ELSEVIER

European Journal of Cardio-thoracic Surgery 14 (1998) 453–459

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

Localized fibrous tumours of the pleura: 15 new cases and review of the literature

M. Suter[a,*], S. Gebhard[b], M. Boumghar[a], N. Peloponisios[a], C.Y. Genton[b]

[a]*Department of Surgery, University Hospital (Centre Hospitalier Universitaire Vaudois), Lausanne, Switzerland*
[b]*Institute of Pathology, University Hospital (Centre Hospitalier Universitaire Vaudois), Lausanne, Switzerland*

Received 15 December 1997; revised version received 6 July 1998; accepted 27 July 1998

Abstract

Objective: To present a series of localized fibrous tumours of the pleura (LFTP), to define the clinical and histopathological diagnostic criteria of this tumour, and to determine the optimal treatment and follow-up. **Methods**: Review of the charts of the patients with the diagnosis of LFTP (formerly called benign fibrous mesothelioma), as well as of all the histological sections, including immunohistochemical stains. Review of the literature with special emphasis on the clinical and histological criteria of malignancy. **Results**: During the last 30 years, we found 15 patients with a complete clinical chart and histological material, particularly paraffin blocks of the tumour. The mean age was 57 years (range 27–79). Eight patients were asymptomatic, and the remaining seven presented with non-specific symptoms. All but one had complete resection of the tumour, including partial lung resection in two and partial chest wall resection in three. The diagnosis was confirmed by histological review in 15 cases. Immunohistochemical stainings showed positivity for vimentin in all cases, for CD 34 in 80%, but were consistently negative for cytokeratins. Nine tumours were histologically classified as malignant. Among them, five recurred, two of which were responsible for death. One benign tumour recurred after 1 year, and was treated successfully by repeat resection and radiotherapy. Overall, 13 patients (86%) were alive with no evidence of disease between 10 months and 27 years after the first resection. **Conclusions**: LFTP is a rare tumour which has a benign clinical course in over 80% of the cases, and is asymptomatic in half the patients. The diagnosis is difficult to establish before operation. Treatment consists of complete resection including adjacent structures if necessary. The clinical behaviour of LFTP cannot be predicted on the basis of histological aspects only. If histologically malignant tumours are more prone to recurrence and poor outcome, broad-based and locally invasive tumours bear a higher risk of recurrence. Long term follow-up is therefore mandatory in all cases in order to perform early re-resection when recurrence occurs.

Keywords: Localized fibrous tumour of the pleura; Pleural tumour; Benign mesothelioma

1. Introduction

Primary tumours of the pleura are of two types: diffuse and solitary. The diffuse type, malignant mesothelioma, is well known for its dismal prognosis and its close relationship with exposure to asbestos. There is more confusion about the solitary type. It has a variety of names, the most common being localized fibrous tumour of the pleura (LFTP) or benign fibrous mesothelioma. LFTP is rare and often asymptomatic, which explains why the diagnosis is often delayed, and usually not made before thoracotomy. There is still controversy about the origin of this tumour and about its malignant potential. The pathologist has to make the distinction between benign and malignant LFTP, but even if the tumour is histologically correctly classified, the clinical outcome cannot definitely be predicted. A large clinico-pathological study was reported by England in 1989, who emphasised histologic features of these tumours [1]. In that series of 223 patients, England and his co-workers analyzed the histological aspects of LFTP and the clinical outcome. They found three histopathological criteria associated with malignancy: marked cellularity with crowding and overlapping of nuclei, increased mitotic activity (>4 mitotic figures/10 high power fields), and nuclear pleomorphism.

* Corresponding author. Tel.: +41 21 3142351; fax: +44 21 3142360

1010-7940/98/$19.00
PII S1010-7940(98)00213-9

In order to clarify the understanding of LFTP, we reviewed our series and present 15 new cases together with a review of the literature.

2. Material and methods

The files of the last 30 years of the Institute of Pathology and the University Hospital (Centre Hospitalier Universitaire Vaudois) in Lausanne were computed to find all the patients with the diagnosis of LFTP or benign fibrous mesothelioma. The patients were included if the clinical chart as well as the pathological specimen were available. Special attention was given to the demographic data such as age and sex, and to the presenting symptoms, the radiological aspects, and the results of the pre-operative investigations. The operative reports were reviewed, and it was noted whether the mass was unique or not, pedicled or not, well delineated or not. The size of the tumour and its origin (visceral vs. parietal pleura) and the completeness of resection were also assessed. Duration of follow-up and any intercurrent event related or not to the tumour were recorded.

