Solitary fibrous tumours of the pleura

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Received 5 May 2011; received in revised form 7 July 2011; accepted 15 July 2011

Summary

Solitary fibrous tumours of the pleura are rare. They are mesenchymal in origin. Initially, they were described in the pleura, but lately they have been reported in many other sites. Although the majority of these tumours are benign, some of them are malignant. Their unpredictable clinical course is probably related to their histological and morphological characteristics. The benign tumours may remain unproblematic for several years before changing into a malignant form. In order to define more accurately the clinical behaviour, diagnosis, management and outcome of these rare tumours, we reviewed the literature with particular attention to clinical presentation, methods of diagnosis, treatment and outcome. Furthermore, a modified algorithm was proposed for the management of these tumours.

Keywords: Solitary fibrous tumours • Malignant pleural tumours • Pleural tumours

BACKGROUND

Primary neoplasms of the pleura are rare tumours with unpredictable behaviour. Generally, they are divided into two major categories: diffuse and localized tumours. The diffuse pleural tumour is mesothelioma, which is known for its association with asbestos and its poor outcome. Diffuse pleural tumours are more common than solitary ones. They arise from the mesothelial tissue [1–5]. Localized pleural tumours are usually rare [6] and remain a subject of controversy. They have been known by a variety of names that reflect their clinical course and controversies surrounding their histogenesis (Table 1).

Few numbers of SFTPs have been reported in the literature. The major series reported recently are shown in Table 2. The majority of them are pedunculated with benign histological features [1–5, 10]. Although they may be relatively large, these tumours are usually treated by simple excision and do not recur if resection is complete microscopically [4, 11, 12]. Around 12% of the SFTPs are found to be malignant and eventually lead to death through local recurrence or metastatic disease [13]. The malignant form of SFTPs still remains mysterious. The behaviour is often unpredictable and does not always correlate with histological findings [10]. It was found that in some cases, the benign SFTPs may remain stable for several years before changing into a malignant one [2]. Localized fibrous tumours have recently been reported in extrathoracic sites such as the meninges, nasal cavity, oral cavity, pharynx, epiglottis, salivary gland, thyroid, breast, kidney, bladder and spinal cord [13, 14]. We reviewed the literature with particular attention to clinical presentation, methods of diagnosis, treatment and outcome.

HISTORY

Wagner [15] reported the first primary localized pleural tumour in 1870. However, Klemperer and Rabin [16] were the first who published the accurate pathological description of this tumour in 1931, in which they classified mesothelioma as either localized or ‘diffuse’. In 1942, Stout and Murray [17] claimed that localized mesothelioma had a mesothelial origin. This was proved later through ultrastructural analysis [18]. However, other investigators showed that the mesothelial layer covering the tumour was intact, and they explained the presence of the epithelial cells by the theory that these cells could be trapped within the growing fibrous mesenchymal tumours [19].

Advances in immunohistochemical studies and electron microscopy have proved the mesenchymal origin of these tumours. Consequently, this led to the localized tumour being specifically named SFTP and has clarified its status as a separate tumour from the pleural mesothelioma. These localized tumours have been shown to lack expression of cytoplasmic keratins and to express vimentin, a marker of mesenchymal cells [1, 5], and CD34 [8], which is a trans-membrane cell surface glycoprotein that is universally observed in a novel family of interstitial spindle cells known as ‘dendritic interstitial cells’ involved in antigen presentation and characterized by slender dendritic prolongation of their cytoplasm [20].
INCIDENCE

SFTP is a rare neoplasm. Approximately 800 cases were reported in the literature [3, 5, 6]. This proves its rarity in comparison to the most common primary pleural tumour, diffuse mesothelioma [3, 21].

SFTPs affect male and female patients equally [10, 11, 13, 14–22], although some authors documented slight female predominance in their studies [1, 13]. Women represented 55% of patients with benign SFTPs and 50% of patients with malignant SFTPs in a review study conducted by Rosado-de-Christenson et al. [1].

SFTPs occur in all age groups (from 5 to 87 years), but they peak in the sixth and seventh decades of life with a reported mean age of 50–57 years [10, 13, 23]. Although Rosado-de-Christenson et al. [1] found that 83% of patients in their series were older than 40 years, only 41% were in the sixth and seventh decades of life.

Only one report of the familial occurrence of SFTP in family members has been published, involving a mother and her daughter [24]. Generally, there is no evidence of correlation with genetic predisposition for the tumour, and there is no relationship to the exposure to asbestos, tobacco or any other environmental agents, although there are only two case reports of patients with SFTP who were exposed to asbestos and one patient developed an SFTP following thoracic irradiation for the treatment of chest wall keloid [25, 26].

It was noted that supernumerary chromosome 8 suggests a more malignant behaviour of the tumour; but in general, cytogenetic data on SFTPs are few [27].

