocrine tumors of the head and neck region and mesentery. Appropriate immunohistochemical stains may be of aid in establishing the correct diagnosis.
CALCIFYING (PSEUDO)TUMOR (CPT) OF THE MEDIASTINUM

- Analogous to other lesions of the soft tissue, serosal surfaces, lungs, esophagus, liver, & spine
- Typically presents as a discrete mass, rather than an infiltrative process such as fibrosing mediastinitis
- Nondescript radiographic & gross appearance, except for the presence of multifocal calcifications
- Paucicellular background fibroblastic proliferation
- Appears to be a singular entity distinct from inflammatory myofibroblastic tumor and solitary fibrous tumor

Abstract
Calcifying fibrous pseudotumor has recently been described in the soft tissues. It is a rare benign lesion characterized by the presence of abundant hyalinized collagen with paucicellular or dystrophic calcifications and tyrosinase-positive cells. We report a case of a young woman with a mediastinal mass treated by a complete resection. The mass had all the pathologic features of calcifying fibrous pseudotumor.
SOLITARY FIBROUS TUMOR OF THE MEDIASTINUM

- Identical pathologically to lesions that are prototypically seen in the pleura
- Approximately 80% arise in the anterior mediastinum, with the remainder being in the middle & posterior mediastinal compartments
- May demonstrate well-demarcated or infiltrative contours radiographically
- Range of histological patterns, including "patternless," epithelioid, and sclerosing-hypocellular variants
- Potential immunoreactivity for CD34, CD99, bcl-2 protein, and STAT6

Solitary fibrous tumor of the mediastinum: A report of 14 cases.

The spectrum of histologic growth patterns in benign and malignant fibrous tumors of the pleura.

Abstract

A review of the histologic growth patterns in 50 cases of benign and malignant fibrous tumors of the pleura localized in solitary fibrous tumor. Sclerosing mesothelioma is described. Two major histologic patterns are observed: in various proportions, solid spindled and diffuse sclerosing. The solid spindled growth pattern assumed various configurations, including fascicular areas, alveolar and hemorrhagic foci, angiomatoso and hemanangiomatoso-like areas, cribriform or pseudocrniform, honeycomb and pseudohoneycomb formations, angiomatoso and hemanangiomatoso-like areas, cribriform or pseudocrniform, honeycomb and pseudohoneycomb formations, angiomatoso and hemanangiomatoso-like areas, cribriform or pseudocrniform, honeycomb and pseudohoneycomb formations.
SCLEROTIC PERIPHERAL NERVE SHEATH TUMORS

• Typically present as well-delimited masses in the posterior mediastinum
• Often asymptomatic; may cause neural-compressive symptoms & signs or back pain
• Predominantly benign in nature; malignant nerve sheath tumors are rare in the mediastinum
• May be represented histologically by neurofibroma, neurilemmoma (schwannoma) or perineurioma
• Potential immunoreactivity for S100 protein, CD34, CD56, & CD57
SCLEROSING METASTATIC CARCINOMA IN THE MEDIASTINUM

- May or may not be lymph node-based, and can be present in all 3 mediastinal compartments
- Metastatic lobular breast carcinoma and signet ring-cell gastric carcinomas are principally represented
- Linear single-file arrays or small nests of neoplastic cells embedded in a desmoplastic or mature fibrous stromal background
- Pankeratin stains are helpful to delineate the distribution of the tumor cells

Mammaglobin