Histology of all the resected specimens was reviewed. Hematoxylin and eosin stained histological sections from formaldehyde-fixed, paraffin-embedded tissues were available for all the patients. Immunohistochemical stains against cytokeratins (low and high molecular weights), vimentin, muscle cell markers (desmin, muscle actins HHF-35 and alpha smooth muscle actin) and CD34 were also performed. For those lesions confirmed to be LFTP, criteria of malignancy as defined by England [1] were evaluated. These included marked cellularity with crowding and overlapping of nuclei, increased mitotic activity (>4 mitotic figures/10 high power fields), and nuclear pleomorphism. Tumours were considered to be malignant if one or more of these parameters were present, even focally.

3. Results

A total of 18 patients with the diagnosis of benign mesothelioma of the pleura or fibrous tumour of the pleura were found during the last 30 years. Three were excluded from further analysis because the paraffin blocks and/or histologic sections of the tumour were missing. Therefore, 15 patients, six men and nine women with a mean age of 57 years (range 27–79) were reviewed. The clinical features and the work-up are summarized in Table 1. In five cases, the tumour was diagnosed between 1 and 7 years before resection was considered. No patient gave a history of exposure to asbestos.

The chest X-ray showed a well delineated mass in 14 cases (Fig. 1). One patient had two masses. Eight patients had computerized tomography. It showed a homogeneous and well defined mass in five, and a large, polycyclic and heterogeneous mass in three. Bronchoscopy was normal in six cases, and showed extrinsic compression of the bronchial tree in four. Transparietal biopsy was performed five times. It was concluded to be a mesenchymal tumour of dubious nature in one, a benign fusocellular tumour in one, LFTP in one, and a tumour of presumed neural origin in one. The material was inadequate in the last case.

All patients underwent thoracotomy (Table 2). In one case, a diagnostic thoracoscopy was performed first. Seven had a mass which moved freely, and was attached by a highly vascular pedicle to the pleura. Complete removal of the lesion with at least a 10 mm margin in all directions was performed in all cases. Three patients had concomitant resection of one, two or four ribs, respectively, because of dense adhesions between the mass and the chest wall. One patient required middle lobectomy, and one upper right lobectomy. No patient underwent extended pleurectomy. The post-operative course was uneventful in all but two patients. One had a persisting apical pneumothorax for several days that resolved spontaneously. Another had a

Table 1
Clinical and radiological features of the patients

	Age (years)	Clinical features	Radiological features	CT	FNA	Bronchoscopy
AMV	27	No symptom	2 WC masses	No	No	No
SD	62	C, P	WC hilar mass	No	No	Yes
RC	63	C, H	Peripheral WC mass	Yes	Yes	No
SP	74	D, HG	Large WC mass	Yes	No	Yes
CN	61	No symptom	WC mass	No	No	Yes
DV	35	No symptom	WC mass	No	No	Yes
EH	36	No symptom	WC posterior mass	Yes	Yes	No
WB	44	No symptom	WC parahilar mass	Yes/No	No	Yes
CW	60	D, C, P, DC	WC basal mass	Yes	No	No
LP	65	No symptom	Large WC mass	No	Yes	Yes
OC	58	C, P	WC apical mass	No	No	Yes
GT	63	C, P	WC mass	No	No	Yes
EP	69	No symptom	Large mass	Yes	Yes	No
RP	63	No symptom	WC mass	Yes	Yes	Yes
GD	69	D	Very large mass	Yes	No	Yes

D, dyspnea; C, cough; H, hemoptysia; P, pain; DC, digital clubbing; HG, hyperglycemia; WC, well circumscribed.

