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Case Report

Late Recurrence of Mucinous Adenocarcinoma after Lung Transplantation: A Case Report and Literature Review

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Abstract
Introduction: Invasive mucinous adenocarcinoma (IMA) of the lung has a less aggressive behavior than other adenocarcinoma subtypes. Overall, the propensity for nodal and distant metastases is low, but spread throughout the lungs is frequent. The radiographic "ground glass" presentation makes differentiation between infectious and inflammatory consolidations challenging, and the diagnosis of malignancy is often unexpected. ***Case Presentation:*** A 50-year-old patient underwent double lung transplantation (LTx) in July 2018 for progressive fibrosing interstitial lung disease (ILD). IMA was unexpectedly found in the explant lungs. Pre-transplant PET-CT scans suggested inflammatory ILD without malignancy. Endobronchial ultrasound-guided transbronchial fine needle aspiration of the enlarged mediastinal lymph nodes demonstrated no evidence of malignancy. Post-transplant pathology confirmed stage IVA IMA with a KRAS G12D mutation. After 3 years, recurrent IMA was detected. The asymptomatic patient remains under close surveillance with stable lung function, and tailored treatment will be

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considered if progression occurs. ***Conclusion:*** IMA is currently rarely considered an indication for LTx. The risk of recurrence after transplantation is substantial, and recurrence negatively impacts long-term post-transplant prognosis. Incidental adenocarcinoma in explant lungs will remain a complication of imperfect transplant recipient selection. A high index of suspicion of disease recurrence in the donor lungs should be maintained in these patients. Further research is required to understand the optimal screening, treatment, and follow-up of these patients.

Introduction

Invasive mucinous adenocarcinoma (IMA) is a distinct lung tumor subtype that features goblet and/or columnar tumor cells with abundant intracytoplasmic mucin. It often exhibits multicentric and bilateral lung involvement, potentially reflecting aerogenous spreading. Multifocal cases involving multiple lung lobes present treatment challenges. Computed tomography (CT) scans typically show ground glass opacities, which can be mistaken for infection or inflammation. Recurrence or progression usually appears as new lung lesions, and systemic therapy may be needed for non-resectable cases [1, 2].

The prevalence of incidental lung cancer in the explanted lung after lung transplantation (LTx) ranges from 0.5 to 2.8%, with adenocarcinoma being the most frequent histology. Lung transplant candidates with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, especially former smokers, are at higher risk of developing lung cancer [3]. They should undergo thorough and repeated lung cancer screenings before being listed and during the waiting time [4]. We here report a case of recurrent IMA in donor lungs 3 years after an incidental finding in explant lungs upon double LTx for interstitial lung disease (ILD).

Case Presentation

A 48-year-old man was referred because of progressive respiratory symptoms secondary to ILD. The patient had been experiencing respiratory symptoms since the beginning of 2016, following a respiratory infection. Chest CT revealed bilateral ground glass opacities and consolidations, most pronounced in the right lower and middle lobes and lingula. The patient had quit smoking in 2016, with a history of 10 pack-years, and had worked in a company manufacturing radiopharmaceuticals, where unprotected contact with nebulized Clinisteril (ethanol, water, isopropanol, 0.125% hydrogen peroxide), used for cleaning, had occurred. Further investigations could not identify a clear diagnosis, but the radiological presentation was most suggestive of an organizing pneumonia. Transbronchial biopsy (TBB) of the right lower lobe revealed non-specific limited fibrosis and lymphocytic inflammation. Parenchymal abnormalities progressed over the next 2 years to a fibrotic pattern with traction bronchiectasis and honeycombing, resulting in progressive respiratory symptoms.