PATHOGENESIS

There are many different theories about the cell origin of SFTPs, which might be the reason for the different nomenclatures used to designate this rare neoplasm [13, 28–30]. The currently accepted nomenclature is localized (solitary) fibrous tumour of the pleura, and a derivation from submesothelial mesenchymal cells with a fibroblastic differentiation is generally acknowledged [30]. Lesions of similar histological characteristics have been reported in extrapleural thoracic locations, including the mediastinum, lung, pericardium and heart [31–33]. Yousem and Flynn [34] described three intrapulmonary localized fibrous tumours and suggested the tissues in the interlobular septa as a common origin for this subset of lesions. Solitary fibrous tumours have also been reported in the abdomen, liver, peritoneum, retroperi toneum, meninges, orbit, thyroid, salivary gland and the soft tissues including the breast [32, 33, 35]. The upper respiratory tract may be the preferred extrathoracic location, with many documented reports of localized fibrous tumours arising in the nose, paranasal sinuses, parapharyngeal tissues, nasopharynx and epiglottis [32, 36].

PATHOLOGY

Macroscopic features

Typical SFTPs are solitary lesions with rare occurrences of conglomerate or multifocal masses. The majority of them arise from the visceral pleura, and nearly 50% are pedunculated, with the vascular supply to the tumour contained within the pedicle [10]. Adhesions to the adjacent pleural surfaces and pericardium are common [10, 13]. SFTPs are usually well-circumscribed masses with lobular or smooth external surfaces and are encapsulated
within a thin, glistening translucent serosa through which a network of prominent blood vessels may be seen [10] (Fig. 1). The cut surface appears grey-white to tan with a whorled pattern and may show areas of haemorrhage and necrosis [10, 37]. Benign tumours may show haemorrhagic and necrotic areas, but these features usually predominate in the malignant forms [10].

Histological characteristics

England et al. [10] suggested that SFTPs originated from the sub-mesothelial connective tissues and proposed a primitive multipotential cell of mesenchymal differentiation as the cell of origin. Histopathologically, localized fibrous tumours appear as low-grade neoplasms of variablecellularity. The tumour cells are ovoid-to-spindle-shaped with round-to-oval nuclei, an equally distributed fine chromatin, inconspicuous nucleoli and bipolar faintly eosinophilic cytoplasm with indistinct cell borders. Nuclear pleomorphism is minimal, and mitoses are usually rare or absent. They have variablecellularity which is inversely related to the collagen content [1, 10]. Collagen ranges from wispy fibrils surrounding tumour cells in hypercellular areas to thick, dense, wire-like forming sclerotic zones in hypocellular areas. These tumours are usually well vascularized [19]. Degenerative features are found in the form of degeneration of collagen and myxoid change. Microscopic examination reveals various architectural patterns. The most frequent pattern is the patternless pattern, in which there is intermingling of tumour cells and collagen in a random fashion [38]. The second most common pattern is hemangiopericytoma-like appearance, which is characterized by hypercellular zones containing a network of open anastomosing or staghorn-shaped vessels. Less frequently, localized (solitary) fibrous tumours may have angiofibroma-like, fibrosarcoma-like and monophasic variant of synovial sarcoma-like patterns [38].

The histological differential diagnosis of SFTPs is broad because of the high variability of their light microscopic appearances. It includes primary and metastatic spindle cell carcinoma, spindle cell melanoma, sarcomatoid mesothelioma and a wide spectrum of primary and metastatic soft-tissue neoplasms. The exclusion of other tumours is relatively straightforward with the aid of immunohistochemical studies [1, 3, 38].

Immunohistochemistry has been an extremely useful tool to differentiate SFTPs from mesotheliomas and other sarcomas over the last few years. De Perrot et al. [5] have summarized most of the important immunohistochemical characteristics in their review in order to facilitate the diagnosis and to distinguish SFTPs from other similar tumours. In fact, SFTP by definition is vimentin-positive and keratin-negative. Furthermore, CD34 is positive in most benign and malignant SFTPs, whereas it remains negative for most of the other pulmonary tumours. However, distinction from other soft-tissue neoplasms can be difficult, especially in cases of hemangiopericytoma, the monophasic variant of synovial sarcoma, and malignant fibrous histiocytoma [38].

Hemangiopericytomas are CD34-positive tumours. This may be the reason that some authors have proposed the possibility that both SFTPs and hemangiopericytomas may represent a single entity [39]. Recently, genetic analyses have suggested that hemangiopericytomas are unrelated to SFTPs [40]. In addition, the anti-apoptotic proto-oncogene bcl-2 is strongly expressed in SFTPs, whereas it is absent or is only poorly expressed by hemangiopericytomas [41].

Malignant SFTPs may be CD34-negative in some occasions, although this finding may be caused by a dedifferentiation of the tumour and reflects poor prognosis [37]; it most likely represents a group of SFTPs that have always been CD34-negative [8]. The expression of bcl-2 can be a useful marker in these CD34-negative tumours to confirm the diagnosis of SFTP [41].