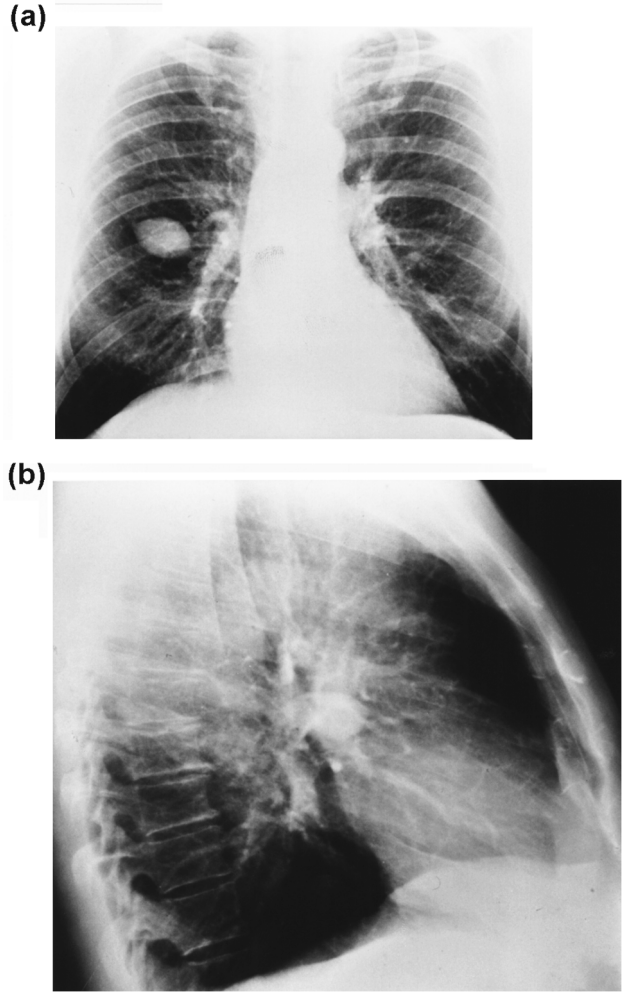

Fig. 1. BW, male, 44 years. Chest X-ray (pa and lateral views): well localized and well delineated oval mass.

severe post-operative haemorrhage, and required two re-thoracotomies within 12 h of resection. There was no peri-operative death.

Two patients died from respiratory failure due to massive local recurrence 5 and 10 months after resection. Another patient had recurrence after 4 years and was reoperated. He was lost from follow-up 2 years later with no evidence of disease. For the remaining patients, duration of follow-up is between 10 months and 27 years. Six patients have been lost after 1–15 years (mean 5.6) but were alive with no recurrence at that time. The others, including one woman who had recurrence after 6 years and complete re-resection, and another patient with recurrences and re-resection 18 and 25 years after primary resection, are doing well between 10 months and 27 years (mean 9 years) after the first operation.

A benign LFTP (formerly called benign fibrous mesothelioma) was diagnosed at the initial histologic examination in 14 cases. In one case, the diagnosis was that of a malignant fibrous tumour of the pleura. Review of the histologic sections and immunohistochemical studies showed microscopic features consistent with the diagnosis of LFTP in all cases (Table 2) [1,2]. The cellularity varied greatly from tumour to tumour, but also from field to field within a single tumour. Nine tumours were classified as malignant in view of England's criteria (initially only one), and the remaining six were confirmed to be benign (Figs. 2 and 3). No correlation was found between microscopic malignancy and the size of the tumour. Foci of necrosis (three cases) were only seen in malignant tumours. Immunohistochemical studies revealed vimentin expression in all these tumours and CD34 in 11 (80%). lmmunoreactivity for cytokeratins was consistently negative. Seven tumours (47%), six of which were histologically malignant, expressed at least one muscle cell marker. Overall, eight tumours were wrongly interpreted as benign at initial histology, but England's criteria were not used at that time.

4. Discussion

The first description of a primary tumour of the pleura is attributed to Lieutaud in 1767 [3]. In 1870, Wagner was the first to report the detailed histologic description of a tumour he thought was derived from the endothelium of the pleural lymphatics. Klemperer and Rabin in 1931 [4] divided primary tumours of the pleura into two categories: diffuse and localized. The diffuse form was assumed to derive from the mesothelial cells, whereas the localized tumours were derived from the submesothelial layer. The diffuse form, malignant mesothelioma, represents 75–90% of the cases [5,6]. It is clearly related to the exposure to asbestos. The localized form, LFTP, represents about 17% of all benign intrathoracic tumours [7].

