Diagnosis of Pleural Lymphoma in a Kidney Transplant Patient by Medical Pleuroscopy with Cryoprobe Biopsies

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Abstract
Kidney transplant recipients are at increased risk of malignancy compared to age and gender matched populations. The development of a pleural effusion after transplantation requires further workup to determine if the etiology is malignant. We report a case of a patient with recurrent left-sided pleural effusion without a definitive diagnosis despite multiple thoracentesis. Positron emission tomography–computed tomography (PET-CT) was performed that showed nodular pleural lesions in the left hemithorax with low level fluorodeoxyglucose (FDG) uptake not amenable to CT guided biopsy. Pleuroscopy allowed for direct visualization of the nodules and a diagnosis of non-Hodgkin lymphoma was obtained with forceps and cryoprobe biopsy. Pleuroscopy is minimally invasive with high diagnostic yield and should be considered early in the setting of abnormal pleura and recurrent pleural effusions that is lymphocytic predominant despite negative cytology.

Introduction
Kidney transplant recipients are at increased risk of malignancy compared to age and gender matched populations [1]. The appearance of a new pleural effusion raises concern for a malignant etiology in the setting of ongoing immunosuppression. In cases of an undiagnosed pleural effusion after thoracentesis, pleuroscopy can be used to obtain a tissue diagnosis in a minimally invasive manner [2].

Case Presentation
An 80-year-old female presented to the emergency department with progressive dyspnea on exertion and lower extremity edema. She has a past medical history significant for monoclonal gammopathy of undetermined significance and a kidney transplant 12-years prior maintained on tacrolimus, azathioprine, and prednisone. Chest X-ray obtained showed moderate left-sided pleural effusion and cardiomegaly and she was admitted for further workup. She denied any fevers, chills, cough, or chest pain. Echocardiogram was completed which showed large pericardial effusion with right ventricular diastolic collapse and pericardiocentesis was completed with 1850 mL straw-colored fluid removed. Pericardial drain was left in place. Due to ongoing high drain output, pericardial window was completed 3 days later. Culture and cytology from the pericardial fluid returned negative. Biopsy of the pericardium taken at the time of the pericardial window showed fibrosis without evidence of malignancy. Thoracentesis was also performed during the admission with 600 mL of amber-colored fluid removed from the left chest. Pleural fluid showed 88 white blood cells with 42% lymphocytes, glucose of 96 mg/dL, lactate dehydrogenase of 127 U/L (serum lactate dehydrogenase of 194 U/L), and total protein of 5.0 g/dL (serum total protein of 6.9 g/dL). Cultures were negative. Cytology showed abundant small mature lymphocytes which was not definitive for a malignancy. Her dyspnea improved and she was discharged home.

Three months later, she was found to have reaccumulation of a large left-sided pleural effusion on a follow-up echocardiogram. She underwent repeat thoracentesis with 1550 mL amber-colored fluid drained. The pleural fluid showed 2051/uL white blood cells with 85% lymphocytes. Remainder of pleural studies were similar to previous pleural fluid results. Culture was negative and cytology again showed marked lymphocytic infiltrate but no definite evidence for neoplasm. She was symptomatically improved, but presented again one month later with dyspnea and reaccumulation of her left-sided pleural effusion. A repeat thoracentesis was performed, and 2100 mL of amber-colored fluid was removed. Pleural studies were similar to previous. Over the same time-frame, she also underwent two additional pericardiocenteses for reaccumulation of pericardial effusion.

She was evaluated in pulmonary clinic 2 weeks later and repeat thoracentesis was ordered with flow cytometry. During the thoracentesis, 1700 mL was removed and flow cytometry showed kappa-monotypic CD19 positive B cells and plasma cells. She was referred to oncology and underwent bone marrow biopsy and PET-CT scan. Bone marrow biopsy showed minimal involvement by monotypic B-lineage cell population. PET-CT scan showed nodular thickening of the pleura in the left hemithorax with associated low level FDG uptake. She was referred to interventional pulmonary for pleural biopsy and pleuroscopy.

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management of her recurrent pleural effusion. A CT-guided biopsy was considered, but after consulting with interventional radiology, a clear target for biopsy could not be identified with certainty. Therefore, medical pleuroscopy and placement of a tunneled pleural catheter (PleurX, Becton Dickinson, Franklin Lakes, NJ) was considered as the best approach.

On the day of the procedure, the patient was prepped using sterile technique. She was positioned in a right lateral decubitus position and ultrasound confirmed presence of pleural fluid. The skin and dermal layers were anesthetized with 1% lidocaine. A 1.5 cm horizontal incision was made with a #10 scalpel and then dissected to the intercostal muscle with a curved Kelly forcep. Once the intercostal margin was identified, the curved Kelly forcep was used to puncture through. The fenestration was widened with digital exploration and the flexible trochar was introduced. The pleuroscope (LTF 160/240, Olympus) was introduced through the trochar and landmarks were identified including diaphragm, chest cavity, mediastinum and lung apex. After some exploration, we identified abnormal lesions in the parietal pleura. We introduced a flexible forcep and collected samples with maximal diameter of 0.2 mm. Given concern for lymphoma, larger samples were required therefore we proceeded to perform biopsies using the 1.9 mm cryoprobe (ERBE USA). Using the cryoprobe, we were able to obtain samples as large as 6 mm in diameter. A total of 5 tissue samples were collected and sent to pathology. Prior to closing, the PleurX was placed using established methodology. She was later discharged to home that day without any complications. Pleural biopsy showed low grade B-cell lymphoma with plasmacytic differentiation (Figure 1). Epstein Barr virus was negative by in situ hybridization. Given her recurrent pleural and pericardial effusion, treatment was recommended, and she was started on rituximab.

