Inflammatory Myofibroblastic Tumor After Lung Transplant—A Rare and Aggressive Complication: A Case Report

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ABSTRACT

Introduction. Malignant diseases are well-known complications after lung transplantation (LT). Among these, inflammatory myofibroblastic tumor (IMT) is a rare neoplasm with a not well-known and often aggressive biological behavior.

Material and Methods. We hereby describe 2 cases of cystic fibrosis patients who underwent bilateral sequential LT (BSLT) complicated by IMT.

Results. A 26-year-old man presented a right endobronchial lesion 6 months after BSLT. Two consecutive fiber bronchoscopic biopsies showed granulation tissue. For the persistent lesion growth, the patient underwent a transthoracic biopsy showing histologic diagnosis of IMT. Therefore, he underwent to right pneumonectomy that was unfortunately complicated after 6 months with a late bronchopleural fistula and empyema with exitus 6 months later. A 31-year-old woman 1 year after BSLT presented with a left voluminous pleural-parenchymal lesion; the histologic examination after biopsy revealed an IMT. She underwent a removal of the lesion with a macroscopic R0 resection. Histologic, immunophenotypic, and cytogenetic examinations showed a strong overexpression of anaplastic lymphoma kinase requiring biological adjuvant therapies; however, the patient refused it. Four years later, she presented a recurrence treated with debulking procedure and adjuvant radiotherapy. At last follow-up, the patient was alive with stable disease and optimal graft function.

Conclusions. Although IMT is a rare complication after lung transplant, to obtain a careful diagnosis, an early and aggressive treatment is mandatory.

LUNG transplantation (LT) is the only viable therapeutic option for selected patients affected by end-stage pulmonary diseases. Although several improvements have occurred in surgical techniques, perioperative management, and immunosuppressive regimens with increased quality of life and long-term survival, the outcome is still influenced by the development of complications occurring in the different post-transplant periods [1]; in particular, the LT recipients show an higher risk to develop malignancies related to continuous administration of immunosuppressive drugs to prevent rejection [2–4]. Although lymphoproliferative disorders and skin cancers are the most frequent

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0041-1345/19
https://doi.org/10.1016/j.transproceed.2019.08.011

neoplasms, other solid cancers may occur [5]. Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal neoplasm showing an indolent biological and clinical behavior, although sometimes a more aggressive behavior and recurrences have been described. The respiratory and the gastrointestinal tracts are the most frequent localizations showing site-specific symptoms, but a general inflammatory syndrome with fever and malaise may often be present [6]. Although surgical resection is the gold standard treatment, adjuvant therapy regimens have recently been proposed. Because approximately one half of IMTs show a translocation activating the anaplastic lymphoma kinase (*alk*) receptor leading to an overexpression of *alk* protein, biological therapies with inhibitors of kinase domain have been administered, showing good results [7]. We hereby describe 2 cases of cystic fibrosis patients undergoing bilateral sequential LT (BSLT) who developed IMT.

CASE #1

At the 6-month follow-up after BSLT, a 26-year-old cystic fibrosis patient presented with a cough, exertional dyspnea, and severe restrictive pattern at the pulmonary function test. A chest computed tomography scan showed a hilar mass extensively invading the right main bronchus. A fiber optic bronchoscopy showed a friable and bloody tissue almost completely occluding the right main bronchus; a histologic examination on multiple biopsies described granulation tissue. In order to obtain airway patency, he underwent mechanical dilation and vaporization with a neodymium-yttrium aluminum garnet laser and prosthesis placement (DUMON 12 x 30 mm; Novatech SA, La Ciotat, France) in the right main bronchus. Because of the impressive and fast growth of the mass, the patient underwent a transthoracic biopsy with the histologic diagnosis of IMT. Histologically, we observed a proliferation composed of spindle cells characterized by eosinophilic, elongated, tapering cytoplasmic processes without striation and oval nuclei with smooth contours, open chromatin, and occasional nucleoli. These cells were admixed with an intense chronic inflammatory infiltrate composed of lymphocytes, plasma cells, and macrophages. The neoplastic spindle cells were immunoreactive for vimentin, smooth muscle actin and EMA and negative for *cd34*, calretinin, human bone marrow endothelial cell marker-1, *s100* and desmin, thus showing a myofibroblastic differentiation (Fig 1). The involvement of the hilum and the fissure plan required a right pneumonectomy. The postoperative course was uneventful. After 6 months, the patient presented with a cough and fever, and a bronchopleural fistula associated to pleural empyema was detected. The patient underwent rigid bronchoscopy and airway stenting with a conical and fully coated self-expanding metallic stent, with a proximal diameter (tracheal) of 22 mm, a distal diameter (bronchial) of 16 mm, and a length of 50 mm (TRACHEOBRONXANE SILMET; Novatech SA,). A chest tube was positioned; through it, pleural lavages with antiseptic solution were daily performed. Because of a *Candida albicans* and *Pseudomonas aeruginosa* infection, therapy with intravenous (IV) colistin (loading dose followed by maintenance therapy: 6-9 million IU 4.5 twice daily) was immediately established in combination with nebulized colistin (1 million IU every 8 hours) and caspofungin (50 mg daily IV). After an initial improvement of clinical conditions, the empyema persisted, requiring an open window thoracostomy. Nevertheless, the patients died of a multiorgan failure caused by sepsis 3 months later.