LFTP arises at varying ages. As our series shows, it is more frequent during the fifth and sixth decades. No case has been reported during childhood, and there is no sex predominance. The cause is unknown, and no relationship with the exposure to asbestos has been found. The lesion is asymptomatic in over 50% of the cases (53% in this series) [3,5,6,8–10]. Most of these tumours are found incidentally

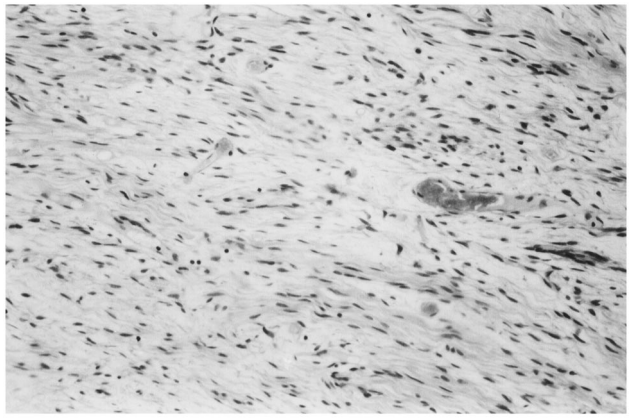

Fig. 2. Localized benign fibrous tumour of the pleura: low cellularity with loosely arranged spindle cells scattered haphazardly among strands of collagen fibers (HE, ×165).

Table 2
Therapy, tumour features and outcome

	Side	Origin	Form	Surgery	Histology	England			Immuno			FU	Outcome
						H	A	M	C	V	D		
AMV	R	P	S	Re	B LFTP	–	–	–	–	+	–	288	Alive
SD	L	V	S	Re	M LFTP	+	–	–	–	+	+	180	Alive
RC	L	V	S	Re	M LFTP	+	–	–	–	+	+	48	Alive
SP	R	M	P	Re	M LFTP	+	+	–	–	+	+	5	Died
CN	L	V	P	Re	B LFTP	–	–	–	–	+	+	36	Alive
DV	L	V	P	Re	B LFTP	–	–	–	–	+	+	12	Alive
EH	L	V	P	Re	B LFTP	–	–	–	–	+	+	18	Alive
WB	R	V	P	Re	B LFTP	–	–	–	–	+	+	36	Alive
CW	R	V	S	L+W	M LFTP	+	–	–	–	+	+	324	Alive
LP	R	V	P	Re	B LFTP	–	–	–	–	+	+	144	Alive
OC	R	V	S	L+W	M LFTP	–	+	–	–	+	–	10	Died
GT	L	P	S	Re+PP	M LFTP	+	+	–	–	+	–	24	Alive
EP	R	P	S	Re	M LFTP	+	–	+	–	+	+	30	Alive
RP	L	V	P	Re	M LFTP	+	+	+	–	+	+	8	Alive
GD	L	P	S	Re+W	M LFTP	+	+	–	–	+	+	36	Alive

R, right; L, left; P, parietal pleura; M, mediastinal pleura; V, visceral pleura;
P, pedicled tumour; S, tumour with large base; Re, resection with 10 mm or more safety margin; Re + W, resection together with part of the chest wall; L, lobectomy; L + W, lobectomy and chest wall resection; Re + PP, resection and total parietal pleurectomy,
B LFTP, benign LFTP; M LFTP, malignant LFTP; H, hypercellularity; A, atypia; M, >4 mitoses/high power field; C, cytokeratine; V, vimentine; D, CD-34.

on routine chest radiographs. Symptoms tend to be more common in larger lesions. As for our patients, symptoms include mainly non-specific thoracic symptoms such as chest pain, dyspnea, cough, and more rarely hemoptysis. The feeling of a moving mass within the chest has been reported. Extrathoracic symptoms may include weakness, fever, weight loss, nocturnal sweating, chills. Digital clubbing (one case in this series) or hypertrophic osteoarthropathy has been reported in up to 20% of the patients [8,9,11,12]. Hypertrophic osteoarthropathy is more commonly associated with LFTP than with bronchial carcinoma, although it was present in none of our patients. This is attributed to the fact that tumour cells may produce hyaluronic acid, which has an osteolytic effect [12]. Recurrent episodes of hypoglycemia (one case in this series) are observed in 2–4% of the cases [3,8,13]. Hypoglycemia could be related to the production by the tumour of insulin-like growth factor II (IGF-II), which causes an increased glucose utilization and an impaired growth hormone counter-regulatory response to hypoglycemia [14]. In our patients, all the symptoms regressed completely after surgical resection, as is normally reported in the literature.

As in most patients in this series, LFTP appears as a well delineated round, ovoid, or polycyclic mass on the standard chest X-ray (Fig. 1). If the lesion is pedunculated, the position of the mass can change, which should be suggestive of the diagnosis. Serous pleural effusion affects fewer than 10% of the patients, and was present in none of our patients [5,8,15–18]. On the other hand, an exsudative effusion is present in 80% of the patients with diffuse malignant mesothelioma [5]. Computerized tomography is an important step in the pre-operative work-up [5,10,18–20]. CT shows a tissular mass which is homogeneous in most cases (seven out of eight who had CT in our series), especially when the size of the lesion is small. Larger tumours may show a heterogeneous aspect. The contour of the mass is well delineated. The tumour usually does not invade adjacent structures. A few cases with calcifications have been reported. The angles between the tumour and the chest wall can be acute and suggest a parenchymal mass. When the tumour is close to the mediastinum or the diaphragm, its relationship with the surrounding structures is sometimes difficult to assess. Magnetic resonance imaging can show the fibrous character of the mass [20]. Echography can help to precisely locate the tumour in relation to the diaphragm. Unfortunately, no radiologic modality is diagnostic for LFTP, or can differentiate between benign or malignant lesions. We do not recommend transthoracic needle biopsy because of its poor diagnostic yield [5,10,20,21]. Five of our patients had such a biopsy, but LFTP was diagnosed in only one. Bronchoscopy is necessary to rule out endobronchial disease [10,17]. Extrinsic bronchial compression can sometimes be seen, as in four of our cases.

Macroscopically, LFTP is a unique mass in most cases. The size is variable, and tumours as great as 36 cm in diameter or weighing up to 4.5 kg have been reported [22,23]. Multiple tumours, such as in one of our patients, are extremely rare [1,8] (Fig. 4). Most tumours are round or ovoid. In large tumours, the shape of the mass is adapted to the anatomy of the hemithorax. The mass is usually well circumscribed and sharply delineated, as in 12 (80%) of our patients. It is often encapsulated within a thin membrane, which consists of collagen covered by normal mesothelial cells. The tumour is attached to the pleura by a highly vascular pedicle in 38–42% of the cases (46% in our cases) [1,9]. The base of the tumour is on the visceral pleura in

about three quarters of the patients (66% in this series) [6,7]. Other tumours have a broad base, and some lesions (7%) grow inward the lung parenchyma [24].

Histologically, the so-called patternless pattern predominates: fibroblast-like spindle cells and connective tissue in varying proportions are arranged at random. In about 25% of the cases, this pattern coexists with a prominent network of capillaries and large vessels, and the general aspect is suggestive of a hemangiopericytoma. The size and shape of the cells and nuclei are usually uniform, and few mitoses can be observed (<4 mitoses/10 high power fields) [1,3]. Small areas of lung tissue, bronchus or even mesothelium can be found within the tumour. England, in an extensive anatomopathological analysis of 223 cases, found 36% of the patients to have a malignant tumour [1]. In another series, 15% of the tumours were microscopically malignant [9]. Interestingly, 60% of our LFTP were histologically malignant according to England's criteria. We have no explanation for this unusually high rate.

Controversy still exists about the origin of LFTP, which explains the many terms that have been used. Contrarily to Klemperer and Rabin, Stout and Murray in 1942 concluded that the mesothelial cell was the origin of LFTP [25]. More recently, other authors again considered fibroblasts from the submesothelial layer to be the origin of the tumour [1,26–28]. They based their conclusions on the ultrastructural aspects and the immunohistochemical characteristics of the tumour cells. As in our series, immunohistochemical studies are positive for vimentin, a marker of mesenchymal differentiation, often positive for CD34, and sometimes positive for muscle cell markers, but negative for cytokeratins and KL1 [1,8,27,29–33]. The positivity for vimentine and negativity for KL1 support the fibroblastic origin of these tumours [32,33]. The ultrastructural aspects of the

