ABSTRACT

Background: In this study, we aimed to evaluate the clinicopathological features of pulmonary inflammatory myofibroblastic tumor cases operated in our clinic.

Methods: A total of 17 inflammatory myofibroblastic tumor patients (5 males, 12 females; median age: 46 years) who were operated in our clinic between February 2000 and July 2019 were included. Data including sex, age, symptoms, accompanying diseases, tumor localization, tumor diameter, endobronchial extension, maximum standard uptake value of the tumors, surgery type, recurrence, and survival data were analyzed.

Results: Two patients were diagnosed preoperatively and two patients were diagnosed during surgery using frozen-section method before resection. Three (17.7%) patients underwent pneumonectomy, five (29.4%) patients lobectomy, three (17.7%) patients segmentectomy, five (29.4%) patients wedge resection, and one (5.8%) patient bronchial sleeve resection. All patients had complete resection with negative margins. None of them had lymph node metastasis. Median follow-up was 122 (range, 8 to 245 months) months. None of the patients received adjuvant therapy, there was no tumor recurrence or tumor-related death.

Conclusion: It is difficult to make a preoperative diagnosis of inflammatory myofibroblastic tumor patients. Systematic lymph node dissection is not required in diagnosed patients. Complete resection is the most important prognostic factor, and it is critical to achieve this with the smallest resection possible.

Keywords: Case series, inflammatory myofibroblastic tumor, rare pulmonary tumors.
Inflammatory myofibroblastic tumor (IMT) is a rare neoplasm that can involve a wide variety of organs, such as the larynx, orbita, intra-abdominal organs, breast, soft tissue, and lungs. Lungs are the most common localization. To date, IMT has been called many different names, such as inflammatory pseudotumor, plasma cell granuloma, fibroxanthoma and fibrous histiocytoma. It is the most common lung tumor in children. In adults, it accounts for less than 1% of all lung tumors and is seen equally among men and women. While half of the patients are asymptomatic, symptoms such as cough, chest pain, fever and shortness of breath may be seen depending on the location and size. Its natural course and prognosis and, also, the most optimal treatment strategy has not been fully known, yet.

In the present study, we aimed to evaluate the clinicopathological features of pulmonary IMT cases operated in our clinic. To the best of our knowledge, this is the first case series of Turkish IMT patients in the literature.

**PATIENTS AND METHODS**

This single-center, retrospective study was conducted at Ankara University Faculty of Medicine, Department of Thoracic Surgery between February 2000 and July 2019. A total of 17 IMT patients (5 males, 12 females; median age: 46 years) who were operated in our clinic were included. Data including sex, age, symptoms, accompanying diseases, tumor localization, tumor diameter, endobronchial extension, maximum standard uptake value (SUVmax) of the tumors, surgery type, recurrence, and survival data were recorded. A written informed consent was obtained from each patient. The study protocol was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (date: 24.12.2020, no: İ11-689-20). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All pathology slides were reviewed to confirm the diagnosis. On microscopic examination, predominant cell component (plasma cell type, fibrohistiocytic type or mix), cellularity, border of lesion (ill-defined or infiltrative); presence of endobronchial component, necrosis, mitosis and pleomorphism were recorded. Using the immunohistochemically stained slides at the time of diagnosis, smooth muscle actin (SMA) (n=15), desmin (n=13), cytokeratin (CK) (n=13), CD34 (n=10), S100 (n=12) expression in spindle cells were evaluated. The Ki67 proliferation index was calculated (n=7). Anaplastic lymphoma kinase (ALK) expression was evaluated by immunohistochemistry in 15 patients with D5F3 (n=3) and ALK01 (n=12) clones. Only in one patient, ALK rearrangement was evaluated by fluorescence in situ hybridization (FISH) (Figure 1).

The follow-up time was defined as the time between curative surgery and final control. As there was no recurrence and only one patient died from an irrelevant cause, no survival statistics were performed.

