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ABSTRACT
The clinical scenario of a pulmonary nodule following lung transplantation is one with limited experience and no supporting guidelines for the approach to diagnosis and management. Given the broad differential diagnosis for pulmonary nodules in this setting, most of which are life-threatening without appropriate treatment, aggressive evaluation is required. Here we present a case of a 70-year-old female with the development of a large pulmonary nodule in the native lung four years following a single lung transplant. She underwent bronchoscopy with endobronchial ultrasound to achieve a tissue diagnosis which showed small cell lung carcinoma. The patient was started on chemotherapy and has shown clinical and radiographic improvement at most recent follow up seven months after the initial diagnosis. In this report we discuss the differential diagnosis and corresponding imaging findings for the pulmonary nodule following lung transplantation to aid in guiding clinicians navigate this challenging clinical situation.

1. Introduction
The pulmonary nodule is a rounded or irregular opacity, measuring up to three centimeters in diameter, that may be either well or poorly defined. In immunocompetent patients the vast majority are due to granulomas, benign tumors, or malignancies. However, in the pulmonary transplant recipient, the differential diagnosis is far more expansive given the combination of the underlying pulmonary disease responsible for transplant, pre-existing risk factors, immunosuppression, and post-operative complications. Furthermore, the experience with diagnosis and therapy for these lesions is limited. For example, the largest single series of data on this topic with histologic samples involves only 23 patients with pulmonary nodules over a 10-year period at a large transplant center. Consequently, any nodule in a transplant patient requires aggressive evaluation. Here, we report a case of a patient with a pulmonary nodule following lung transplantation and discuss the differential diagnosis and imaging considerations for this challenging clinical scenario.

2. Case report
A 70-year-old female presented to the emergency department (ED) with a one-week history of dyspnea, right-sided chest pain, and fatigue. The patient’s history included a single left lung transplant four years prior for combined pulmonary fibrosis with emphysema. Her post-operative course had been complicated by two episodes of acute rejection as well as the development of chronic kidney disease. The patient was on an immunosuppressant regimen of tacrolimus, myco-phenolate mofetil, and prednisone. On presentation to the ED she was afebrile and had mild tachycardia (heart rate, 110 beats per minute), tachypnea (respiratory rate, 22 breaths per minute), and leukocytosis (white blood cell count, 14.7 K/ul). Frontal and lateral chest radiographs were performed, which prompted a subsequent computed tomography (CT). Imaging showed a rounded 2.8 cm pulmonary nodule in the right upper lobe, with ipsilateral hilar lymphadenopathy - these abnormalities are in the native lung with pulmonary fibrosis and emphysematous changes. The main diagnostic considerations for a pulmonary nodule following lung transplantation are malignancy and infection. Given the patients immunocompromised status, Aspergillus sp. infection was also considered, and she was started

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on voriconazole. She later underwent a bronchoscopy with endobronchial ultrasound and transbronchial needle aspiration of the enlarged right hilar lymph node. Tissue samples confirmed a diagnosis of small cell carcinoma, and staging evaluation revealed hepatic diffuse osseous metastases. She was treated with etoposide and cisplatin chemotherapy and has shown both clinical and radiographic improvement (Figs. 4, 5) at interval follow-up, being seen last in the clinic seven months following diagnosis.

3. Discussion

The finding of a pulmonary nodule following lung transplantation requires aggressive evaluation. The differential diagnosis for these lesions is broad, and the most common etiologies are all life-threatening [2]. In the largest case series with histologic samples evaluating pulmonary nodules following lung transplant, 9.8% of patients were found to have developed a pulmonary nodule, with the most common

Fig. 1. Posteroanterior chest radiograph (A) and coronal computed tomography (B) images one year prior to transplant with corresponding images one month following left lung transplant for combined pulmonary fibrosis with emphysema (C and D).