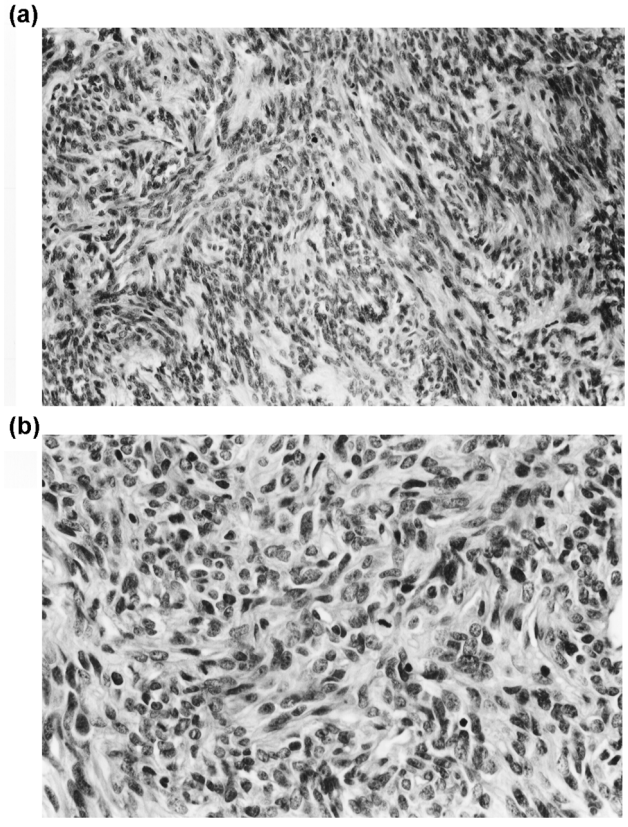

Fig. 3. Localized malignant fibrous tumour of the pleura: (a) high cellularity with interlacing fascicles of plump cells and scanty collagen fibers (HE, ×165); (b) high power view showing nuclear pleomorphism and mitotic activity (HE, ×330).

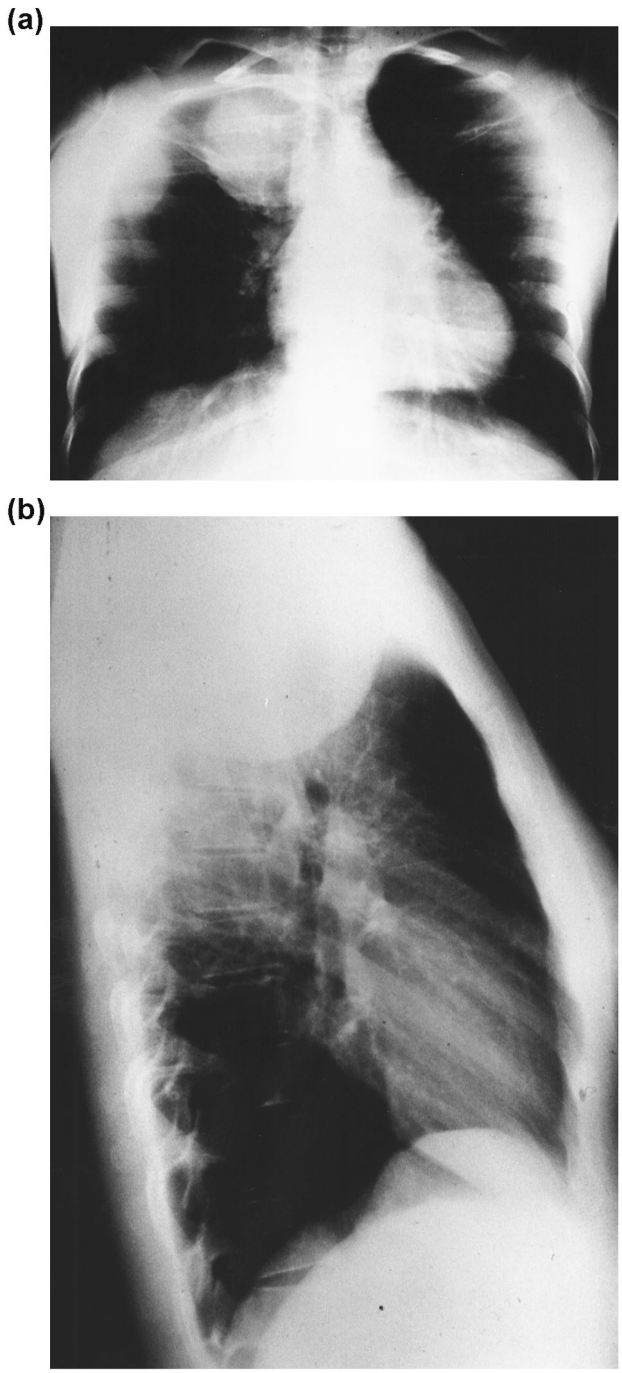

Fig. 4. AMV, 27 years, female: chest X-ray (front and lateral views) showing two well circumscribed masses in the right upper thorax, both of which proved to be benign LFTPs.

cells (absence of microvilli, basal lamina, desmosomes, tonofilaments, but developed rough endoplasmic reticulum) also support a non-mesothelial, but fibroblastic origin [28].