Nowadays, some authors have demonstrated that the O-13 (CD99) and factor XIIia could be expressed by solitary fibrous tumours located in the pleura and in other locations [42, 43]. However, CD99 and factor XIIia are not strongly expressed by SFTPs and can also frequently be positive with other tumours such as synovial sarcomas or neural tumours and so they are less specific as a diagnostic tool for the diagnosis of SFTPs [40, 44-46]. El-Naggar et al. [7] analysed 14 histologically benign fibrous tumours by flow cytometry. His group concluded that the number of mitoses and corresponding S-phase may reflect the rapidly growing lesions that exhibit locally aggressive behaviour. In a more advanced stage of malignancy, SFTP may become partially aneuploid and could be associated with a high mitotic index [47].

Cytogenetic analyses have shown anomalies such as trisomy 8, trisomy 21 or more complex translocations in solitary fibrous tumours that may help to differentiate them from mesothelioma and other sarcomas [48-50]. Chromosomal anomalies were shown mainly in the tumours larger than 10 cm by the aid of genomic hybridization [47]. This relationship between the size and the chromosomal anomalies may suggest that genomic changes may promote tumour growth. Further analysis may help researchers to appreciate the types of genetic anomalies and the risk of recurrence of SFTPs.

The fact that chromosomal anomalies and genetic mutations of the apo-apoptotic gene p53 are located only in some areas of the tumours and that the benign tumours may recur with histological signs of malignancy several years after resection of benign forms could emphasize the possible malignant degeneration of the SFTPs [5, 37, 40].

The anti-apoptotic proto-oncogene bcl-2 is constitutively expressed by all benign and malignant SFTPs. This suggests that these tumours may originate from a long-lived CD34-positive fibroblastic stem cell [51]. Yokoi et al. [37] showed that all
malignant tumours were p53-positive. Moreover, they demonstrated that the index of positive staining for Ki67, which is a marker of cellular proliferation, was greater in malignant than in benign tumours and roughly paralleled the clinical outcome. Hanau and Miettinen [52] have shown similar results. Unfortunately, the cut-off between benign and malignant lesions is not always clear. This was proved by Hasegawa et al. [51] as they showed that benign tumours could have a Ki67 index of up to 10%. Another index of cell proliferation, which is named the proliferating cell nuclear antigen, showed less striking differences between benign and malignant tumours [37]. Hence, successive mutations in bcl-2 and p53 may lead to an excessive proliferation rate and to the formation of malignant forms of SFTPs.

England et al. [10] have defined the criteria of malignancy in a large study, which include (i) abundant cellularity with crowding and overlapping of nuclei, (ii) high mitotic activity of more than four mitotic figures per 10 high power fields, (iii) pleomorphism with cytonuclear atypia, (iv) large necrotic or haemorrhagic areas, (v) associated pleural effusion and (vi) atypical location and inversion of adjacent structures. The presence of occasional large bizarre cells or focal high cellularity in the absence of cellular atypia or mitosis is usually insufficient to categorize the tumour as malignant (52). A brief summary of different characteristics of benign and malignant SFTPs is given in Table 3.

Solitary fibrous tumours are now well recognized as a single entity in the pleura and in other sites. Moreover, it seems that morphological and histological characteristics of these tumours are important predictors of outcome [9]. For that reason, De Perrot et al. [5] have established a classification for SFTPs depending on the results that they have found from their review to the literature. They have classified the SFTPs into five stages: Stage 0 included pedunculated SFTPs without signs of malignancy; Stage I included those sessile or inverted SFTPs without signs of malignancy; Stage II is composed of pedunculated SFTPs with histological signs of malignancy; Stage III included sessile or inverted SFTPs that show histological signs of malignancy and Stage IV included multiple synchronous metastatic tumours.

They described in their classification the criteria of malignancy that they have used to classify the tumour either malignant or benign. The signs of malignancy that they have used in their classification include presence of high cellularity, crowding and overlapping of nuclei, cellular pleomorphism, high mitotic count (more than four per 10 high power fields), necrosis and stromal/vascular invasion.

Because of the diversity of histological patterns displayed by SFTPs, even large biopsy specimens may pose a significant diagnostic problem. The biopsy samples obtained with percutaneous techniques may be insufficient for diagnosis. These lesions remain problematic even for experienced general surgical pathologists. This is explained by the fact that over one half of the benign tumours and about 75% of the malignant lesions in the study conducted by England et al. [10] were initially misclassified.