Fig. 2. Posteroanterior (A) and lateral (B) chest radiographs show a pulmonary parenchymal nodule (arrow), and hilar lymphadenopathy (arrowhead).
etologies post-transplant lymphoproliferative disorder (PTLD) and invasive pulmonary aspergillosis [2]. These diagnoses should be given strong consideration in any case of a pulmonary nodule following lung transplant. An additional cause of high consideration in our patient’s case, and ultimately the final diagnosis, is bronchogenic carcinoma. Below we discuss the diagnostic considerations, timing (Table 1), and imaging approach to the post-lung transplant pulmonary nodule.

The most common cause of a pulmonary nodule following lung transplant is PTLD [2]. PTLD is a spectrum of lymphoid neoplasms ranging from benign hyperplasia to invasive malignant lymphoma [3,4]. In lung transplant recipients, PTLD has an incidence of approximately 5% and the mortality approaches 50% [3,4]. Patients may present with constitutional symptoms or be completely asymptomatic [3]. PTLD generally occurs during the first postoperative year and is most frequently seen around 3–4 months post-transplant [3]. A key risk factor is Epstein Barr Virus seronegative status at the time of transplant [5]. Radiographic features include solitary (most commonly) or multiple nodules or masses with or without mediastinal adenopathy [5].

Fig. 3. Sagittal (A) and axial (B, C) images from computed tomography of the chest without contrast demonstrate a 2.8 × 2.8 cm rounded pulmonary nodule (arrow) in the right upper lobe and right hilar lymphadenopathy (arrowhead). In addition, the native right lung shows changes of fibrosis and emphysema.

Fig. 4. Sagittal (A) and axial (B, C) images from computed tomography of the chest without contrast obtained two weeks after the initiation of chemotherapy demonstrate a reduction in the size of the rounded pulmonary nodule (arrow) in the right upper lobe to 2.0 × 2.4 cm, as well as a decrease in the right hilar lymphadenopathy (arrowhead).
Extrathoracic disease may also be seen [4]. In addition to PTLD, other malignancies such as bronchogenic carcinoma and metastatic disease may also present with pulmonary nodules. Bronchogenic carcinoma is the leading cause of cancer death worldwide [6]. The risk of developing lung cancer following solid-organ transplantation is approximately 20–25 times higher than the general population [7]. In the lung transplant population, the highest risk is in those who received a lung transplant for chronic obstructive pulmonary disease or idiopathic pulmonary fibrosis — together, these conditions account for more than half of all lung transplants [7,8]. It is anticipated that rates are likely to increase due to the growing number of transplants and longer survival. Other risk factors for post-transplantation lung malignancy include advanced age, smoking history, and personal or family history of lung cancer [5,7].

Imaging features suggestive of malignancy include nodules that are solitary, larger in size (especially if >20 mm), have irregular or spiculated margins, lobulated contours, are located in the upper lobes, or found in the native lung of a single-lung recipient [2,6,9]. Although the majority of pulmonary nodules in single-lung transplant recipients involve the transplanted lung, those due to bronchogenic carcinoma more commonly affect the native lung [4]. Timing is an important consideration, as bronchogenic carcinoma is rarely encountered in the first post-transplant year [4]. Additionally, certain imaging features may suggest one histological subtype over another. For example, adenocarcinoma is more likely than squamous and small cell to present with consolidation or ground-glass opacity [9,10]. Squamous cell carcinoma is associated with cavitation in up to 82% of cases [9]. Small cell carcinoma often presents with a small or inapparent primary nodule with significant mediastinal lymphadenopathy [9]. The prognosis of bronchogenic carcinoma in transplant patients tends to be poor as the disease progresses rapidly, likely a result of the loss of the innate immune surveillance due to high levels of immunosuppression [4,5].