In our series, the differences between the initial histologic diagnosis and the diagnosis after histological review using England's criteria reflects the difficulties encountered by the pathologist who faces these tumours. Even if LFTP was correctly recognised in 100% of our cases, 53% of those initially interpreted as benign, were in fact malignant.

The differential diagnosis of an intrathoracic mass is wide, and as a rule, such lesions should be considered as malignant until proved otherwise. The diagnosis of LFTP is very difficult pre-operatively, and even if it can be made, the difference between benign and malignant lesions is difficult as the histological aspects can vary between different areas in the same tumour. Although our experience is limited to one case, we believe that thoracoscopy could be used at least for diagnosis, or even for resection of small pedunculated tumours in some cases. In the remaining patients, thoracotomy is indicated for diagnosis and treatment. The latter includes complete surgical resection of the tumour, with a margin of normal tissue that depends on the general aspects of the mass, but should include a safety margin of at least 10 mm. Pleurectomy is not necessary. For pedunculated tumours, resection at the base of the pedicle with a small patch of lung parenchyma is sufficient. Care must be taken, however, because the pedicle is usually highly vascular. Formal lung resection, i.e. lobectomy or segmentectomy along with the tumour is seldom required, even for tumours broadly based on the visceral pleura or inverted into the parenchyma. A lobectomy had to be performed in two of our cases. For tumours originating from the parietal pleura, extrapleural resection, and sometimes partial excision of the chest wall with reconstruction is necessary to achieve a sufficient safety margin, as in three of our patients. In most cases, however, separation of the mass from adjacent structures is easy to achieve. As shown by our series, the post-operative course is usually uncomplicated, and the pre-operative symptoms disappear after resection. In the asymptomatic patients, it may be argued that resection is not necessary because some of these tumours are benign. Thoracotomy, however, is often the only way to establish the diagnosis, and even benign tumours may recur, as shown by one of our cases.

The vast majority of LFTP have a benign clinical course. Long term survival with no recurrence is the rule in 80–88% of the cases [1,8,10]. The macroscopic as well as the histologic aspect of the tumour have prognostic implications. In the series of 223 cases reported by England, two (1.4%) of the 141 patients with a benign tumour had recurrence, but there was no mortality related to the tumour in this group. On the contrary, 55% of the histologically malignant tumours had an aggressive behaviour. In our series, five patients with a malignant LFTP had recurrence, which was responsible for death in two. Of interest is our patient who had subtotal resection followed by radiotherapy for recurrence 15 months after total excision of two separate histologically benign LFTPs. This patient is alive with no evidence of disease 24 years after the first resection. We could not find any data in the literature regarding the role of radiotherapy in LFTP. Histological malignancy alone, however, does not necessarily imply a poor outcome. The macroscopic characteristics of the tumour are also important. Local invasiveness, a broad based tumour, absence of a pedicle, necrosis and haemorrhage within the tumour, and poor delimitation all worsen the prognosis, as does incomplete surgical resection, which, taken alone, is the most important prognostic factor. Recurrence is usually local. Although not always possible, re-resection should be attempted whenever possible. Three of our patients with recurrence had a second resection, with a good outcome. Diffuse recurrence within the chest and distant metastases have been reported [1].

5. Conclusion

Over 80% of LFTP are clinically benign, and more than 50% are asymptomatic. The pre-operative diagnosis is difficult to establish. Transparietal needle biopsy has a low diagnostic yield, and thoracotomy is very often necessary for diagnosis. Treatment consists in complete resection. Thoracoscopy may be sufficient for small lesions. Strict histological and immunohistochemical criteria have been established to diagnose LFTP. Histologically malignant lesions, broad-based or locally invasive tumours, as well as poorly delineated masses, bear a high risk of recurrence, even after complete surgical resection. On the other hand, local recurrence may occur even after removal of macroscopically and microscopically clearly benign tumours. Long term follow-up therefore is mandatory in all cases. The role of radiotherapy remains to be defined.

Acknowledgements

We are especially thankful to Mr. P. Hahnloser, MD, Professor of surgery, JF Schmid, MD and G. Lanitis, MD, for their help in providing some of the clinical material, and to Mrs Carol Suter for her help in the preparation of this manuscript.

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