**Table 3:** Clinical presentation and pathological characteristics of benign and malignant SFTPs

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Benign SFTP</th>
<th>Malignant SFTP</th>
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<tbody>
<tr>
<td>Symptomatic</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Accidental discovery</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Pain</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Macroscopic features</td>
<td></td>
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</tr>
<tr>
<td>Atypical location</td>
<td>Infrequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Size &lt;10 cm</td>
<td>Infrequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Sessile</td>
<td>Infrequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Pedunculated</td>
<td>Frequent</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Rare</td>
<td>Frequent</td>
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<tr>
<td>Haemorrhage</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Calcification</td>
<td>Frequent</td>
<td>Rare</td>
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<tr>
<td>Microscopic features</td>
<td></td>
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</tr>
<tr>
<td>High cellularity</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Cellular pleomorphism</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>High mitotic count</td>
<td>–</td>
<td>Frequent</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Surrounding tissue invasion</td>
<td>–</td>
<td>Frequent</td>
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</table>

**CLINICAL FEATURES**

SFTPs often have a silent clinical course for several years. They are usually discovered incidentally during chest X-ray examination [53–55]. Most of the patients with SFTPs are asymptomatic when these tumours reach large sizes [5, 10, 56]. About 54–67% of patients with benign SFTPs have symptoms, whereas 75% of the patients with malignant SFTPs are asymptomatic [57].

Symptoms include cough, chest pain and dyspnoea. Rarely, haemoptysis and obstructive pneumonitis are observed as a result of airway obstruction [5, 10]. Chest pain occurs more commonly in patients whose tumours arise from the parietal pleura. Occasionally, large tumours cause compression of a bronchus and result in atelectasis with symptoms or rarely haemoptysis [3].

Paraneoplastic syndromes may occur but are more likely with large tumours. Digital clubbing and hypertrophic pulmonary osteoarthropathy (Pierre-Marie–Bamberg syndrome) have been described in 10–20% of patients with either benign or malignant SFTPs [4, 10]. These clinical features usually resolve within 2–5 months or sometimes longer after removal of the tumour, but they may reappear with recurrence of it [4, 10, 58]. The causes of digital clubbing and hypertrophic pulmonary osteoarthropathy could be an abnormal production of heparocyte growth factor or an excessive release of hyaluronic acid by the tumour, respectively [54, 59]. Those patients with hypertrophic pulmonary osteoarthropathy commonly report bilateral arthritic-like symptoms [3]. In <5% of patients, SFTPs can also secrete insulin-like growth factor II, which causes refractory hypoglycaemia (Doege–Potter syndrome) [10, 13, 60]. A high serum level of insulin-like growth factor II is typically associated with low levels of insulin and insulin-like growth factor I, which return to normal values within 3–4 days after resection of the tumour [4, 58]. Some patients may present with gynaecomastia or galactorrhoea [3].

Sometimes, large tumours might present with unusual presentation, such as the two cases presented by Santambrogio et al. [55] and Shaker et al. [61]. The first described a patient in whom the large tumour presented with episodes of situational syncope on coughing, whereas the second described a female patient who presented with leg oedema and dyspnoea caused by large SFTP compressing the right atrium and inferior vena cava.

Abdominal pain has been reported in patients with supra diaphragmatic tumours [28]. Non-specific systemic complaints may accompany these tumours in the form of chills, sweats, weakness and weight loss [13].
Table 3 summarizes the frequency of different symptoms in each of both benign and malignant types of SFTPs, whereas Table 4 shows different symptoms that may be associated with SFTP categorized according to its frequency based on the revision of the literature.

**DIAGNOSIS**

**Radiography**

Chest radiographs of patients with small SFTP typically demonstrate a well-defined, lobular, solitary nodule or mass, which may appear at the lung periphery and typically abuts the pleural surface or is located within a fissure (Fig. 2) [62]. In 1977, Ellis [63] described the incomplete border sign of the extrapleural lesions to differentiate them from parenchymal masses. Pedunculated tumours may show mobility within the pleural space or changes in shape and orientation on fluoroscopy or with changes in the patients’ position [23].

SFTPs affect mostly the middle and inferior hemithorax [23, 64]. They may show slow growth rate over time and may reach very large sizes [65]. Large lesions and those that arise from paramediastinal pleural surfaces may manifest with typical radiographic features of pulmonary or mediastinal masses, respectively [31, 66]. Pleural effusion is reported in 6–17% of patients [10, 30, 35]. Radiographic evidence of chest wall involvement with SFTP was reported in only one patient [64].

**Computed tomography**

Computed tomography (CT) of small SFTPs typically demonstrates homogeneous, well-defined, non-invasive, lobular, soft-tissue masses, which typically abut a pleural surface. It may form obtuse angles against the adjacent pleura or may be located within a fissure [2, 30, 62]. Larger lesions are typically heterogeneous and may not exhibit the CT features, suggestive of focal pleural tumours [67]. SFTPs usually form acute angles against adjacent pleural surfaces [30, 38, 62, 65, 67].

It may be difficult to differentiate the tumours arising in an interlobar fissure from an intraparenchymal mass [68]. Calcifications may be observed in few tumours, either those of benign or malignant histological features [2, 10], and can be difficult to distinguish from those in large bronchial carcinoids [44].