**RESULTS**

The median follow-up was 122 (range, 8 to 245 months) months. During the study period, 1,952 patients were operated for lung tumors in our clinic, and 17 of them (0.87%) were diagnosed with IMT. There were only two patients in the pediatric age group (3 and 16 years old). The rate of patients under the age of 40 was 41%. One patient who underwent pneumonectomy due to right hilar IMT had a history of chemoradiotherapy after right mastectomy due to breast carcinoma 13 years previously. Nine (52.9%) patients had symptoms such as cough, back pain, and fever. Nine (52.9%) tumors were in the left, whereas eight tumors were in the right lung. There was a predominance of upper lobe localization (47% upper lobes, 29.4% lower lobes, 23.6% hilar and middle lobe). The mean tumor size was 35.4±18.5 mm (range, 10 to 76 mm). Seven (41.1%) patients had endobronchial tumor extension and one (5.8%) patient had a totally endobronchial tumor. Both of the pediatric cases had endobronchial tumor extension. Eight patients had positron emission tomography (PET)/computed tomography (CT), and the mean SUVmax of the masses was 9.8±5.4 (3.5-19.7). Eight patients had preoperative biopsy and only two patients had preoperative IMT diagnosis. One patient was diagnosed with bronchoscopic biopsy and one patient with an open lung biopsy in an external clinic. Ten patients had intraoperative frozen-section analysis from their masses and only two of them received an IMT diagnosis (four patients were reported as mesenchymal tumor and four patients as benign tumors). Three (17.7%) patients underwent pneumonectomy (one carinal sleeve pneumonectomy), five (29.4%) patients lobectomy, three (17.7%) patients segmentectomy, five (29.4%) patients wedge resection (one patient with laminectomy) and one (5.8%) patient bronchial sleeve resection. All patients had complete resection with negative margins. Eleven (64.7%) patients underwent lymphadenectomy due to uncertain intraoperative frozen-section analysis and none of them had lymph node metastases. There was no intraoperative mortality. None of the patients received adjuvant therapy and there was no tumor recurrences.
recurrence (Table 1). Only one patient (81-year-old) died seven years after the operation due to an unrelated cause.

In one patient who underwent pneumonectomy due to left hilar IMT, Takayasu arteritis was diagnosed postoperatively. A 16-year-old female patient (No. 7) had right thoracotomy with incomplete resection in another clinic. The tumor progressed under infliximab and radiotherapy. Finally, six years later from the initial diagnosis, she was referred to our clinic and right carinal sleeve pneumonectomy was performed. Currently, she is alive with no sign of the disease for 10 years.

In microscopic examination, all tumors were composed of spindle cells and inflammatory cells in variable distribution. Spindle cells showed fascicular pattern in some of the tumors. Necrosis, mitosis, and pleomorphism were seen in 12.5%, 11.8% and 11.8% of the tumors, respectively. Predominant cell component was plasma cell in 23.5%, fibrohistiocytic in 41.2%, and mixed in 35.3% of the tumors. Cellularity was low in 23.5% and intermediate or high in 76.5% of the tumors. Two (11.7%, No. 6 and 16) patients had infiltrative tumors. Spindle cells were positive with SMA (64.3%), desmin (23.1%) and negative with CK, CD34 and S100. Ki67 index ranged from 1 to 10% with a median value of 5%. The ALK expression was noted in 28.6% of the tumors. The FISH was performed only in one ALK-positive tumor and this tumor had ALK rearrangement based on the FISH analysis.

**DISCUSSION**

Inflammatory myofibroblastic tumor is a borderline tumor of the lung which have the potential
Table 1. Patient characteristics of operated inflammatory myofibroblastic tumors in our clinic between 2000 and 2019

| No | Age/Sex | Symptoms | Medical history | Localization | Diameter (mm) | Endobronchial extension | SUV_{max} | Frozen section analysis | Surgery | Follow-up (month) |
|----|---------|----------|----------------|--------------|--------------|-----------------------|-----------|------------------------|---------|--------------------|
| 1  | 34/F    | -        | -              | Left upper lobe | 40          | +                     | -         | -                      | Lobectomy | 245                |
| 2  | 46/M    | -        | -              | Left upper lobe | 10          | +                     | -         | -                      | Bronchial sleeve resection | 210                |
| 3  | 3/F     | Cough    | -              | Left lower lobe | 17          | +                     | -         | -                      | Lobectomy | 186                |
| 4  | 42/F    | Cough, fever | 1992 right mastectomy and right side chemoradiotherapy | Right hilar | 19          | +                     | -         | -                      | Pneumonectomy | 186                |
| 5  | 36/F    | Cough    | -              | Left lower lobe | 17          | -                     | 7.3       | Mesenchymal tumor       | Lobectomy | 155                |
| 6  | 49/F    | Cough, side pain | Takayasu’s arteritis | Left hilar, in the left main pulmonary artery | 30          | -                     | 10.3      | -                      | Intrapericardial pneumonectomy | 145                |
| 7  | 16/F    | Dyspnea  | Previous incomplete resection, infliximab use, radiotherapy | Right hilar | 76          | +                     | -         | Carinal sleeve pneumonectomy | 134                |
| 8  | 52/F    | -        | Hypertension   | Left lower lobe | 15          | -                     | IMT       | Wedge                  | 133                |
| 9  | 59/F    | Cough, chest and side pain | - | Right upper lobe | 60          | +                     | 10.0      | Mesenchymal tumor       | Lobectomy | 116                |
| 10 | 24/M    | Cough, fever | - | Left upper lobe | 40          | +                     | -         | -                      | Segmentectomy | 120                |
| 11 | 39/F    | -        | -              | Left lower lobe | 30          | -                     | Benign    | Wedge                  | 122                |
| 12 | 33/F    | Cough    | -              | Right upper lobe | 40          | -                     | 15.4      | Mesenchymal tumor       | Segmentectomy | 112                |
| 13 | 54/M    | -        | -              | Left upper lobe | 60          | +                     | 19.7      | Benign                 | Segmentectomy | 53                 |
| 14 | 55/M    | -        | -              | Right upper lobe | 26          | -                     | 4.4       | Benign                 | Wedge       | 84                 |
| 15 | 62/F    | -        | -              | Middle lobe    | 24          | -                     | 8.2       | IMT                    | Lobectomy   | 16                 |
| 16 | 81/F    | Cough, back pain, difficulty to walk | - | Right lower lobe, spinal canal extension | 55          | -                     | Mesenchymal tumor | Wedge+ laminectomy | 91                 |
| 17 | 46/M    | -        | -              | Right upper lobe | 20          | -                     | 3.5       | Benign                 | Wedge      | 8                  |