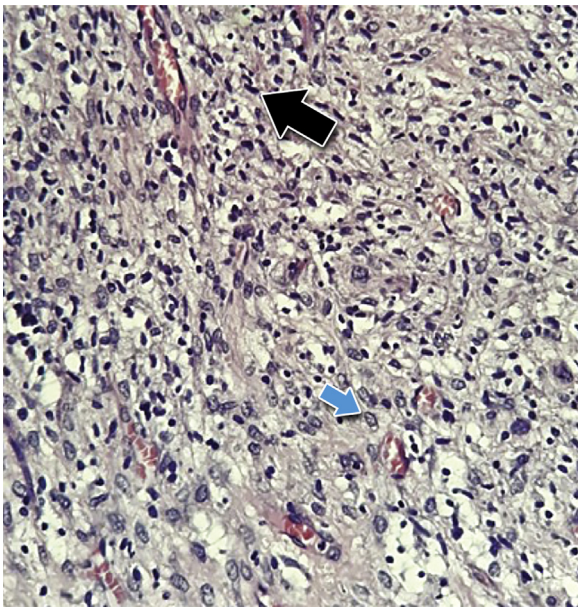

Fig 1. Inflammatory myofibroblastic tumor. Areas of spindle cells (blue arrow) with plump nuclei and minimal cytological atypia admixed with chronic inflammatory infiltrate (black arrow) composed of lymphocytes and plasma cells. (Hematoxylin-eosin, magnification 20x).

CASE #2

One year after BSLT, a 31-year-old cystic fibrosis female reported with a hacking cough. A chest computed tomography scan showed a left voluminous pleural-pulmonary mass, and the histologic examination after biopsy revealed an IMT, a myofibroblatic proliferation of spindle cells with small size nuclei, and scanty cytoplasm mixed with abundant inflammatory lymphoplasmocellular infiltrate and amorphous eosinophilic extracellular matrix. At the immunohistochemistry examination, the neoplastic cells were positive for smooth muscle actin, vimentin and *alk* and negative for *cd34*, *bcl2*, *cd99*, desmin, and *s100*. She underwent a removal of the lesion with a macroscopic R0 resection. The postoperative course was uneventful, and the patient was discharged 7 days after surgery. The rearrangements of the *ALK* gene was confirmed by FISH, and this data required biological adjuvant therapies; however, the patient refused it. Four years later, she experienced an IMT recurrence; she underwent a redo surgery, but this time the surgical

resection was R1. Postoperative prolonged air leaks were treated with multiple autologous blood patches. The patient was discharged 20 days after surgery, and she underwent adjuvant radiotherapy on the surgical field with a total of 50.4 Gy in 28 fractions of 1.8 Gy each (IMRT and TomoTherapy HI ART, Madison, Wisc). At her 1-year follow-up, the patient was alive with stable disease and optimal graft function.