Dedrick et al. [62] stated that a smoothly tapering margin adjacent to the tumour was a more characteristic finding that could help to establish the pleural location of these tumours. They also reported diaphragmatic crural thickening in one of their cases and a fissural location in another. Furthermore, CT findings may not allow differentiation of a fissural SFTP from a peripheral lung lesion or exclusion of a tumour of abdominal origin when the inferior hemithorax is affected [2, 68].

Pedicle visualization by CT is rare. Masses originating in the mediastinal pleura may mimic mediastinal neoplasms. In fact, Mendelson et al. [65] stated that the diagnosis of SFTPs should be considered when lesions abut the mediastinum or the paraspinal areas. However, it should be noted that lesions of identical histological characteristics (i.e. localized fibrous tumours) may arise in the mediastinum without any relationship to the pleura [31].

Table 4: Clinical presentation of the SFTPs according to the frequency of symptoms

<table>
<thead>
<tr>
<th>Frequent symptoms</th>
<th>Infrequent symptoms</th>
<th>Rare symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>Haemoptysis</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Obstructive pneumonitis</td>
<td>Gynaecomastia</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Digital clubbing</td>
<td>Galactorrhoea</td>
</tr>
<tr>
<td></td>
<td>Hypertrrophic pulmonary osteoarthropathy (Pierre-Marie-Bamberg syndrome)</td>
<td>Lower limb oedema</td>
</tr>
<tr>
<td></td>
<td>Bilateral arthritic-like symptoms</td>
<td>Situational syncope on coughing</td>
</tr>
<tr>
<td></td>
<td>Stuffness or swelling of the joints</td>
<td>Pain along the long bones, mostly in the tibias</td>
</tr>
<tr>
<td></td>
<td>Oedema of the ankles</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td></td>
<td>Arthralgias</td>
<td>Gynaecomastia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Galactorrhoea</td>
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</tbody>
</table>

**Figure 2:** (a) Chest X-ray P-A view showing a basal opacity occupying the right hemithorax. (b) Chest X-ray lateral view showing a basal opacity continuous with the diaphragm and cannot be differentiated from it.
effect on the adjacent lung and mediastinum was described as a typical finding [62]. Interestingly, although there was little difference in size between the malignant and benign SFTPs in their series, atelectasis, mass effect on the mediastinum and pleural effusion were more common in malignant SFTPs. Calcification was documented in 7% of cases, mostly in large lesions in association with necrosis [30, 35]. Intralobular calcification was reported in 26% of patients in a study conducted by Rosado-de-Christenson et al. [1] and was characterized as punctate, linear or coarse. Local invasion is rarely reported, and lymphadenopathy is not a feature of SFTP [69]. In addition, chest wall involvement was seen using CT in 8% of cases in the same study, manifested as sclerosis or pressure erosion on adjacent ribs, a characteristic feature of chest wall and mediastinal neoplasms of neurogenic origin that is rarely reported in association with SFTP [64].

SFTPs have been reported to exhibit intermediate-to-high attenuation on unenhanced CT scans due to the high physical density of collagen and the abundant capillary network within these lesions [1]. However, Francis et al. [70] denied this relationship between CT attenuation and histological content of the lesions. Enhancement may correlate with the vascular nature of these lesions and may result in higher attenuation than that of other soft tissues in the thorax [66]. Lee et al. [67] studied nine cases of SFTPs with CT and demonstrated a significant enhancement in all. Enhancement is typically heterogeneous with central areas of low attenuation, which have been shown to correlate with myxoid change, haemorrhage, necrosis or cystic degeneration [4, 30, 65, 67].

Heterogeneity may become more evident after intravenous administration of contrast material. The contrast material enhancement could not be encountered in all cases. Only benign SFTPs exhibited homogeneous attenuation, which was more commonly seen on unenhanced scans. Homogeneity of attenuation may indirectly relate to the size of the tumours as small lesions may exhibit necrosis less frequently [1].

In a study conducted by Rosado-de-Christenson et al. [1], haemorrhage, necrosis or cystic change was absent in (88%), with homogeneous attenuation on unenhanced scans and in all eight SFTPs with homogeneous attenuation on contrast-enhanced CT scans. Heterogeneous areas of low attenuation on unenhanced CT scans correlated with the gross presence of necrosis, haemorrhage or cystic changes in 86% of benign SFTPs. Heterogeneous attenuation of SFTPs after contrast material administration was typical and correlated with gross descriptions of haemorrhage, necrosis or cystic change in 55% cases of benign SFTPs with intrinsic areas of low attenuation. Little has been written about the CT appearance of malignant SFTPs. They are described as indistinguishable from benign lesions: large masses of heterogeneous attenuation and patchy enhancement [69, 71]. Although there was no difference in lesion size when the benign and malignant SFTPs were compared, low-attenuation areas were seen in all malignant SFTPs whether the scans were obtained before or after the administration of intravenous contrast material and correlated with gross descriptions of haemorrhage, necrosis or cystic change in 60% of unenhanced and 54% of enhanced CT studies [1].