IMT: Inflammatory myofibroblastic tumor.
for relapse and metastasis.\textsuperscript{[5]} It can occur in both pediatric and adult populations with a wide age distribution\textsuperscript{[5]} The incidence of the IMT among lung tumors in our series is 0.87%, compatible with the literature.\textsuperscript{[3]} The etiology and pathogenesis of IMT has not been still fully understood. Although IMT is usually seen as a well-limited peripheral lesion, it may also occur centrally, may be locally invasive or may be seen as pneumatic infiltration. It can be observed as single or multiple masses.\textsuperscript{[5]} One (5.8%) patient had spinal canal extension of the tumor as local invasion and all the tumors were presented as single masses in our series. The tumor can be endobronchial in 10 to 20\% of the cases and also be localized within trachea.\textsuperscript{[6,7]} In our series, only one (5.8\%) patient had a totally endobronchial tumor. Calcification and cavitiation can be seen at a rate of 10\%. Mediastinum, chest wall, and pleural invasion are rare (Figure 2).\textsuperscript{[8]}

In previous studies including 10 or more cases, 41.7\% of the patients are females and the mean age is 40.2±11.4 years. In the present study, 70.5\% of cases were females and the mean age was 43±18.3 years. Mean tumor diameter was 38.4±6 mm and 24.5\% of tumors were centrally located in the previous literature, whereas mean tumor diameter was 35.4±18.5 mm and 17.6\% of tumors were centrally located in this study. One of our patients (No. 6) had a tumor in the left main pulmonary artery. A total of 56\% of the patients were symptomatic in the literature and, similarly, 52.9\% of our patients were symptomatic. Recurrence was observed in five patients who underwent complete resection and the mean follow-up was 73.8±40 months in the publications (Table 2).\textsuperscript{[2-6,8-14]} In the present study, the median follow up was 122 months and there was no recurrence.

An 81-year-old patient (No. 16) had walking difficulty, and the tumor had spinal canal extension in this patient. Mass excision was made with wedge resection to the lung and for spinal canal extension by laminectomy. This case is a good example of the extraparenchymal extension of IMT. Takayasu arteritis was detected in the Patient No. 6 after surgery. Although there is no proven relationship between the
Table 2. Case series of inflammatory myofibroblastic tumor including over 10 patients

