Giant solitary fibrous tumour of the pleura an unpredictable entity: case series and literature review

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ABSTRACT

Solitary fibrous tumours of the pleura account for less than 5% of pleural tumours, and originate from mesenchymal cells of the submesothelial layer. They typically follow an indolent course with 'giant' tumours, which occupy greater than 40% of the hemithorax, developing in a small proportion of patients. The majority of tumours are benign with a 10-year survival rate of 90% reported.

A small proportion of tumours can undergo malignant transformation. We report a case series of five patients diagnosed with giant solitary fibrous tumours of the pleura. These cases highlight the unpredictable nature of this disease process, with significant variability in clinical course observed, from indolence to aggressive progression. Three patients were found to have malignant disease on explant, with two of these having preoperative imaging and histology suggesting benign pathology. This finding emphasises that accurately differentiating between benign and malignant disease on imaging and/or biopsy has low specificity and sensitivity and cannot be relied upon in guiding the management of these tumours. Patients with solitary fibrous tumours of the pleura should be managed cautiously, owing to the unpredictable and potentially aggressive clinical course. We would advocate the position that all patients with solitary fibrous tumours of the pleura should be managed as if they have malignant disease. Prolonged follow-up is required due to the risk of disease recurrence, even in patients with benign disease.

KEYWORDS

Giant solitary fibrous tumour of the pleura – Solitary fibrous tumour – Pleural tumour – Malignant transformation

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Introduction

Solitary fibrous tumours of the pleura (SFTP) are rare fibroblastic mesenchymal tumours. To date, around 800 cases have been reported in the literature, and they account for less than 5% of pleural tumours.^{1–5} Histologically, these tumours have a characteristic appearance: they are variably cellular and have a patternless distribution of spindle to ovoid cells within prominent collagenous stroma.⁶ In the past, there has been controversy surrounding the histogenesis of these tumours, with suggestions that they derive from serosal, mesothelial or submesothelial cells; and they have been described with various terms including haemangiopericytoma and localised pleural mesothelioma.^{6,7} More recently, ultrastructural and immunohistochemical studies have concluded that SFTP originate from mesenchymal cells of the submesothelial layers of the pleura, rather than mesothelial cells.^{8–10} In keeping with this more ubiquitous cell of origin, tumours with similar histological characteristics have been reported from a wide range of extrapleural

tissues and organs including the liver, peritoneum, orbits, thyroid gland, breast, kidney and meninges.^{5,11,12}

SFTP are said to mostly follow an indolent course, with only around 15–20% fulfilling criteria for malignancy.¹⁵ Here, we present five cases of SFTP highlighting the unpredictable nature of this disease and suggest that patients with this diagnosis should be managed with caution.

Methods and Results

We identified all cases of patients with SFTP referred for surgical management over a 5-year period from January 2012 to December 2016 at our institution. Five patients were identified and their case notes and all electronic records pertaining to their diagnosis were reviewed and data collected (Table 1).

Patient 1

A 69-year-old woman presented with a 6–12-month history of wheeze, dry cough and anterior chest discomfort

Table 1 Summary of patient characteristics and clinical course.