**Magnetic resonance imaging**

Only few reports of magnetic resonance imaging (MRI) features of SFTPs were reported [23, 72–74]. Unfortunately, it has a limited use in the assessment of the pleural disease [75]. SFTPs are described as masses of predominant low or intermediate signal intensity on both T1- and T2-weighted images and on proton density-weighted images, which is thought to be as a result of high content of fibrous collagenous tissue, hypocellularity and small numbers of mobile protons [28, 30, 73, 74]. However, high signal intensity on T2-weighted images has also been reported and may relate to necrosis, cystic or myxoid degeneration, prominent vascular structures and hypercellular areas [23, 74]. On the other side, MRI could be better than CT to delineate the morphology and the relationship of large SFTPs to adjacent mediastinal and major vascular structures [76]. It is helpful in differentiating the tumour from other structures and in confirming intrathoracic localization when the tumour abuts the diaphragm [2, 35, 67, 76]. Although the tumour localization within the thorax and the diaphragmatic evaluation could sometimes be difficult with the use of CT, it is not the case with the sagittal and coronal images of MRI. Flow voids reflecting the vascular nature of some SFTPs have previously been reported [74].

**Angiography**

Angiography is an important diagnostic tool as it can determine the vascular supply to the lesion, which typically enters through the pedicle [77]. Demonstration of the blood supply from the inferior phrenic, intercostal or internal mammary arteries may be a helpful clue to determine the extrapulmonary origin of large SFTPs [28]. Furthermore, angiography and arterial embolization may be good approaches in selected patients with giant SFTPs before the actual surgery to decrease the incidence of haemorrhage [78].

**Ultrasonography**

The use of ultrasonography in the diagnosis or the evaluation of SFTPs is uncommon. It is sometimes used in the evaluation of large masses located in the inferior hemithorax through visualization of the diaphragm and establishment of their intrathoracic location [56, 62]. Lu et al. [79] documented that the use of ultrasound-guided core needle biopsy combined with immunohistochemical analysis might be safe and rapid procedure to provide preemptive diagnosis.

**18-Fluorodeoxyglucose-positron emission tomography**

Recently, it was documented that 18 fluorodeoxyglucose-positron emission tomography (FDG-PET) is a valuable addition to the diagnostic tools of SFTPs. It could be used in the diagnosis and follow-up of the treated patients. Cardillo et al. [54] have confirmed in their study the high negative predictive value of PET scan in assessing the malignancy of such lesions. Moreover, the presence of multiple SFTPs and high-grade 18 FDG metabolism at PET should alert the clinician to the high possibility of a malignant variety of SFTPs [80].
Other diagnostic tools

Besides the radiographic studies, bronchoscopy, sputum analysis and analysis of the pleural fluid are used as diagnostic tools for SFTPs. Bronchoscopy is found to be of little or no benefit other than to rule out other lesions. The same is for the sputum analysis and pleural fluid analysis [3].

Tissue biopsy

SFTPs cannot be diagnosed only through using radiological tools. This is because the classically described radiographic features (incomplete visualization of the lesion borders and fissural location) and cross-sectional imaging features (obtuse angles, mobility and pedicle visualization) of solitary pleural masses are usually not present in the majority of cases [1]. The diagnosis of SFTPs is rarely reached before surgical excision and pathological examination of the mass. Sometimes, preoperative diagnosis can be made with large-bore cutting needle biopsies. The risk of pneumothorax could be minimal through avoiding aerated lung on the introduction of the needle [81]. Although fine-needle aspiration may yield characteristic and diagnostic morphological features, it was difficult to reach a histological diagnosis in most studies [4]. This was attributed to the small biopsy specimens and variability of the histological structure in each tumour. Cutting needle biopsy (Tru-cut needle biopsy) is probably preferable because of wider tissue sampling [29, 80, 81], allowing histological and immunohistochemical studies with high preoperative diagnostic accuracy [4]. Generally, most authors [5, 57, 82] prefer not using needle biopsy in this neoplasm since it does not influence the need for surgical treatment of this obviously respectableable mass.

DIFFERENTIAL DIAGNOSIS

The preoperative differential diagnosis in a patient with an SFTP is essentially that of any mass lesion in the chest, ranging from carcinoma of the lung to various intrapleural sarcomas. Posterior intrathoracic location may suggest a neoplastic tumour or round aetelectasis. Anterior and mediastinal locations raise the possibility of a thymic neoplasm, germ cell tumour or teratoma [3].

The main differential diagnoses of malignant SFTPs include pleural mesothelioma, neurogenic sarcoma, synovial sarcoma, hemangiopericytoma, fibrosarcoma and malignant fibrous histiocytoma [45, 83, 84]. Pleural mesotheliomas are malignant and usually present as multiple pleural nodules or as a diffuse tumour that encases a portion of the lung. However, SFTPs have been clearly recognized now as a single entity by means of specific immunohistochemical staining techniques. Pleural mesotheliomas may rarely appear as localized tumours [85, 86]. Misdiagnosis of synovial sarcoma, neurogenic sarcoma, fibrosarcoma and malignant fibrous histiocytoma with SFTPs can occur due to dense monotonous spindle cell proliferation and the similar histological patterns that are encountered with these tumours. However, in contrast to other sarcomas, malignant SFTPs are not histologically uniform, and they present with different patterns inside the same tumour [87].