Before transplantation, in July 2017 and March 2018, a positron emission tomography CT (PET-CT) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) was performed because of enlarged mediastinal lymph nodes (Fig. 1). There was moderately increased ^{18}F-FDG uptake in bilateral parenchymal consolidations with a maximum standardized uptake value (SUV_{max}) of 8.8, interpreted as inflammatory activity in the context of known ILD, with bilateral mildly hypermetabolic mediastinal lymph nodes (SUV_{max}: 4.6). Endobronchial ultrasound-guided

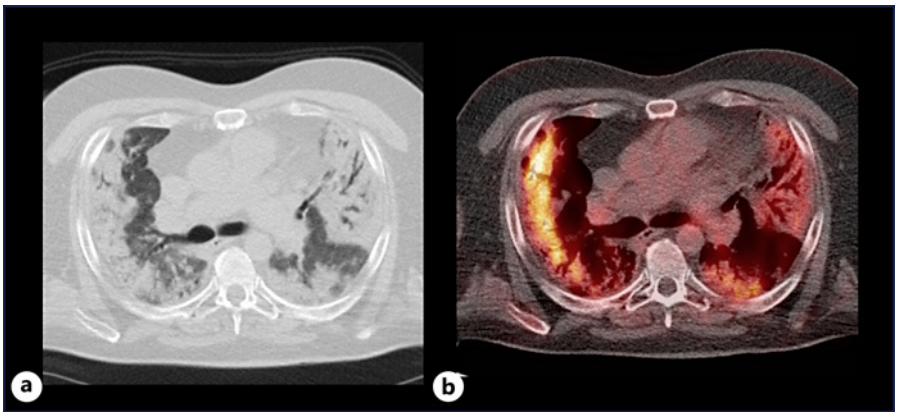

Fig. 1. a Chest CT scan in March 2018 prior to LTx. **b** Corresponding ^{18}F-FDG PET image. CT, computed tomography; PET, positron emission tomography. Moderate hypermetabolic consolidations bilaterally in the lungs. Accompanying mildly hypermetabolic glands bilaterally hilar and mediastinal.

transbronchial fine needle aspiration of the enlarged lymph nodes in stations 4R and 7, in May 2018, demonstrated no evidence of malignancy.

Double LTx was subsequently performed in July 2018. Pathological examination of both explant lungs demonstrated the presence of multifocal IMA (with an extensive lepidic component) on a background of non-specific interstitial pneumonia. The tumor involved all lobes on both sides. Bronchial resection margins were free of cancer. Assessed hilar lymph nodes were negative for malignant invasion; however, a systematic lymph node resection was not performed during transplantation. Thus, the patient was diagnosed with a stage IVA IMA, pT4 pNx pM1a. Tumor PD-L1 immunohistochemistry was negative. Molecular analysis by targeted next generation sequencing revealed a KRAS G12D mutation.

After multidisciplinary discussion, close radiographic surveillance was implemented. Three months post LTx, ^{18}F-FDG PET-CT showed no signs of malignant disease activity. After healing of bronchial structures, mycophenolate mofetil (MMF) was switched to the mTOR inhibitor everolimus, which was given in addition to tacrolimus and methylprednisolone. Everolimus was again switched to low dose MMF in January 2021 because of leg edema. Annual chest CT in 2019 and 2020 revealed no particular findings.

However, on chest CT in July 2021, small irregularly delineated subpleural nodular consolidations appeared in both lungs, which were slowly growing on subsequent imaging in June 2022. ^{18}F-FDG PET-CT in August 2022 demonstrated no enhanced ^{18}F-FDG uptake. Bronchoscopy with TBB did not show rejection nor infection, and a close surveillance approach was maintained. Given further progression of the lung lesions on CT in June 2023, ^{18}F-FDG PET-CT was repeated in October 2023, which now revealed a mildly increased ^{18}F-FDG uptake (SUV_{max}: 3.4) in the different parenchymal consolidations, but not in the lymph nodes (Fig. 2). Subsequent endoscopic evaluation by radial endobronchial ultrasound-miniprobe with TBB of the right upper lobe found an adenocarcinoma with lepidic growth pattern, with insufficient material for predictive testing. Additional CT-guided transthoracic needle biopsy confirmed the presence of a mucinous adenocarcinoma with a predominant lepidic growth pattern, with negative tumor PD-L1 staining. Molecular analysis revealed the same characteristics as the lung adenocarcinoma identified in the explant lungs in 2018, with a KRAS G12D mutation. So, recurrent stage IVA IMA was diagnosed 3 years after LTx. The Multidisciplinary Oncologic Board proposed active surveillance given an asymptomatic patient with a stable (normal) graft function (FVC 78 %pred and FEV1 78 %pred), and slowly progressive lesions. The patient also favored a watchful waiting approach after discussing the