Patient no.	Sex	Age (years)	Presentation	Side	CT finding	CT-guided biopsy	Histology and size of resected mass	Surgery	Adjuvant therapy	Follow-up to January 2017
1	Female	69	6-month history of wheeze, dry cough, discomfort right chest and decreased exercise tolerance.	Right	Extensive pleural based mass right upper zone 10.2 × 84 × 12.5cm compressing (possibly invading) the lung.	Benign solitary fibrous tumour	15.5 × 11 × 9 cm Tumour adherent to but not invading chest wall. Benign solitary fibrous tumour with clear resection margins. Strong bcl-2, CD34 and CD99 expression.	Right thoracotomy and chest wall resection, August 2012	Nil	Alive and well. No evidence of recurrence.
2	Male	58	Progressive shortness of breath with decreasing exercise tolerance and cough; some sharp anterior chest pain. Mass on chest radiograph observed.	Left	Large pleural-based mass left lower hemithorax 17 × 11 × 8 cm. Compression and displacement of the left lower lobe.	Benign solitary fibrous tumour	18 × 15 × 9 cm 819 g Benign solitary fibrous tumour with clear pulmonary and mediastinal resection margins. No immunostains reported.	Left thoracotomy, September 2012	Nil	Alive and well. No evidence of recurrence.
3	Male	80	Incidental finding on chest radiograph.	Right	Large pleural-based mass in right chest measuring 7.6 × 12 × 14 cm.	Benign solitary fibrous tumour	17 × 12 × 6 cm 858 g Malignant fibrous tumour with hypercellularity, high mitotic activity and necrosis. Clear pulmonary resection margin. Strongly positive CD34, CD99 and bcl-2.	Thoracotomy, August 2013	Nil	Alive and well. No evidence of recurrence.
4	Male	75	Incidental finding on chest radiograph. Intermittent cough, no shortness of breath reported at presentation.	Left	March: large pleural-based mass in left upper zone medially. 8.7 × 7.8 cm causing compressive atelectasis left upper lobe. June: significant progression – 11 × 14 × 13 cm, multiple areas of enhancement. Multiple pleural-based nodules left upper lobe. Early invasion of chest wall. Pleural effusion.	Benign solitary fibrous tumour	22 × 20 × 5 cm (debulking). Solitary fibrous tumour with malignant transformation. Patchy cytokeratin and bcl-2; strong CD99 expression. Negative CD34 expression.	Left thoracotomy Palliative and debulking of chemotherapy, June 2014	Palliative (doxorubicin)	CT Nov 2014: progressive disease; tumour measuring 14 × 6 × 10.6 cm; multiple mediastinal lymphadenopathy. Died January 2015.

5	Male	37	July 2015 shortness of breath on exertion, chest discomfort, attended accident and emergency department. Chest radiograph suggested left-lobe lung infection, treated with antibiotics. Ongoing shortness of breath, repeat chest radiograph 4, then 8 weeks later revealed rapidly enlarging mass, right cardiophrenic angle.	Mass arising from mediastinum 11.7 × 10.8 cm with possible invasion into the right atrium. Compressing right lower lobe, possibly extending into it.	Solitary fibrous tumour with features suggestive of malignancy	32 × 22 × 9 cm 3500 g a solitary fibrous tumour with areas of hypercellularity, necrosis and high mitotic activity. Clear pulmonary resection margin; positive mediastinal pleural edge. Moderate bcl-2 and CD99; focal CD34; weak cytokeratin.	Right thoracotomy, October 2015	Radical radiotherapy (66 Gy) to the tumour bed	Alive and well. No evidence of recurrence.
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associated with reduced exercise tolerance. A chest radiograph revealed a right-sided mass 10.2 × 8.4 × 12.5 cm, in the right upper zone possibly invading the lung. A positron emission tomography-computed tomography (PET-CT) was performed, which revealed low-grade tracer uptake with a maximum standardised uptake values (SUV) of 2.8. CT-guided biopsy confirmed the diagnosis of a benign solitary fibrous tumour. The mass was resected in August 2012. Intraoperatively, the lesion was adherent to the chest wall and adjacent lung and so a chest wall resection and pulmonary wedge resection was performed. Final histology confirmed the lesion to be a benign solitary fibrous tumour with clear resection margins, and the patient therefore received no adjuvant therapy. The patient remains well to date.

Patient 2

A 58-year-old man presented with progressive shortness of breath, reducing exercise tolerance and anterior chest discomfort of a sharp nature. A left-sided mass was observed on a chest radiograph. CT subsequently revealed a large pleural based mass in the left lower hemithorax 17 × 11 × 8 cm with compression of the left lower lobe. CT-guided biopsy confirmed a diagnosis of benign SFTP. The lesion was surgically resected in September 2012. Final histology confirmed a benign SFTP with clear resection margins. The patient received no adjuvant therapy and remains well to date.