DISCUSSION

Malignant diseases are well-known complications after LT [2]. Transplant recipients show an increased risk compared to the general population to develop malignancies, and approximately 16% and 32% of them experience cancer within 5 and 10 years after the transplant, respectively [8]. The immunosuppressive regimen plays a crucial role as shown by several studies, although the pathogenesis of lung cancer in this specific subset of patients is not completely known [9]. IMT has been reported with a number of synonyms: plasma cell granuloma, inflammatory pseudotumor, xanthogranuloma, and fibrous histiocytoma. IMT represent less than 1% of all lung tumors and rarely can involve the airway; its biological behavior is not well known [10,11]. This tumor is the most frequently diagnosed pediatric lung neoplasm, and its precise cause is unknown, although it seems to be related to an uncontrolled response to tissue damage of chronic inflammation normally after pulmonary infections or in patients who had an history of cancer [12]. The diagnosis is not simple, and different histologic classifications have been proposed. The World Health Organization defined it as lesion composed of a myofibroblastic spindle cell population accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils [13,14].

Approximately 50% of IMTs contain *ALK* gene rearrangements [7]. *ALK* gene rearrangements or the resulting fusion proteins may be detected in tumor specimens using immunohistochemistry, and thus fluorescence in situ hybridization should be used to confirm the results. Although the true neoplastic nature of the lesion has not been established yet, the evidence of chromosomal rearrangement involving the *ALK* gene that results in the activation of a tyrosine kinase receptor has been supposed to be involved in the pathogenic process [15]. In patients with *alk*-positive IMT that otherwise show only 10% response with traditional chemotherapy, new biological therapies using inhibitors of the kinase domain of *alk* protein have shown an impressive response rate. There is no clear correlation between the *alk* expression and the clinical behavior of the tumor, although the high rate of response in *alk* inhibitors seems to correlate the *alk* positivity to a good prognosis [15].

To the best of our knowledge, these are the first 2 cases of IMT after LT. In literature, only few cases of IMT after solid organ transplant have been reported. Tepeoğlu et al reported a case of a 9-month-old child who underwent liver transplant for biliary atresia (the donor was his mother). Two months after transplant, the authors detected post-transplant lymphoproliferative disorder and IMT concurrently, advocating this entity to highlight possible Epstein-Barr virus involvement [16]. IMT is an uncommon secondary malignancy after hematopoietic stem cell transplant, too. Shash et al reported the case of highly aggressive and metastatic IMT in an 8-year-old girl following an umbilical cord blood transplant [17]. Furthermore, the interaction of an immunosuppressive regimen and infections has been supposed in a case of IMT secondary to invasive pulmonary aspergillosis in a patient with chronic graft-versus-host disease [18]. IMT of the lung usually shows locally invasive behavior with high rate of recurrence that has been reported to range from 18% to 40% and metastatic potential. Complete surgical resection, when feasible, is the gold standard [10,19]. After R0 resection, an excellent prognosis has been reported. Fabre et al reported [10] a 10-year survival rate of 89% and Cerfolio et al (12) a 5- and 10-year survival of 91% and 77%, respectively, although a 60% recurrence rate in patients undergoing R1 resection has been described. After surgery in cases of incomplete resection or metastatic spread or as the primary treatment when surgery is not feasible, radiotherapy and conventional chemotherapy seem to be useful [20].

After major lung resection and LT, postoperative complications can occur both in the first postoperative period and for a long time following the operation. Among these infections, postoperative air leaks and bronchopleural fistula are extremely common. Early detection and fast treatment are crucial for a positive outcome because these conditions are often associated with high rates of morbidity and mortality [21]. Pulmonary infections due to viral, bacterial, or even fungal pathogens are common complications after lung transplant due to an immunosuppressive regimen; robust therapy is needed to avoid hematic dissemination and sepsis. In MDR-GN infections, colistin is widely used administered by inhalation and IV with good results [22]. Postoperative air leaks contribute to prolonged hospitalization and can delay adjuvant chemotherapy or radiotherapy. Many techniques have been proposed for the treatment of this complication, and autologous blood patches have shown good results [23]. Postpneumonectomy bronchopleural fistula associated with empyema still remains a dreaded complication in thoracic surgery. The positioning of a conical fully coated SEMS together with a toilette of the infected pleural space usually allow a complete resolution, as we previously reported [24,25]. Unfortunately, the immunosuppressive regimen in these patients played a negative role, and in the first case, this procedure was not able to clear the infection and suddenly led to the patient's death.

In conclusion, although IMT is a rare complication after LT, an early diagnosis is mandatory to correctly treat and obtain good results. When feasible, complete surgical resection is the gold standard. Chemotherapy and radiotherapy, especially after incomplete resection, could be useful to prevent disease progression.

ACKNOWLEDGMENTS

The authors acknowledge Matteo Sala for figure editing.

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