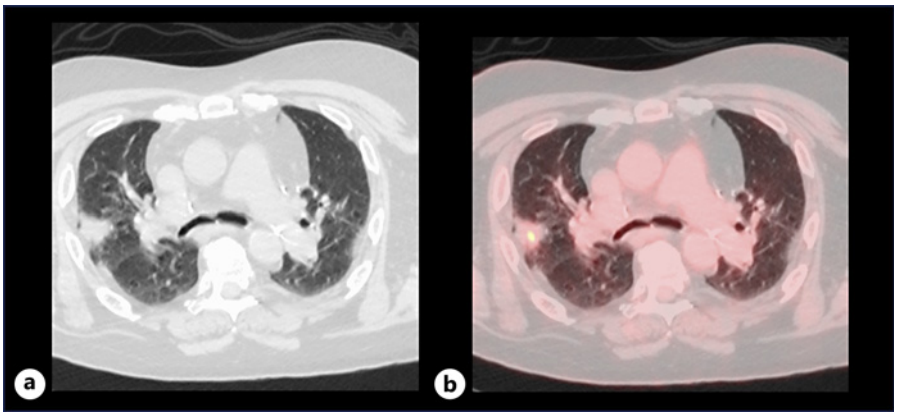

Fig. 2. **a** Chest CT scan in October 2023. **b** Corresponding ^{18}F-FDG PET image. CT, computed tomography. PET, positron emission tomography. Irregular delineated consolidations (with surrounding ground glass opacities) bilaterally, with minimal FDG uptake.

risks and benefits of systemic therapy with the medical team. Clinical and CT-graphic evaluation in January 2024 showed stable findings. In case of significant or symptomatic progression in the future, treatment with platinum doublet chemotherapy will be considered; no immunotherapy will be added given the objective risk of allograft rejection. Meanwhile, MMF is stopped, and tacrolimus and methylprednisolone are continued as maintenance immunosuppression. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000545190).

Discussion

For a selected group of patients experiencing end-stage pulmonary failure, LTx is an effective and safe treatment. According to the International Society of Heart and Lung Transplantation (ISHLT) report from 2023, idiopathic pulmonary fibrosis has become the primary indication for LTx, followed by chronic obstructive pulmonary disease [5]. Both respiratory diseases have been identified as independent risk factors for lung cancer development [6].

Globally, lung cancer ranks as the second most common cancer and the leading cause of cancer-related death. Interestingly, the first LTx was performed by Hardy and colleagues [7] in 1963 for a patient with lung cancer. From 1995 to 2001, lung cancer constituted the indication for only 0.1% of LTx cases [8]. Currently, individuals with active lung cancer are excluded from consideration for LTx, especially because of a concern about cancer control under intense immunosuppression required for transplant maintenance [9].

Even with careful pre-transplant screening, literature reports that lung cancer is incidentally discovered in 0.5%–2.8% of explanted lungs after LTx, reflecting the difficulty of radiographically and metabolically differentiating parenchymal abnormalities in patients with end-stage lung disease [4]. Incidental lung cancer negatively impacts post-transplant survival in a lung cancer stage-dependent matter [4, 10]. A recent systematic literature review of 169 LTx patients with incidental lung cancer in their explant lungs showed an overall survival (OS) of 60.8%, 25.5% and 23% at 1 year, 3 years and 5 years, respectively. Explant lung pathology identified diffuse lepidic adenocarcinoma in 10.7% of these patients [10]. To limit the risk of lung cancer recurrence in the donor lungs post-transplantation,

immunosuppression is to be minimized with a lower targeted calcineurin target through and elimination of a cell cycle proliferation inhibitor (MMF or azathioprine). In addition, close CT-graphic follow-up should be installed.