Patient 3

An 80-year-old man presented with dyspnoea and was found to have a right-sided mass on a chest radiograph. This proved to be a large 7.6 × 12 × 14 cm pleural-based mass on CT imaging. A CT-guided biopsy confirmed a diagnosis of benign solitary fibrous tumour. This was subsequently resected in August 2013. Postoperative histology found the lesion to have evidence supporting malignant transformation. No adjuvant therapy was advised by the oncologists following multidisciplinary team review. The patient remains well to date, but under regular surveillance.

Patient 4

A 75-year-old man presented with an incidental finding on a chest radiograph. A left-sided lesion was observed and this was found to be a large pleural-based mass in the left upper zone measuring 8.7 × 7.8 cm. A CT-guided biopsy confirmed the diagnosis of a benign solitary fibrous tumour. Subsequently he developed dyspnoea and was found to have a large pleural effusion. The effusion was drained and no malignant cells were found on cytology. Repeat CT at this time (10 weeks following the initial CT scan) revealed significant progression (Fig 1). The lesion now measured 11 × 14 × 13 cm and had a heterogeneous appearance, with multiple areas of enhancement; and suggestion of chest wall invasion. There were also multiple pleural-based nodules within the left upper lobe. Unfortunately, radical resection was not possible at surgery due to invasion of the major vessels and pericardium, so debulking was performed. Postoperative histology confirmed malignant transformation of a SFTP. The patient received three cycles of adjuvant chemotherapy (doxorubicin). CT performed 5 months following

Figure 1 Transverse and coronal computed tomography of patient 4, demonstrating the significant progression between (a) presentation and (b) surgery.

the surgery revealed progressive disease. The patient died 2 months following this scan.

Patient 5

A 37-year-old man initially presented with dyspnoea, chest discomfort and feeling unwell, and was diagnosed with a

right-sided pneumonia treated with two courses of antibiotics. On the post-treatment chest radiograph 4 weeks later, resolution of consolidation was seen, and what was reported as a prominent right pericardial fat appendage was noted. He remained symptomatic and a further chest radiograph, 4 weeks later, revealed a rapidly enlarging mass in the right cardiophrenic angle (Fig 2). CT revealed a large mass arising from the mediastinum $11 \times 14 \times 13$ cm with possible invasion into the right atrium. CT-guided biopsy confirmed a diagnosis of SFTP with features suggestive of malignancy. The rapidly growing lesion was ^{18}F -2-fluoro-2-deoxy-d-glucose (FDG) avid on PET-CT imaging (SUV 10), further suggesting malignant transformation. The patient underwent radical surgical and final histology confirmed malignant transformation of this rapidly growing SFTP (Fig 3). He subsequently received radical radiotherapy (66 Gy) to the surgical bed, owing to the suggestion of a positive mediastinal pleural margin. The patient remains well to date and CT performed 6 months postoperatively revealed no evidence of tumour recurrence.

Discussion

Solitary fibrous tumour of the pleura is a rare pathology of the thorax. What is striking from the five cases presented is the variability in clinical course. As patients 4 and 5 demonstrate, following malignant transformation (which may not be evident on initial CT-guided biopsy), these usually slow growing and indolent tumours can progress rapidly. The aggressiveness of this progression requires them to be managed with caution.

Figure 2 Chest radiograph and computed tomography (CT) of patient 5, demonstrating the aggressive clinical course in this patient. Serial chest radiographs demonstrate significant enlargement of the lesion (a–b). Significant increase in volume of disease can be seen over the 4-week period between diagnostic imaging (c) and preoperative CT-positron emission tomography confirming radioisotope avidity (standardised uptake value 10) suggestive of malignant transformation (d).