TREATMENT

Surgery

The treatment of the patients with SFTPs is complete surgical excision. Aggressive surgery is recommended due to the high probability of their recurrence [83]. Massive intraoperative bleeding may occur due to either vascular adhesion to adjacent tissues or highly vascular tumours. This could be avoided through good exposure, prompt removal of the mass and meticulous hemostasis or preoperative embolization of the feeding vessel [78, 88]. The type of surgical resection differs according to the size of the tumour, its location and extent of invasion to adjacent structures. Complete en bloc surgical resection is the mainstay therapy for all benign and malignant SFTPs and is the one recommended by most of the authors. A distance of 1–2 cm from the tumour is usually recommended to be in healthy tissue. Pedunculated tumours can be safely resected with a wedge resection of the lung, and large sessile tumours can sometimes be difficult to resect because of extensive adhesions and may occasionally require lung resection (segmentectomy, lobectomy, bilobectomy and pneumonectomy), partial pleurectomy or en bloc chest wall resection in order to achieve a complete resection [54, 56, 89, 90]. Frozen section can be helpful in the assessment of the resection margins and documenting its freeness from tumour cells. Tumours adherent to the parietal pleura require an extrapleural dissection [4, 54]. Concomitant chest wall resection can be necessary if the tumour densely adheres to or invades the chest wall [65]. Inverted tumours [34] that grow inside the lung parenchyma (<3% of cases) may require lobectomy or sleeve lobectomy [37, 54, 91, 92].

Thoracoscopic approaches can be safely used to excise small pedunculated tumours located on the visceral pleura [54, 93]. Cardillo et al. [54] described 55 patients with SFTPs who underwent resection via video-assisted thoracoscopic surgery (VATS) and thoracotomy with no operative deaths. In the majority of patients, resection of the lesion with its pedicle and a small patch of adjacent lung may be sufficient [4]. Some authors have also recommended the assistance of a video camera (video-assisted thoracic surgery) to obtain a more precise view of the resection margins in some large, broad-based tumours of the parietal pleura. Contact metastases and local recurrence at the port sites were encountered in some patients following surgical excision of SFTPs with VATS. Consequently, it is recommended that extreme caution should be used to avoid contact between the tumour and the thoracoscopic sites [54, 90]. Long-term imaging follow-up is recommended in all cases to exclude tumour recurrence or metastases. Recurrent disease typically affects the ipsilateral pleura or the lung. Repeat resection of recurrent lesions is recommended [2, 56].

Adjuvant therapy

The role of adjuvant therapy is doubtful because of the low cellular content and low mitotic rates of SFTPs [94–96]. In addition, it has not been systematically explored because of the limited number of patients [2, 54, 84]. However, some indices suggest that radiotherapy and chemotherapy could be beneficial in some patients. Suter et al. [56] have reported one patient who is alive with no evidence of disease more than 20 years after subtotal
resection of the tumour followed by radiotherapy. Moreover, Veronesi et al. [96] have observed significant reduction in an inoperable recurrent SFTP with ifosfamide and adriamycin. In addition, Park et al. [97] have found that combination of temozolomide and bevacizumab had high rates of overall response and long duration of disease control. In their study, patients received temozolomide 150 mg/m² orally on days 1–7 and days 15–21 and bevacizumab 5 mg/kg intravenously on day 8 and day 22 on a 28-day cycle. Currently, the administration of adjuvant therapy after resection of malignant sessile tumours is recommended, particularly if they are recurrent.

Neoadjuvant therapy

Although neoadjuvant therapy could be helpful in large malignant tumours, its use is limited because of the difficulty in obtaining a precise preoperative diagnosis even with an open biopsy [98].

Other treatment modalities

Additional therapies, such as brachytherapy and photodynamic therapy, have been developed for malignant mesotheliomas. These new modalities of therapy could be applied for other pleural tumours, especially if they cannot be completely resected. However, their use in SFTPs has rarely been reported, and their utility remains unproven [98].

De Perrot et al. [5] have proposed an algorithm for the treatment of SFTPs based on the pathological characteristics of the SFTP either benign or malignant and also sessile or pedunculated. Although it is a well-defined algorithm, they did not suggest adjuvant therapy after surgical resection for malignant pedunculated SFTPs. In contrast, we proposed a modified algorithm for the treatment of SFTPs in which we stressed on the aggressive treatment for the malignant SFTPs and suggested the adjuvant treatment following radical resection of those tumours (Fig. 3).