| Author                   | Patient number | Sex female (%) | Age (mean) | Mean tumor diameter (mm) | Localization (central/periferic; % central) | Symptoms symptomatic (%) | Histological subtypes                              | Recurrence | Mean Follow-up (month) |
|--------------------------|----------------|----------------|------------|--------------------------|-------------------------------------------|--------------------------|---------------------------------------------------|------------|------------------------|
| Bahadori and Liebow[2]   | 40             | 62.5           | 28.6       | 42                       | 42.5                                      | 40                       | 25 plasma cell                                    | -          | 40                     |
| Spencer[9]               | 27             | 40.7           | 36         | 11.1                     | 51                                         |                          | 2 malignant histiocyta 25 plasma cells/histiocyta - |
| Matsubara et al.[10]     | 32             | 51.7           | 50         | 12.5                     | 40.6                                       |                          | 14 organizing pneumonia 14 fibrous histiocyta 4 lympho-plasmacytic plasma cells 17 fibro-histiocytic 13 organizing pneumonia |
| Pettinato et al.[11]     | 20             | 55             | 26.2       | 40                       | 20                                         | 45                       | - plasmacytic                                    | 1          | 44                     |
| Agrons et al.[8]         | 61             | 40.9           | 28         | 44                       | 14.7                                       | 54                       | 17 fibro-histiocytic 13 organizing pneumonia      | -          |                        |
| Cerfolio et al.[12]      | 23             | 52.1           | 47         | 40                       | 30.4                                       | 78.2                     | 11 noninvasive 12 invasive                        | -          | 156                    |
| Kim et al.[13]           | 28             | 21.4           | 37.9       | 48                       | 21.4                                       | 85.7                     | - plasmacytic                                    | 1          | 63                     |
| Melloni et al.[3]        | 18             | 27.7           | 57.8       | 35                       | 11.1                                       | 44.4                     | 13 fibrous histiocytic 4 lympho-plasmacytic 1 organizing pneumonia | -          |                        |
| Lee et al.[9]            | 15             | 33.3           | 31.3       | 27                       | 46.6                                       | 86.6                     | - plasmacytic                                    | 1          | 32.4                   |
| Chen et al.[14]          | 19             | 21             | 53.9       | 32.8                     | 36.8                                       | 42.1                     | 15 organized pneumonia 2 fibrous histiocytic 2 lympho-histiocytic | -          | 78.3                   |
| Fabre et al.[5]          | 25             | 56             | 33         | 35.4                     | 36                                         | 52                       | 16 inflammatory myofibroblastic 8 fibrous histiocytic 1 plasma cell granuloma | 1          | 80                     |
| Peretti et al.[4]        | 36             | 38.8           | 53.5       | 40                       | 11.1                                       | 61.1                     | 4 plasma cell type 7 fibrohistiocytic type 6 mix type | -          | 96.9                   |
| **Present case series**  | 17             | 70.5           | 43         | 35.4                     | 17.6                                       | 52.9                     | - plasmacytic                                    | -          | 122                    |
two conditions, we believe that this association may be supportive of the link between chronic inflammation and IMT development.

Furthermore, IMT is composed of myofibroblastic spindle cells, which are arranged in fascicular pattern, with eosinophilic cytoplasm and ovoid vesicular nuclei. Mitotic rate is variable, nuclear atypia is absent or minimal. Spindle cells are associated with a plasma cell predominant chronic inflammatory infiltrate. Foamy histiocytes, multinucleated giant cells, or neutrophils can accompany to the infiltrate. Spindle cells can show positivity with vimentin, SMA, desmin, muscle-specific actin (MSA), and focal positivity with epithelial markers such as CK and epithelial membrane antigen (EMA). Half of IMTs have ALK gene rearrangement and spindle cells can show positivity with ALK antibody in immunohistochemical analysis. Histopathological subtypes varied significantly due to the different classifications used. The most commonly preferred classification of IMT is based on predominant cellular component as fibrohistiocytic type and plasma cell type; however, histopathological classification has no prognostic value. In this study, predominant cell component was fibrohistiocytic in the majority of tumors (41.2%), and two (11.7%) patients had microscopically infiltrative type tumors, but all the patients had excellent outcomes independent of their histopathological types.

It is quite difficult to obtain a definite preoperative diagnosis in IMT. Therefore, routine examinations performed before lung surgery should be requested. It would be appropriate to perform blood tests, pulmonary function tests, cranial CT, thoracic CT and PET/CT. Frozen section is important both to clarify the diagnosis and to determine the width of resection intraoperatively. In Peretti et al.’s study, 35 patients underwent intraoperative frozen-section analysis and only five (14.2%) patients received IMT diagnosis. In our series, we had 10 frozen-section analysis cases and only two (20%) of them were reported as IMT. If there is a need for extended resection or pneumonectomy and the frozen section analysis is indeterminate, a second surgery after definitive diagnosis may be plausible. Of note, IMT may mimic inflammatory reactions and hematolymphoid proliferations. Microscopic features, immunohistochemical and molecular profile can help in the differential diagnosis. Spindle cell proliferation admixed with inflammatory cells and positivity of spindle cells with SMA, desmin, MSA showing myofibroblastic differentiation are diagnostic clues. The ALK expression or ALK gene rearrangement in the spindle cells support the diagnosis of IMT.