Figure 3 Histopathology: (a) Low power view of a benign solitary fibrous tumour (patient 2). (b) CD34 immunostain showing strong, diffuse positivity in keeping with the diagnosis. (c–d) Core biopsy of a large left sided upper lobe lung/pleural mass (patient 4). High magnification of the core biopsy showing a bland spindle cell tumour with a whorled architecture, scarce mitoses and no significant cytological atypia favouring a benign solitary fibrous tumour. (e–f) Section from the resected tumour of the same patient, appearing malignant at surgery. High magnification showing large atypical epithelioid cells with numerous mitoses, morphologically different from the core biopsy appearance and in keeping with a malignant transformation. All images haematoxylin and eosin stained unless otherwise stated.

SFTP are found to have a peak incidence between the fifth and seventh decades of life, and affect both sexes equally. There are no known aetiological risk factors and, specifically, no association has been demonstrated with cigarette smoking or asbestos exposure.^{1,5} There is one case in the literature suggesting a genetic component with possible familial transmission, although the genetic mutation was not identified.¹⁴

The natural history of these tumours remains incompletely understood. Approximately 50% present as an asymptomatic mass discovered incidentally on a chest radiograph or other radiological imaging, indicating that there is an asymptomatic course, although the longevity of this phase is difficult to characterise.^{1,12} Other patients present with symptoms attributable to mass or pressure effects of much larger tumours on adjacent intrathoracic structures – most commonly cough, dyspnoea with reducing exercise

tolerance and chest pain. Haemoptysis, obstructive pneumonitis and atelectasis are rarer presentations.¹⁵ SFTP may also present with extrathoracic paraneoplastic symptoms including weakness, nocturnal sweating, weight loss, digital clubbing, hypertrophic osteoarthropathy and hypoglycaemia.^{5,15} Hypertrophic pulmonary osteoarthropathy (Marie–Bamberger syndrome) is seen in as many as 20% of cases, both benign and malignant, and is thought to be caused by production of hepatocyte growth factor or an excessive release of hyaluronic acid by the tumour.¹⁶ In 2–4% of cases, SFTP can secrete insulin-like growth factor II, which is responsible for the refractory hypoglycaemia occasionally observed (Doege Potter syndrome).¹⁷

Thoracic CT is the standard radiological modality for investigating patients with SFTP. These tumours are usually large, well-defined, lobulated, solid and vascular masses, often with a prominent feeding vessel. The enhancement pattern can vary depending on cellularity, vascularity and density of the collagenous or fibrous stroma. Central hypo-enhancing or non-enhancing areas may be seen in the tumour, which represent necrosis or cystic change. Calcification is rare and can be seen in large benign or malignant tumours.^{12,18} Tumours can demonstrate remarkable heterogeneity, with variable degrees of enhancement, necrosis or haemorrhage, and these appearances are not found to accurately enable differentiation between benign and malignant lesions.^{12,18} If there is any suggestion of mediastinal invasion, magnetic resonance imaging (MRI) can be useful for surgical planning. There may also be a place for MRI in aiding distinction between benign and malignant lesions, with heterogeneous signal intensity and heterogeneous contrast uptake found to correlate with malignancy.¹⁹ With the increased availability of PET-CT, many patients are now undergoing these scans during assessment, to facilitate diagnosis of malignant lesions and/or detect potential metastases. Areas of uptake within SFTP are sometimes observed, corresponding to hypercellular areas, which may indicate malignant transformation. However, the ability of PET-CT to accurately diagnose malignant SFTP is not absolute, with both false positive and false negative results reported.^{12,20} In our two patients who underwent a PET-CT, the result did appear to correlate with postoperative histological findings and clinical behaviour.

Following diagnosis on radiological imaging, most patients will have a CT-guided biopsy for tissue diagnosis. A diagnosis of SFTP can usually confidently be made on histological and immunohistochemical analysis of the sample (Fig 4). The ‘patternless’ appearance of spindle cells within a collagenous matrix, found to be positive for CD34, is considered diagnostic of a SFTP.⁶ Positive staining for vimentin and bcl-2, and absence of staining for cytokeratin further aids differentiation from other pleural tumours such as mesothelioma.^{21,22}

Malignancy in such lesions is defined on the basis of identifying the following features on the background of otherwise typical morphological appearances:^{6,20,25}

- > abundant cellularity with crowding and overlapping of nuclei

- > high mitotic activity of more than four mitotic figures per 10 high power fields
- > at least focal pleomorphism with cytonuclear atypia
- > infiltrative margins
- > large necrotic or haemorrhagic areas.