Infection is the most common cause of mortality in the first six months following lung transplantation [3,5]. The rate of infectious complications in lung transplant recipients is higher than in those undergoing transplants of other solid organs, in large part due to the higher load of immunosuppression as well as exposure of the lung allograft to the atmosphere [4,5,11,12]. The most common infectious organism to cause a nodule following lung transplant is Aspergillus sp., which is seen in up to 40% of patients, most often in the first 3–6 months after surgery [3,5]. Infections can manifest as aspergillosis, necrotizing pneumonia, empyema, or invasive aspergillosis. Additionally, Aspergillus sp. can cause ulcerative tracheobronchitis, a form of infection specific to lung transplants that can lead to bronchial dehiscence, stenosis, or fistula [13,14]. Common imaging findings include solitary or multiple nodules surrounded by a rim of ground-glass opacity (the “halo” sign), mass-like regions of consolidation, or cavitary lesions [4,15].

Bacterial infections comprise at least half of all infections, most commonly manifest as pneumonia, and are often seen in the first month following transplantation [3,5]. While gram-negative species such as Pseudomonas aeruginosa and Klebsiella sp. are most common [4,11,12], Staphylococcus aureus should also be considered [16]. Bacterial infections may be a predominant etiology of nodules following lung transplant [17]. However, clinicians should exercise caution and maintain close follow up when attributing a nodule to bacterial infections given the propensity of invasive fungal disease and malignancy when tissue sampling is pursued [2]. Imaging findings may include patchy consolidation, bronchocentric opacities, and cavitation [4]. Nodular opacities from bacterial infections are likely to be branching, centrifilobular or “tree-in-bud” nodules [4].

Other infectious causes of nodules include cytomegalovirus (CMV) and mycobacterium. CMV is the most common viral pathogen to affect lung transplant recipients and is commonly seen between 1 and 6 months post-transplantation [5,18]. CT typically shows ground-glass opacities, but disseminated centrifilobular tree-in-bud nodules or
consolidation may also be seen [15,18]. In rare cases, CMV has been associated with masses or mass-like infiltrates [19]. Mycobacterial infections usually occur at least 4 months after surgery [20]. Mycobacterium tuberculosis is most common and carries an incidence up to 74 times that of the general population [21]. Infection most commonly results from reactivation of latent disease [21]. Infection by nontuberculous mycobacteria is also seen, with Mycobacterium avium complex being most common [20]. Imaging findings in mycobacterial diseases shows clusters of small nodules, nodular ground-glass opacities, consolidation, cavitation, pleural effusions, and mediastinal lymphadenopathy [20].

While malignancy and infection are by far the most common causes of nodules in lung transplant recipients, other causes that clinicians should be aware of include cryptogenic organizing pneumonia (COP), primary disease recurrence, and post-biopsy changes. COP occurs in 10–28% of patients after lung transplantation [4]. It is frequently associated with concurrent infection or rejection, and most often occurs in the first year after transplant [22]. Imaging shows airspace consolidation that may be nodular or mass-like, ground-glass opacities, and linear or reticular opacities [4]. Sarcoïdosis accounts for approximately 3% of lung transplants and is the most common disease to recur following transplant (approximately 35% of cases) [4]. Primary disease recurrence can be as early as 2 weeks following transplant or as late as 2 years [4]. Typical imaging findings of sarcoïdosis include hilar lymphadenopathy with a nodular or reticulonodular pattern of parenchymal disease [15]. Nodules tend to be less than 3 mm, have a peribronchovascular distribution, and predominantly involve the middle and upper lung zones [15]. Post-biopsy changes are a final consideration, given that bronchoscopic surveillance for rejection and infection may lead to six or more bronchoscopies with transbronchial biopsies in the first 2 years following transplant. On CT this leads to small nodular opacities that may be solid or cavitary and are most often adjacent to the pleura [4]. Surrounding ground-glass opacities may also be present and represent local hemorrhage at the site of biopsy [4]. These abnormalities may last up to 30 days [13].

In conclusion, the finding of a pulmonary nodule following lung transplantation is a scenario in which clinicians have limited experience and no guidelines for diagnosis or management [2]. In these cases, a broad differential diagnosis must be considered. Given the high mortality associated with the most common diagnoses, aggressive diagnostic evaluation is warranted.

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References


