Voriconazole-induced periostitis in a lung transplant recipient

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Abstract:
Lung transplantation is a viable option for end-stage lung diseases. However, it comes with numerous complications that may lead to various morbidities due to surgical procedures, rejections, and medical treatments. Fungal infection is a common complication of immunosuppressive treatment. On the fifteenth postoperative day, bronchoscopy of a female recipient, who had undergone bilateral sequential lung transplantation for bronchiectasis, revealed an appearance consistent with aspergillus pseudomembranes around the left bronchial anastomosis. After microbiologically confirming the diagnosis, systemic voriconazole treatment was initiated. The recipient made it through the first three months of treatment without complications. However, since the membranes did not fully resolved, the decision was made to extend the treatment. From the fourth month of treatment, the recipient began experiencing generalized pain. Subsequent examinations revealed diffuse periostitis in the bones. After consultations and evaluations with relevant departments, other differential diagnoses were ruled out, leading to a diagnosis of voriconazole-induced periostitis. This diagnosis was further confirmed when symptoms improved three days after discontinuing the drug. Clinicians should be alert to this potential complication and correlate it with the clinical history of solid organ transplantation to avoid unnecessary investigations.

Keywords:
Antifungal drugs, bone pain, infectious diseases, lung transplantation, periostitis, radiodiagnostics, tracheobronchial aspergillosis

Introduction
Solid-organ transplantation (SOT) presents significant morbidity and mortality challenges due to both surgical complications and long-term medical issues. Lung transplant (LuTx) recipients are subjected to higher levels of immunosuppressive drugs, given the elevated risk of rejection post-LuTx compared to other SOTs. Consequently, opportunistic infections are more prevalent post-LuTx than post other SOTs.[1] This report presents a case of periostitis resulting from systemic voriconazole treatment in a recipient diagnosed with tracheobronchial aspergillosis after lung transplantation.
Case Report

A 44-year-old female underwent bilateral sequential lung transplantation (LuTx) for bronchiectasis. Post-operative immunosuppressive therapy was initiated with basiliximab induction, followed by triple immunosuppressant therapy with tacrolimus, mycophenolate mofetil (MMF), and methylprednisolone. On the 15th day post-transplant, a surveillance bronchoscopy revealed pseudomembrane formation in the left bronchial anastomosis area, suggestive of tracheobronchial aspergillosis. Bronchoalveolar lavage (BAL) fluid samples tested positive for *Aspergillus fumigatus* via polymerase chain reaction (PCR). A chest computed tomography scan found no cavities or nodules. The patient was treated with voriconazole (Viend®, Pfizer; 200 mg orally twice daily). Following a successful post-operative recovery, she was discharged on the 33rd day. However, a bronchoscopy in the third month post-transplant showed persistent pseudomembrane formation, prompting an extension of the voriconazole therapy. By the fourth month, the patient reported generalized pain across the chest and both upper and lower extremities, although her range of motion remained unaffected. Apart from elevated levels of sedimentation, C-reactive protein, and alkaline phosphatase (ALP) – which were previously within normal range – no other clinical or laboratory findings indicated potential drug side effects. Other liver and kidney function returned normal results. Hemogram analysis showed hypochromic anemia, indicative of iron deficiency (Hemoglobin 10.4 g/dL, hemocrit 31.3%, mean corpuscular volume 76.7 fl, mean corpuscular hemoglobin 24.8 pg/cell, mean corpuscular hemoglobin concentration 28.5 g/dL, platelets: 181,000). Consultations with rheumatology, endocrinology, and orthopedics identified no specific pathology. Bone scintigraphy revealed diffuse periostitis reminiscent of metastases [Fig. 1]. Suspecting this might be a side effect of voriconazole, the treatment was halted. The patient's symptoms subsided within three days of discontinuation, thereby confirming the diagnosis of voriconazole-induced periostitis. A surveillance bronchoscopy to evaluate the anastomoses revealed full improvement of the pseudomembranes, and the PCR for *A. fumigatus* was negative. Therefore, no further antifungal therapy was applied. Blood biochemical parameters also normalized in the days that followed. Six months after stopping voriconazole, a bone scintigraphy showed complete resolution [Fig. 2].

On the 14th month post-transplant, the recipient experienced an acute cellular rejection episode, which was successfully treated with pulse steroid therapy (1000 mg/day methylprednisolone for three days, then 1 mg/kg/day, with the dose halved weekly until a maintenance dose of 5 mg/day prednisolone was established). She is now in her 48th post-operative month, exhibiting chronic rejection symptoms and signs.

Discussion

After lung transplantation, recipients encounter various complications, including metabolic diseases, drug side effects, immunosuppression-related infections, and malignancies. *Aspergillus* infection, an opportunistic pathogen, can particularly affect LuTx recipients. Several studies report that approximately 15% of lung transplant recipients experience *aspergillus* infections, with a mortality rate between 50-100%. Aspergillus infections are more prevalent in LuTx recipients than in other SOTs due to heightened immunosuppression, compromised mucociliary clearance and cough reflex, frequent colonization resulting...
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from the primary pulmonary condition, and constant exposure to external environmental factors. Voriconazole is a preferred treatment option given its efficacy against both *aspergillus spp.* and *Candida spp.* The most common side effects of voriconazole include transient visual disturbances, rash, and elevations in hepatic transaminases. Periostitis is a very rare complication of this drug and can be challenging to diagnose. Fluoride, a major component of voriconazole, is believed to play a central role in the pathophysiology of periostitis. Long-term use of voriconazole seems to be the primary risk factor for skeletal fluorosis. Voriconazole-induced periostitis (VIP) manifests as diffuse body pain and swelling, elevated serum ALP and fluoride levels, periosteal reaction evident on radiographs, and multiple areas of technetium uptake on bone scintigraphy resembling metastases.

Wang et al. documented five VIP cases affecting the radius, ulna, tibia, and femur. