Inflammatory myofibroblastic tumor of the lung

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Received 30 August 2003; received in revised form 21 October 2003; accepted 22 October 2003

Abstract

Objective: Inflammatory myofibroblastic tumor (IMT) is a rare disease that usually occurs in the lung. Recently, several reports have suggested that IMT is a true neoplasm rather than a reactive lesion. In this retrospective study, we reviewed clinicopathological characteristics and prognoses for all patients with surgically resected IMT of the lung at our institute. Methods: From January 1985 to December 2002, nine patients had surgical intervention for IMT of the lung at the National Cancer Center Hospital, Tokyo. The resected lesions were studied histologically, immunohistochemically, and ultrastructurally. Follow-up was complete in all patients and varied from 3 months to 16 years 2 months (median, 6 years 2 months). Results: These nine patients included five men and four women. They ranged in age from 25 to 66 years. Seven patients were asymptomatic. The two symptomatic patients had problems including cough, hemoptysis, and dyspnea. For all these patients, the diagnostic procedure was surgical excision. The resected tumor size ranged from 1.0 to 4.0 cm in diameter. Histologically, a variety of inflammatory and spindle cells were observed. The spindle cells corresponded ultrastructurally to myofibroblasts or fibroblasts. With the exception of one patient who had spontaneous resolution of a recurrent tumor, there was no recurrence in these patients, and all of them are in good health. Conclusions: Histopathologically, IMT is characterized by myofibroblasts that are mixed with chronic inflammatory cells, including plasma cells, lymphocytes, and histiocytes. Surgical resection, when possible, can be chosen as the treatment. Complete resection leads to excellent survival. © 2003 Elsevier B.V. All rights reserved.

Keywords: Lung pathology; Surgery; Survival; Inflammatory pseudotumor; Pulmonary neoplasm

1. Introduction

Inflammatory myofibroblastic tumor (IMT) is a rare disease that usually occurs in the lung. IMT has been described by various terms because of its variable cellular components, which includes plasma cell granuloma, inflammatory pseudotumor, xanthogranuloma, and fibrous histiocytoma [1–18]. The notion of IMT being a reactive lesion or a neoplasm was controversial [18]. However, this entity has been characterized by not variable chronic inflammatory cells but myofibroblasts, and the recent cytogenetic studies have suggested that IMT is a true neoplasm [14–16]. There is little information on the clinicopathological features because IMT is rare and its terminology was confusing.

To examine the clinicopathological characteristics and prognosis, we reviewed a set of patients with surgically resected IMT of the lung.

2. Material and methods

2.1. Patients

Between January 1985 and December 2002, nine patients had surgical intervention for IMT of the lung at the National Cancer Center Hospital, Tokyo. These patients comprised 0.18% of 4893 patients who had thoracic surgical procedures at our institute during the same period. The clinical characteristics of these patients are shown in Table 1. Preoperative work-up included laboratory examinations, fiberoptic bronchoscopy, chest radiograph, and computed tomographic (CT) scans. Follow-up was complete in all
patients and ranged from 3 months to 16 years 2 months (median, 6 years 2 months).

2.2. Pathological and ultrastructural evaluations

In each case, the tissue was fixed in 10% buffered formalin, processed routinely, and embedded in paraffin. Sections 4 μm thick, were cut and then stained with hematoxylin and eosin. Each section was also evaluated immunohistochemically. Immunohistochemical staining was accomplished by the labeled streptavidin-biotin method using an LSAB kit (Dako Corporation, Carpinteria, CA). Primary antibodies against various antigens were used in this study: vimentin (V10 clone; Dako; 1:200), cytokeratin (CAM5.2 clone; Becton Dickinson, San Jose, CA; 1:100), cytokeratin (AE1/AE3 clone; Dako; 1:125), desmin (Dako; 1:500), smooth muscle actin (1A4 clone; Dako; 1:100), CD34 (My10 clone; Becton Dickinson; 1:100), S100 protein (Dako; 1:2000), and epithelial membrane antigen (Dako; 1:100).

