Pleural Malignant Solitary Fibrous Tumor With Sarcomatous Overgrowth Showing PDGFRβ Mutation

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Our patient proceeded to acquire life-threatening airway obstruction requiring emergency tracheostomy despite receiving steroid therapy. In contrast, all previous cases were steroid responsive (three complete, one partial), and only one patient required intubation or a surgical airway.4

Anti-tumor necrosis factor agents have been used for a variety of conditions including Crohn disease.6,7 However, there is very limited experience with anti-tumor necrosis factor for pulmonary complications. We found one case report of successful infliximab therapy in bronchiolitis obliterans with organizing pneumonia associated with Crohn disease in a patient intolerant of corticosteroids.8 To our knowledge, this case demonstrates the first successful use of infliximab in treating severe upper airway obstruction associated with a granulomatous disease, most likely Crohn disease, with rapid and enduring results.

References

Pleural Malignant Solitary Fibrous Tumor With Sarcomatous Overgrowth Showing PDGFRβ Mutation*

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Pleural malignant solitary fibrous tumors (SFTs) are uncommon, and little is known about their histogenesis and molecular features. We report a case of pleural SFT with sarcomatous overgrowth that showed expression for PDGFRβ and a missense mutation on exon 18 of the PDGFRβ gene. The involvement of the PDGFRβ gene in SFT is compatible with a pericytic derivation, also supporting a possible role of this tyrosine kinase in malignant transformation and in the adoption of novel molecular therapies. (CHEST 2006; 130:581–583)

Key words: molecular biology; oncology; surgery; tumor markers

Abbreviations: SFT = solitary fibrous tumor; TK = tyrosine kinase

Solitary fibrous tumor (SFT) is a distinctive mesenchymal neoplasm mainly affecting the pleura. The majority of SFTs have good clinical behavior, but occasionally an SFT is characterized by a more aggressive outcome.1 Basically, the features predicting a worse clinical course are related to infiltrative tumor margins or sessile growth pattern, and some histologic findings (ie, high mitotic rate, necrosis, increased cellularity, and pleomorphism).2 Complete surgical excision remains the mainstay of treatment, but little is known about histogenesis, the molecular mechanisms of neoplastic growth, and alternative “targeted” therapies in SFT patients. We first report a pleural SFT showing a clear-cut, high-grade sarcomatous overgrowth in which a missense mutation on exon 18 of the PDGFRβ gene was found and discuss the possible role of PDGFRβ as histogenetic and therapeutic marker in SFT.

Case Report

A 65-year-old nonsmoker, a woman with a medical history negative for cancer, was admitted to the hospital because of chest pain and dyspnea. On physical examination, breath sounds were diminished at the left lung base. The findings of hematologic laboratory tests, including those for serum tumor markers (ie, carcinoembryonic antigen, CA19.9, and CA125), as well as arterial blood gas analyses were unremarkable. Chest radiographs showed a large solid mass occupying the left upper thoracic cavity almost completely. A chest and abdomen CT scan confirmed the presence of a solid mass with central necrosis, 12 cm across, possibly arising from the mediastinum or the pleura with concomitant pleural effusion. The mass compressed the left central bronchial and vascular structures as well as the main branch of the left pulmonary artery, apparently without infiltration of the lung parenchyma (Fig 1, top left, A). Neither lymph node enlargement nor other lesions outside the chest was detected. Bronchoscopy showed a narrowing of the left main bronchus, but BAL fluid cytology findings were negative. A transbronchial biopsy revealed a spindle cell proliferation of bland-looking elements dissected by collagen bands that strongly reacted with CD34 and

