Elevated circulating cell free DNA in lung transplant: Beyond infection and rejection

Alonso Marquez[1], Stephen Dachert[1], Zehra Dhanani[1], Fatima Anjum[1,2]

1 Pulmonary and Critical Care Medicine, Temple University, Philadelphia, PA, United States; 2 Thoracic Medicine and Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, United States

Introduction

Lung transplantation remains the definitive treatment for patients with end-stage lung diseases. Recently, cell-free DNA (cfDNA), which consists of fragments of DNA released into the bloodstream due to cell death, has gained significant attention as a promising biomarker for the early detection of allograft injury. First introduced by Mandel and Metais in 1948, cfDNA's clinical utility became more apparent in the late 20th century, particularly in oncology and prenatal diagnostics.

In the context of organ transplantation, cfDNA was first proposed as a biomarker for transplant rejection in the early 2000s. Traditionally, elevated cfDNA levels, typically considered abnormal when they exceed 1% to 1.5% of total DNA, have been associated with acute rejection or infection. However, this case suggests that elevated cfDNA can also arise from non-immune or non-infectious causes, such as primary graft dysfunction or procedural trauma. This underscores the importance of understanding the broader spectrum of factors influencing cfDNA levels to optimize post-transplant care and avoid unnecessary interventions.

Methods

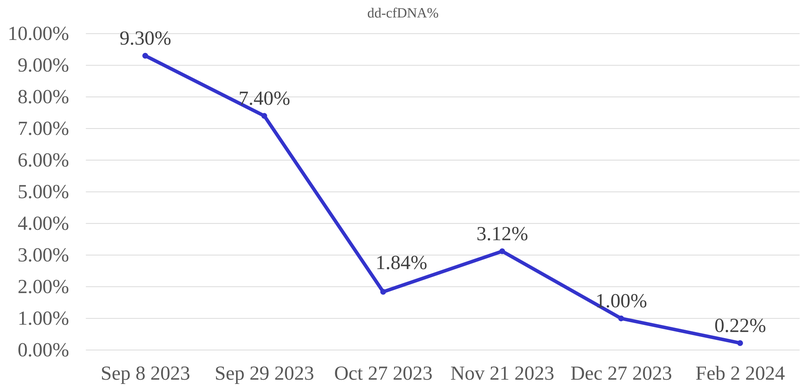
A retrospective review was performed on the described patient to obtain clinical, radiographic, and treatment data.

Results

A 42-year-old patient diagnosed with interstitial lung disease with autoimmune features in 2016 initially responded to treatment with nintedanib and mycophenolate, but the condition progressively worsened. In June 2023, the patient underwent a left lung transplant. The postoperative course was complicated by severe primary graft dysfunction (PGD), requiring extracorporeal membrane oxygenation (ECMO) and renal replacement therapy. After several weeks, the patient was discharged in stable condition on immunosuppressive and prophylactic therapy.

Results

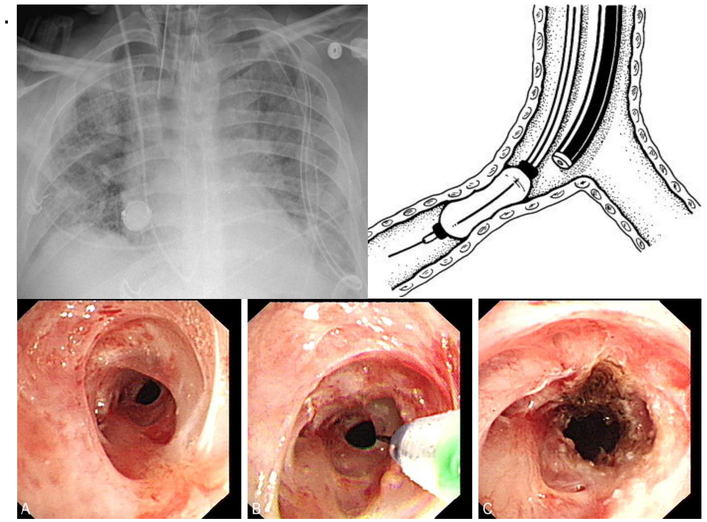
In September 2023, routine monitoring revealed elevated cell-free DNA (cfDNA) levels at 9.3%. A bronchoscopy with transbronchial biopsy and bronchoalveolar lavage showed no signs of acute cellular rejection or infection. Despite the unexplained elevation, cfDNA levels were rechecked, showing a decline to 7.40% on October 8, 2023, and further to 1.84% on November 8, 2023. In early November 2023, the patient was readmitted with worsening dyspnea and new-onset stridor. A CT scan revealed moderate narrowing at the distal left bronchial anastomotic site, with bronchoscopy identifying granulation tissue obstructing the left main stem bronchus.



Treatment involved argon plasma coagulation (APC) and balloon dilation. However, cfDNA levels rose again to 3.12% on November 21, 2023, still without evidence of rejection or infection.

In late November 2023, the patient experienced respiratory distress due to recurrent bronchial stenosis, necessitating multiple bronchoscopy procedures with balloon dilations. Subsequent cfDNA measurements showed a decline to 1.00% on December 27, 2023, and further to 0.22% on February 1, 2024.

Results



Conclusion

In this case study, we propose that elevated levels of cfDNA in the context of lung transplantation may not necessarily signify acute rejection or infection, traditionally considered the primary culprits. It underscores the crucial need to consider alternative etiologies, such as severe primary graft dysfunction and procedural trauma from interventional procedures such as APC. In conclusion, this report aims to expand our comprehension of factors affecting cfDNA levels in lung transplant recipients, highlighting the importance of differential diagnosis. A precise interpretation of cfDNA elevations is critical to avoid superfluous interventions and treatments that may escalate healthcare costs and morbidity.

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