Small fresh fragments of tumor tissue in four cases (cases 3, 4, 7 and 9) were fixed in 2.5% glutaraldehyde, post-fixed in 1% osmium tetroxide, and embedded in epoxy resin. After contrasting with uranyl acetate and lead citrate, ultrathin sections were examined with a transmission electron microscope.

3. Results

3.1. Clinical findings

These nine patients included five men and four women. They ranged in age from 25 to 66 years, with a mean age of 44.6 years. Seven patients were asymptomatic and were found to have pulmonary nodules on routine chest radiography (Fig. 1). One of these patients (case 6) was clinically suspected of pulmonary metastasis. This was pointed out during postoperative follow-up of a right nephrectomy for renal cell carcinoma that the patient had undergone 5 years before. The two symptomatic patients had problems including cough, hemoptysis, and dyspnea. The preoperative laboratory results were within normal limits for eight patients, but one patient (case 5) had a C-reactive protein (CRP) rate of 9.4 mg/dl and a white blood cell (WBC) count of 10,000/μl. These findings returned to normal within 10 days after operation. All patients underwent a fiberoptic bronchoscopy preoperatively. Six patients did not have any bronchial abnormality. One (case 1) had a stenosis of the right basal bronchus. The other two had an endobronchial tumor. One patient (case 7) with an endobronchial tumor had complete atelectasis of the left lung (Fig. 2). Chest CT showed a solitary, well-circumscribed nodule or mass in all patients. A definitive diagnosis of IMT was not made in any of the patients, although all patients had undergone transbronchial biopsy or transthoracic needle biopsy for diagnosis preoperatively. The spindle cells and inflammatory cells in small biopsied specimen, even if they were taken by biopsy, were useless for

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**Table 1**

Clinical characteristics of patients with inflammatory myofibroblastic tumor

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age</th>
<th>Symptom</th>
<th>Location</th>
<th>Tumor size (cm)</th>
<th>Mode of operation</th>
<th>Prognosis after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/59</td>
<td>None</td>
<td>HLN</td>
<td>2.5</td>
<td>Extirpation</td>
<td>16 years 2 months, alive</td>
</tr>
<tr>
<td>2</td>
<td>F/41</td>
<td>None</td>
<td>LLL</td>
<td>1.0</td>
<td>Lobectomy</td>
<td>13 years 9 months, alive</td>
</tr>
<tr>
<td>3</td>
<td>F/58</td>
<td>Cough/Hemoptysis</td>
<td>RIB</td>
<td>2.0</td>
<td>Bilobectomy</td>
<td>1 year 4 months, alive</td>
</tr>
<tr>
<td>4</td>
<td>M/25</td>
<td>None</td>
<td>LUL</td>
<td>2.2</td>
<td>Segmentectomy</td>
<td>2 years 3 months, alive</td>
</tr>
<tr>
<td>5</td>
<td>M/49</td>
<td>None</td>
<td>LUL</td>
<td>3.6</td>
<td>Segmentectomy</td>
<td>9 years 6 months, alive</td>
</tr>
<tr>
<td>6</td>
<td>M/66</td>
<td>None</td>
<td>LUL</td>
<td>3.5</td>
<td>Segmentectomy</td>
<td>6 years 6 months, alive</td>
</tr>
<tr>
<td>7</td>
<td>M/47</td>
<td>Cough/Dyspnea</td>
<td>LMB</td>
<td>4.0</td>
<td>Segmental bronchial resection</td>
<td>6 months, alive</td>
</tr>
<tr>
<td>8</td>
<td>M/26</td>
<td>None</td>
<td>LLL</td>
<td>3.0</td>
<td>Segmentectomy</td>
<td>5 years 2 months, alive</td>
</tr>
<tr>
<td>9</td>
<td>F/30</td>
<td>None</td>
<td>RUL</td>
<td>3.2</td>
<td>Lobectomy</td>
<td>3 months, alive</td>
</tr>
</tbody>
</table>

HLN, hilar lymph node; LLL, left lower lobe; RIB, right intermediate bronchus; LUL, left upper lobe; LMB, left main bronchus; RUL, right upper lobe.