PROGNOSIS

The prognosis for patients with SFTPs is generally favourable. The majority of lesions behave in a benign fashion (88%), but approximately 12% of patients die of extensive intrathoracic tumour growth or an unresectable recurrence [13]. Malignant tumours may metastasize, and the local recurrences are more common in cases of malignant lesions than in benign lesions [99–101]. The recurrence may occur up to 17 years after surgical resection and is usually located in the same hemithorax [102]. Intrathoracic recurrence may be fatal because of mediastinal compression and inferior vena cava obstruction [13]. Metastases are usually blood-borne and are located in the liver, central nervous system, spleen, peritoneum, adrenal gland, gastrointestinal tract, kidney and bone by order of frequency [10].

The risk of recurrence is high after resection of malignant sessile SFTPs. Most of them are initially located inside the pleural cavity, whereas distant metastases occur later in the course of the disease. Some recurrences can be extremely locally aggressive, leading to patients’ death through local invasion and compression without evidence of distant metastasis [37, 56]. The majority of the recurrences after the initial resection of malignant sessile tumours were found to occur within the first 2 years, and approximately 50% of the recurrences were the cause of death during that period. Hence, 6 months radiological control with chest radiography or CT scan during the initial 2 years after the resection and yearly thereafter is recommended and may be of value to reduce the mortality from malignant SFTPs. Aggressive surgical resection remains the treatment of choice for the recurrences of SFTPs and may lead to long-term survival [69]. Adjuvant therapy should be considered if the tumour proved to be histologically malignant.

Most important predictors of the outcome are morphological and histological indicators [9]. In 1981, Briselli et al. [13] presented 8 new cases and reviewed 360 cases from the literature. About 12% of the tumours followed a malignant course and led to death. The growth pattern of the tumour was found to be the most important indicator for the prognosis than the histological characteristics. Recently, England et al. [10] reported in their study that none of the patients with a histologically benign disease died. In contrast, 55% of those with a malignant form died because of recurrences or metastases. The authors observed that among the malignant variants, complete resectability was the single most important predictor for the outcome.

Histological characteristics are useful in the evaluation of the risk of recurrence in SFTPs [5, 101, 103]. Table 3 summarizes the main macroscopic and microscopic differences between benign and malignant SFTPs, and this can help in the determination of the recurrence risk. De Perrot et al. [5] provided a classification of SFTPs according to their characteristics and prognosis: (i) benign pedunculated tumours had 2% recurrence rate; (ii) benign sessile tumours had 8% recurrence rate; (iii) malignant pedunculated tumours had 14% recurrence rate and (iv) malignant sessile tumours had 63% recurrence rate and 30% mortality rate with most deaths occurred within 24 months.

Some authors have observed that the size of the tumour is a prognostic factor for the clinical behaviour of SFTPs [104]. However, other studies could not prove such correlation [51, 56]. In a review of the literature presented by De Perrot et al. [5], they observed that all the patients reported with a benign tumour >10 cm had a good clinical outcome, whereas 16 out of the 28 malignant tumours >10 cm were associated with recurrence or death. However, small malignant SFTPs have been associated with recurrence. Hence, although the vast majority of the malignant tumours were >10 cm, histological finding rather than size is the principal indicator of the clinical outcome [10]. However, Sung et al. [105] recommended further studies to identify those factors affecting therapeutic response.

SUMMARY

Solitary (localized) fibrous tumours are rare primary pleural neoplasms that fortunately are benign in 80% of the time. They may attain large sizes and typically affect both men and women over the age of 40 years. Small SFTPs may be discovered incidentally on chest radiographs of asymptomatic individuals. Although small lesions may exhibit the characteristic imaging features of the pleural masses, the classic findings of the focal pleural disease are usually absent. The majority of SFTPs occupy the inferior hemithorax, and those that abut the ipsilateral hemidiaphragm may mimic diaphragmatic elevation or evagination. The diagnosis should be considered in symptomatic adults who
present with solitary, large, lobular, heterogeneous intrathoracic masses in the absence of local invasion, lymphadenopathy or metastatic disease. CT and MRI are the main radiological tools in the diagnosis of these tumours. Radiological tools cannot differentiate between malignant and benign SFTPs as there are no imaging features that definitively distinguish benign from malignant subtypes of SFTPs, but heterogeneity on cross-sectional images, mass effect and pleural effusion may be slightly more common in malignant lesions.

Tissue biopsy is essential to reach a diagnosis where it could be obtained by either fine needle or Tru-cut needle, although most of the authors advocate their use as it will not alter the plan of the management and frequently could not reach a solid diagnosis. Although the less common malignant variety of SFTPs has the higher recurrence rate and higher tumour-related mortality, aggressive surgery and careful postoperative surveillance may still permit long-term survival in majority of patients. Generally, after complete surgical resection in all patients, CT scan should be used to monitor for recurrence every 6 months for the first 2 years and then yearly. All SFTPs need long-term follow-up, which may extend to 15–20 years due to the possibility of late recurrence.

Conflict of interest: none declared.

REFERENCES