No significant difference was observed in survival and recurrence in 17 patients who underwent major (pneumonectomy, lobectomy) or minor (segmentectomy, wedge resection) resections in the case series of Chen et al. This result is also consistent with the results of our study. Wedge resection is sufficient in small and peripheral tumors; for larger and aggressive tumors, lobectomy, pneumonectomy or extended resections can be performed. Complete resection is the most important prognostic factor and incomplete resection may result in tumor recurrence as seen in one of our patients (No. 7). Although there are reports about spontaneously disappearing tumors or good respond to steroid therapy, main method of treatment is surgery. Radiotherapy can be considered for incomplete resections or inoperable cases. Lymph node metastasis was not observed in our patients, similar to the aforementioned series. It is not necessary to make a systematic lymph node dissection for IMT patients, if a pre- or intraoperative diagnosis of IMT can be achieved.

There are two major limitations for this study. This is a retrospective case series study and as there is one exitus and no recurrence in the study population, survival analysis could not be done.

In conclusion, it is difficult to make a preoperative diagnosis of inflammatory myofibroblastic tumor. Systematic lymph node dissection is not required in diagnosed patients. Complete resection is the most important prognostic factor, and it is of critical importance to achieve this with the smallest resection possible. Further studies are warranted to confirm these findings.

Declaration of conflicting interests
The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding
The authors received no financial support for the research and/or authorship of this article.

REFERENCES
1. Borczuk A, Coffin C, Fletcher CDM. Inflammatory myofibroblastic tumor. In: Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG, editors. WHO Classification of Tumors of the Lung, Pleura, Thymus and Heart. 4th ed. Lyon: International Agency for Research on Cancer (IARC); 2015. p. 121-2.
2. Bahadori M, Liebow AA. Plasma cell granulomas of the lung. Cancer 1973;31:191-208.
3. Melloni G, Carretta A, Ciricato P, Arrigoni G, Fieschi S, Rizzo N, et al. Inflammatory pseudotumor of the lung in adults. Ann Thorac Surg 2005;79:426-32.
4. Peretti M, Radu DM, Pfeuty K, Dujon A, Riquet M, Martinod E. Surgical resection of pulmonary inflammatory pseudotumors: Long-term outcome. Asian Cardiovasc Thorac Ann 2017;25:440-5.
5. Fabre D, Fadel E, Singhal S, de Montpreville V, Mussot S, Mercier O, et al. Complete resection of pulmonary inflammatory pseudotumors has excellent long-term prognosis. J Thorac Cardiovasc Surg 2009;137:435-40.
6. Lee HJ, Kim JS, Choi YS, Kim K, Shim YM, Han J, et al. Treatment of inflammatory myofibroblastic tumor of the chest: The extent of resection. Ann Thorac Surg 2007;84:221-4.
7. Özgül MA, Toru Ü, Acat M, Özgül G, Çetinkaya E, Dinger HE, et al. A rare tumor of trachea: Inflammatory myofibroblastic tumor diagnosis and endoscopic treatment. Respir Med Case Rep 2014;13:57-60.
8. Agrons GA, Rosado-de-Christenson ML, Kirejczyk WM, Conran RM, Stocker JT. Pulmonary inflammatory pseudotumor: Radiologic features. Radiology 1998;206:511-8.
9. Spencer H. The pulmonary plasma cell/histiocytoma complex. Histopathology 1984;8:903-16.
10. Matsubara O, Tan-Liu NS, Kenney RM, Mark EJ. Inflammatory pseudotumors of the lung: Progression from organizing pneumonia to fibrous histiocytoma or to plasma cell granuloma in 32 cases. Hum Pathol 1988;19:807-14.
11. Pettinato G, Manivel JC, De Rosa N, Dehner LP. Inflammatory myofibroblastic tumor (plasma cell granuloma). Clinicopathologic study of 20 cases with immunohistochemical and ultrastructural observations. Am J Clin Pathol 1990;94:538-46.
12. Cerfolio RJ, Allen MS, Nascimento AG, Deschamps C, Trastek VF, Miller DL, et al. Inflammatory pseudotumors of the lung. Ann Thorac Surg 1999;67:933-6.
13. Kim JH, Cho JH, Park MS, Chung JH, Lee JG, Kim YS, et al. Pulmonary inflammatory pseudotumor--a report of 28 cases. Korean J Intern Med 2002;17:252-8.
14. Chen CH, Huang WC, Liu HC, Chen CH, Chen TY. Surgical outcome of inflammatory pseudotumor in the lung. Thorac Cardiovasc Surg 2008;56:214-6.
15. Moran CA, Suster S. Unusual non-neoplastic lesions of the lung. Semin Diagn Pathol 2007;24:199-208.
16. Sagar AES, Jimenez CA, Shannon VR. Clinical and histopathologic correlates and management strategies for inflammatory myofibroblastic tumor of the lung. A case series and review of the literature. Med Oncol 2018;35:102.