Although biopsies can aid diagnosis of an SFTP, they are not so helpful in differentiating between benign and malignant lesions, with low diagnostic accuracy.^{16,24} With such large lesions it is difficult to be certain of a representative sample when obtaining a biopsy. From our series, in two patients a preoperative diagnosis of benign SFTP was made, in whom the final histology was malignant, highlighting the problem with relying on such biopsies.

Radical surgical resection is considered to be the gold standard of treatment. Completeness of the surgical excision has been identified as an important prognostic factor for both benign *and* malignant SFTP. As such, every effort is directed towards achieving negative margins, as any residual microscopic disease negatively affects survival.^{16,24,25} This may require extended resections such as chest wall resections, excision of parietal pleura, pericardium and even lobectomies. In the case of large SFTP, open surgery is performed, usually through a thoracotomy. With smaller lesions, video assisted thoracoscopic surgery can be attempted. There have been reports of the use of angiography and preoperative percutaneous embolization to reduce intraoperative bleeding in cases of large tumours with major feeding vessels.^{11,26}

The use of adjuvant therapies has been reported in some cases, particularly in patients with malignant postoperative histology.^{6,11} There are recent studies demonstrating the benefit of using both chemotherapeutic agents, such as anti-angiogenic agents,²⁷ and radiotherapy²⁸ as adjuvant therapies. To date, though, there is no consensus guideline on the use of these therapies in SFTP and their role has yet to be defined.

In patients confirmed to have benign SFTP with clear resection margins, outcomes are generally very good, with an 89% 10-year survival reported.^{3,16} However, local recurrence and even metastatic disease has been reported.⁶ Long-term outcomes in terms of tumour recurrence are found to depend on histological characteristics. De Perott and colleagues developed a classification and quantified the following risks of recurrence:^{1,29}

- > benign pedunculated tumour – 2%
- > benign sessile tumour – 8%
- > malignant pedunculated tumour – 14%
- > malignant sessile tumour – 63%.

The overall median survival of patients with a malignant SFTP is reported to range from 59 months to 94 months.^{20,25} Although the majority of recurrences are reported to occur within 2 years following resection, recurrences have been reported many years later. For example, Abe *et al.* report a case of a patient developing several recurrences over a 24-year period following the original resection.³⁰ Local recurrences have been managed successfully surgically, with long-term survival reported, and so aggressive surgical

management is justified in such cases.^{25,30} Rarely, some patients develop metastatic disease, with sites including the lung, liver and bone. Despite systemic therapy, patients who develop metastatic disease have a very poor prognosis, with median survival as low as 22 months.³¹

In view of the unpredictable nature of this disease, long-term follow-up is advocated, even for patients with benign disease because of the possibility of late recurrence of these slow-growing tumours. It has been recommended that patients be followed up with 6-monthly CT for the first 2 years, and then yearly thereafter, with follow-up suggested for as long as 15–20 years.^{21,29}

Conclusion

Solitary fibrous tumour of the pleura is a rare diagnosis, but one which should be managed cautiously, owing to its unpredictable and potentially aggressive clinical course. Although the majority of patients have benign lesions, which typically follow an indolent course, malignant transformation occurs in as many as 20% of cases. Malignant SFTP is an aggressive disease (as highlighted in patients 4 and 5) with poor prognosis if not managed effectively. Radical surgical resection should be considered the gold standard, with increasing reports of adjuvant therapies playing a role in patients with malignant SFTP or benign lesions incompletely resected. Since accurately differentiating benign and malignant disease on imaging and biopsy is challenging preoperatively, we would advocate the position that all patients with SFTP should be managed as if they have malignant disease. Prolonged follow-up is required because of the risk of disease recurrence, even in patients with benign disease.

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