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Fig. 1. Chest radiograph shows a well-defined mass in the left lung (case 5).
the definitive diagnosis because they followed a variety of lesions such as inflammation or malignancy. One patient (case 6) had an erroneous diagnosis of adenocarcinoma by aspiration cytology, because the cytologic findings showed atypical epithelial-like cells with lymphocytes and histiocytes. For all these patients, the diagnostic procedure was surgical excision. Although an intraoperative frozen section was done for the tumor in all cases, the confirmed diagnosis could not be made. However, all the tumors were regarded as low-grade malignancy because of low nuclear atypia and infrequent mitosis. The extent of surgical excision was as follows: segmentectomy in four patients, segmental bronchial resection in one, lobectomy in two, bilobectomy with bronchoplasty in one, and extirpation in one. Complete resection of the tumor was accomplished in eight patients (89%). One patient (case 7) had a pathological residual tumor in the submucosal tissue of the left main bronchus. None of the operations resulted in death. On the follow-up CT one patient (case 6) had a suspected recurrent tumor developing adjacent to the resected line four years after the initial resection, although this tumor was not evaluated histologically. Interestingly, spontaneous resolution of this tumor has been observed (Fig. 3). In the other eight patients, no recurrence of IMT occurred. All of the patients have remained healthy.

3.2. Pathological and ultrastructural findings

The resected tumor size ranged from 1.0 to 4.0 cm in the greatest diameter, with a mean of 2.8 cm. For gross appearance, most of the tumors were well-circumscribed masses without fibrous capsules and yellow to whitish in color on cut section.

Microscopically, the lesions consisted of a variety of inflammatory and mesenchymal cells, including plasma cells, histiocytes, lymphocytes, and spindle cells. All of the tumors showed interlacing fascicles, or a storiform pattern of spindle cells and an admixture of diverse inflammatory cells (Fig. 4A). The spindle cells had low cellular atypia and no mitotic activity (Fig. 4B). Blood vessel invasion was identified in one instance (case 4).

Immunohistochemically, most of spindle cells in all nine cases showed diffuse and strong reactivity for vimentin. All tumors exhibited reactivity for smooth muscle actin (Fig. 5). The staining was diffuse in eight of nine cases (89%) and focal in one (11%). One tumor exhibited focal staining for desmin. All tumors were negative for cytokeratins, CD34, S100 protein, and epithelial membrane antigen.

Ultrastructurally, two tumors (cases 3 and 9) out of four contained a varying proportion of myofibroblastic cells, as well as fibroblastic cells with a prominent Golgi apparatus.
and well developed rough endoplasmic reticulum (RER). The myofibroblastic tumor cells were recognized by the presence of an often well developed branching RER and primarily peripheral bundles of actin microfilaments with interspersed fusiform densities (Fig. 6). Subplasmalemmal attachment plaques, focal basal lamina-like material, and micropinocytotic vesicles were present to variable degrees in these cells. The other tumors consisted of fibroblastic and histiocytic cells with lysosomes and lipid droplets.

4. Discussion

IMT of the lung is rare, and its incidence is reported to be 0.04–1% of all tumors of the lung [1,3]. Although IMT can grow at a wide variety of other sites [19,20], it usually arises within the lung [1]. Concerning the age of patients at diagnosis, the mean age of 44.6 years in this study was relatively older than those reported previously [4,5,7,10,17]. According to previous reports, most of the patients were under 40 years old, with a mean age of 27–50 years. There was no predominance of either sex. The precise etiology of IMT of the lung is still unknown. Although a history of prior pulmonary infection in some patients with IMT has been pointed out [4], this type of patient was not found in the present study. Patients with IMT usually are asymptomatic, with a solitary nodule or mass detected by routine chest roentgenogram [5]. Endobronchial growth of IMT has only rarely been observed [2,6,7], with a prevalence of between 0 and 12%. In this study we had a relatively high prevalence (two of nine, or 22%) of patients with endobronchial growth of IMT. On the other hand, it has been known that IMT carries a risk of extension to neighboring organs [1,4,9,11], in particular to the mediastinum, although we did not observe this. Preoperative laboratory findings indicated that only one patient (11%) with a solitary pulmonary mass had an elevated CRP rate and WBC count, and the IMT appeared to have no connection with these laboratory findings [3,4]. The preoperative diagnosis of IMT is seldom confirmed, and small biopsied specimens are generally considered insufficient for diagnosis because of the predominance of inflammatory cells.