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bcl2, and were admixed with a clear-cut, high-grade malignancy that was characterized by spindle-shaped cells with prominent nucleoli and a high mitotic rate that reacted with vimentin, but not with the other tested immunohistochemical markers (ie, CD34, bcl2, smooth-muscle actin, desmin, cytokeratins, h-caldesmon, CD117, CD21, CD10, CD31, and estrogen receptors). A diagnosis of malignant SFT was determined. The patient then underwent surgical excision of the mass, which, on intraoperative examination, was determined to originate from the left pleura with infiltration of the left upper pulmonary lobe. Several other small pleural nodules were also excised, but the tumor was not radically resected. Grossly, the mass had a whitish cut surface with hemorrhagic areas and central necrosis. Histologically, the tumor displayed the double component seen on biopsy specimens (Fig 1, top right, B). In fact, the minority of the mass consisted of a typical SFT with bland spindle cells arranged in a

![Image](image1.png)

**Figure 1.** The chest CT scan showed a large pleural-based mass with concomitant pleural effusion (top left, A). During histology, the mass consisted of a typical SFT (top right, B [on the right], and middle left, C) displaying a sarcomatous overgrowth (top right, B [on the left], and middle center, D). CD34 immunoreacted in the classic SFT only (middle right, E) [immunohistochemistry for CD34, original ×100], while both components immunostained for PDGFRβ (bottom left, F) [immunohistochemistry for PDGFRβ, original ×200]. Molecular analysis by polymerase chain reaction revealed a somatic missense mutation on exon 18 of the PDGFRβ gene in the high-grade sarcomatous component (bottom right, G [antisense sequence]).
“patternless” pattern, separated by bands of hyaline “keloid-type” collagen and with a peculiar “hemangiopericytoma-like” vascular network (Fig 1, middle left, C). At the periphery, a high-grade neoplasm that was characterized by spindle cells with a high mitotic rate was noted (Fig 1, middle center, D). The low-grade component had the characteristic CD34+/βcld2+ immunoprofile (Fig 1, middle right, E), while the sarcomatous tumor part reacted with vimentin only. Of note, both components stained for PDGFRβ (Fig 1, bottom left, F). A diagnosis of pleural malignant SFT with sarcomatous overgrowth was performed. During molecular analysis by a direct-sequencing polymerase chain reaction of exons 12, 14, and 18 in the PDGFRβ gene, a missense puntiform mutation was detected on exon 18 (Asp850 was substituted for Val) encoding for the protein kinase domain in the sarcomatous component only (Fig 1, bottom right, G). The postoperative course was uneventful, but the patient died 2 months after undergoing surgery for acute respiratory and cardiovascular failure due to intrathoracic tumor growth.

**DISCUSSION**

SFTs are relatively uncommon tumors of uncertain histogenesis that generally behave in a benign fashion once they are radically resected. However, up to 19% of SFTs are complicated by local recurrences and/or distant metastases, generally related to morphologically malignant features. In these cases, SFTs may lose the usual morphology as well as CD34 immunoreactivity, and then resemble an undifferentiated spindle cell sarcoma. In this case, surgery or chemoradiotherapy has a limited role, and no alternative molecular therapies have been identified so far to treat malignant SFTs. Here, we first describe a malignant SFT showing the expression of PDGFRβ, a type III tyrosine kinase (TK), and a missense mutation on exon 18 of the PDGFRβ gene in the sarcomatous component (Fig 1, bottom left, F). A diagnosis of malignant SFT showing the expression of PDGFRβ in a pleural malignant SFT in which strong expression and reactivity for CD34, and recent ultrastructural findings further support this hypothesis. Most important, the PDGFRβ gene mutational event detected in our case is characterized by the same amino acid substitution (Asp850 was substituted for Val) as homologous mutations that were found in other TKs such as c-kit (Asp816) and PDGFRα (Asp842) in GI stromal tumors, or c-met (Asp1246) in papillary renal carcinomas, which are tumors in which these mutations represent molecular targets for selective TK inhibitors.

**CONCLUSION**

We have first shown the key role of the PDGFRβ gene in a pleural malignant SFT in which strong expression and a missense gain-of-function mutation on exon 18 was detected. Although this preliminary report needs further investigation, PDGFRβ gene involvement in SFTs seems to support a histogenetic origin from pericyte-like cells and possibly represents a molecular target for alternative therapies in unresectable malignant forms.

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