IMA is a distinctive subgroup in the spectrum of lung adenocarcinoma, accounting for 3–10% of this group [1]. This subgroup is characterized by well-differentiated goblet or columnar tumor cells containing abundant intracytoplasmatic mucin vacuoles. The lepidic growth pattern often dominates, though an acinar, papillary, and micropapillary pattern is possible. Lepidic growth entails the spread along preexisting alveolar/bronchial structures. CT findings characteristically involve pneumonic-like areas of consolidation often with multifocal and bilateral lung involvement, not easy to differentiate from infectious or inflammatory lesions. It is reported that more than 50% of IMAs harbor a KRAS mutation, with G12D being the most frequent type of KRAS mutation. Prognosis is favorable for localized/resectable lesions, approaching a 100% disease-specific survival after resection. For patients exhibiting multifocal lepidic predominant adenocarcinoma involving multiple lobes in one or two lungs, the indication for resection is more debatable [1, 2, 11]. However, long-term outcomes are still favorable. Overall, when recurrence occurs after resection, it is predominantly in the form of new pulmonary lesions. For multifocal diseases not amenable to resection, systemic therapy based on the results of predictive molecular testing can be initiated. The start of treatment is based on patient symptoms and rate of disease progression. Patients presenting with a diffuse pneumonic-type involvement of IMA, however, are typically symptomatic as alveolar spaces are gradually being filled by mucin and/or tumor cells. This subtype, clinically often presenting as a non-resolving pneumonia and histologically often showing features of IMA, is associated with worse survival and many patients will eventually succumb to respiratory failure [2, 12].

Given LTx being established as a treatment for symptomatic end-stage pulmonary failure and the overall more indolent behavior of lepidic predominant adenocarcinoma (including non-mucinous invasive adenocarcinoma and IMA) with low propensity for nodal and distant metastases even in case of diffuse pulmonary involvement, LTx has been explored as a treatment option for lepidic predominant adenocarcinoma [12]. At present, transplantation is not indicated for multifocal lung adenocarcinoma, although subject to investigation in the prospective DREAM trial. In older retrospective multicenter series, the reported 5-year OS ranged from 39% to 57% [13, 14]. A recurrence rate of 59% was reported in a group of 22 patients transplanted for multifocal lepidic predominant adenocarcinoma, with recurrences being between 5 and 49 months after transplantation. In 88% of these patients, the site of recurrence was limited to the transplanted lungs [13]. The risk of tumor recurrence in several smaller single-center series varied between 33 and 75% [15]. Molecular testing can establish the recipient origin of the tumor recurring in the donor lungs [16]. However, the exact site from which the recurrence arises within the donor lungs remains uncertain but may involve the trachea, proximal mainstem bronchi, or even extrapulmonary sites.

Conclusion

Symptomatic relief and long-term disease-free survival are hence possible after LTx for lepidic predominant adenocarcinoma refractory to standard anti-cancer treatment. However, based on current data, the risk of recurrence after transplantation is substantial, and recurrence negatively impacts long-term post-transplant prognosis. In addition, given the current donor organ shortage and the growing number of patients with non-malignant end-stage lung disease eligible for transplantation, lepidic predominant adenocarcinoma is currently rarely considered an indication for LTx. On the other hand, incidental

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adenocarcinoma in explant lungs, as in our patient, will remain a complication of imperfect transplant recipient selection [15]. A high index of suspicion of disease recurrence in the donor lungs should be maintained in these patients. Immunosuppression should be minimized, with a lower-targeted calcineurin target trough and elimination of a cell cycle proliferation inhibitor (MMF or azathioprine). At recurrence, treatment can be initiated according to the disease stage. However, further research is required to understand the optimal screening, treatment, and follow-up of these patients.

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Statement of Ethics

Oral and written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors have accepted responsibility for the entire content of this manuscript, consented to its submission to the journal, reviewed all the results, approved the final version of the manuscript, and provided critical feedback. Eveline Claeys, Nico De Crem, Robin Vos, and Els Wauters conceptualized and designed the report, reviewed the literature, and drafted the manuscript in consultation with Laurens Ceulemans, Dirk Van Raemdonck, and Christophe Dooms. Christophe Deroose and Walter De Wever performed radiological assessments and contributed images. Birgit Weynand conducted the pathological examination and analyzed histopathological findings. Isabelle Vanden Bempt conducted the molecular testing. All authors provided critical feedback. Pierre Van Mol and Arno Vanstapel aided in editing and revising the manuscript after peer review.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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