Pathologically, IMT is composed of a variable inflammatory and mesenchymal cellular mixture including plasma cells, histiocytes, lymphocytes, and spindle cells. Therefore, depending on the predominant cellular components, many synonyms for this disease have been described. In 1990, Pettinato and colleagues referred to this entity as IMT because the bulk of the lesion invariably consisted of not specific inflammatory cells, but proliferative myofibroblasts and fibroblasts [17]. Most of the spindle cells were myofibroblasts, which showed immunohistochemical staining for vimentin and smooth muscle actin, and consistent ultrastructural features. The spindle cells commonly have low cellular atypia and no mitotic activity. Inflammatory cells are mature and have no cellular atypia, and do not show monoclonal proliferation [3,17,18]. IMT occasionally invades bronchi or blood vessels [8,18]. We treated one patient (11%) with IMT who showed blood vessel invasion (case 4). However, it is doubtful that these are truly the tumor infiltrations, because the existing histologic architecture of the lung can also be destroyed by infiltration of only inflammatory cells. Furthermore, distant metastases from IMT are hardly ever reported. The differential diagnosis of IMT is multifarious because of its variable cellular admixture. It includes malignant lymphoma, lymphoid hyperplasia, pseudolymphoma, plasmacytoma, malignant fibrous histiocytoma, sarcomatoid carcinoma of the lung, sclerosing hemangioma, sarcoma, and/or nodular chronic pneumonitis. These lesions can be differentiated by careful attention to cellular atypia, necrosis, mitotic activity, immunoreactivity, or clonality [1,9,18]. IMT of the lung also has the histologic resemblance to the fibromas of the parietal or visceral pleuras. The fibromas shows short fascicles or haphazard fashion of spindle cells with few inflammatory cells, whereas IMT shows interlacing
fascicles or a storiform pattern of spindle cells and an admixture of diverse inflammatory cells [21]. Although the notion of IMT being a reactive lesion or a neoplasm had been controversial, IMT has been recently thought of as a neoplasm rather than a reactive lesion because of clonal chromosomal abnormalities [15], chromosomal rearrangements involving the ALK receptor tyrosine-kinase locus region (chromosome band 2p23) [16], or DNA aneuploidy in IMT [14]. IMT usually grows locally and slowly. Therefore, taking into account these histopathologic and biological findings, IMT may be regarded as low-grade malignancy or benign tumor.

Surgical resection is recommended as the treatment of choice. Cerfolio and colleagues reported that the residual tumor became enlarged in 60% of patients who had incomplete resection [1]. They advocated the importance of initial complete resection of the tumor. Surgical removal usually fills the role of both diagnosis and treatment. The effectiveness of radiotherapy, chemotherapy, or steroids is uncertain [1,12]. The spontaneous regression of IMT has been reported only infrequently [9]. Likewise, we cared for one patient with spontaneous regression of the recurrent tumor, although this was not confirmed histologically. The causes of these remissions are unknown. The outcome after resection is usually excellent, and all of the patients in this study have also remained well over the longer term. However, long-term follow-up is necessary because of reported cases of recurrences many years after resection [2,22].

In conclusion, IMT of the lung is rare. Histopathologically, IMT is characterized by myofibroblasts that are mixed with chronic inflammatory components, consisting of plasma cells, lymphocytes, and histiocytes. Surgical resection, when possible, is recommended as the treatment of choice. The outcome after complete resection is excellent.

References