Figure 1. Pleuroscopic view and biopsies of the pleural lymphoma. A) Gross view the left parietal with abnormal nodular lesions on the pleural surface. B) Cryoprobe biopsy of the pleural based nodular lesions. A 2.4 mm ERBR Cryoprobe used to freeze and remove the nodular lesions. C) Low power photo (4X): Hypercellular infiltrate of small round blue cells, and concerning for neoplasm at this magnification. D) High power (50X): The cellular infiltrate is composed of uniform population of lymphocytes which have monotonous appearance of small mature lymphocytes and plasma which are cytologically bland.

Discussion

Risk of cancer is higher in kidney transplant recipients (KTR) compared to age and gender matched populations, due in part to the use of immunosuppressive drugs [1]. It is controversial though whether cancer mortality in KTRs are higher than the general population with studies showing both no difference or increased risk of cancer death [2,3]. The cancers with the highest relative risk of developing in this population include Kaposi’s sarcoma, non-Hodgkin lymphoma, and cancers of the anogenital track. In regards to non-Hodgkin lymphoma (NHL), there is greater than an 8-fold risk in KTRs with the highest incidence occurring after the first year post-transplant, but there remains a steady increase over the next 10 years [1,4]. Intrathoracic involvement in NHL is common, with the most common manifestation being mediastinal lymphadenopathy, which was not present in this case. Over the course of the disease, 24% of patients with NHL will develop parenchymal involvement and 16% will have a pleural effusion, of which one cause is direct pleural involvement by tumor with cells shed into the pleural space. In NHL, if a pleural effusion is present, then 90% will have evidence of disease elsewhere. Pleural effusions may be bilateral and may be more common on the left side. They are typically exudates with normal glucose levels, and occasionally may be chylous. Thoracentesis results in a positive cytological diagnosis in 60-90% of patients with NHL and the presence of a pleural effusion portends a poor overall prognosis [5,6].

The results of the flow cytometry in this case raised concern for post-transplant lymphoproliferative disorder (PTLD), and combined with the nodular pleural findings on PET CT scan, further workup with pleuroscopy was pursued in this case. PTLD is a recognized complication of allogeneic and hematopoietic stem cell transplantation as well as solid organ transplantation. PTLD is associated with Epstein-Barr virus (EBV), due to reactivation or primary infection [8]. In a single center study in Korea, of their 3305 kidney transplant cases, only 24 cases were diagnosed with PTLD (0.72%), 9 within 2 years of transplantation. Over the same time frame, there were also 24 cases of lymphoma [9]. Another study in British Columbia found a 1.7% incidence of PTLD with primary sites including lymph nodes, peritoneum, liver, small intestine, cecum, tonsil, and vertebrae. No thoracic involvement was found [10]. In a case series specifically looking for thoracic cases of PTLD, no pleural involvement was found [11]. Given the location of the biopsy result and the negative EBV in situ hybridization, a diagnosis of NHL was made rather than PTLD.

In our case, the final diagnosis was obtained with the use of medical pleuroscopy (Figure 2). While the cytology from the multiple thoracenteses showed an abundance of lymphocytes, this was not a definitive diagnosis. Pleuroscopy, first used more than 100-years ago to explore and lyse pleural adhesions in pleural tuberculosis patients, had advanced to become a useful tool in diagnosing the etiology of pleural effusions. The diagnostic sensitivity is almost 95% in a study comparing the use of pleuroscopy vs CT-guided needle biopsy [12]. In a study specifically looking at the diagnosis of malignant pleural effusion in patients with NHL, pleural biopsy via pleuroscopy achieved a definitive diagnosis in 9 out of 10 patients [13]. Pleuroscopy is minimally invasive and can be performed in an endoscopy suite under local anesthesia or conscious sedation and done with either rigid or semi-rigid instruments, by one or two ports of entry. It allows for
inspection of the entire pleural cavity, lysis of adhesions, and direct visualization of biopsy site [2]. In our case, a cryoprobe was used in addition to forceps. Cryobiopsy utilizes a blunt probe cooled by nitrous oxide that draws moisture out of tissue and freezes it to the probe, reducing crush artifact and obtaining larger specimens in comparison to forceps biopsy. Previous studies have shown that use of cryoprobe with pleuroscopy is safe and does not increase bleeding, but there have been a few reports of chest pain after the procedure. Given the small sample size in these studies, it is not known if diagnostic yield from cryobiopsy is superior to forceps biopsy [14-16]. However, larger samples with preservation of architecture for review, ultimately, allowed for a definitive diagnosis in this case.

### Figure 2. A) Pleuroscope (LTF 160/240, Olympus) with flexible trochar. B) 2.4mm ERBE Cryoprobe demonstrating iced balloon formation during activation.

Our case report demonstrates the diagnostic benefit of using pleuroscopy for a diagnosis of pleural lymphoma that could not be identified despite multiple thoracenteses. It is possible that the use of cryobiopsy with pleuroscopy increases diagnostic yield for malignant conditions, but further studies will have to be done to answer this question. Pleuroscopy should be considered as a tool in the diagnosis of recurrent pleural effusions especially when fluid analysis is lymphocytic predominant and there is evidence of pleural abnormality.

### Conflicts of Interest

There are no conflicts of interest or funding support to disclose.

### References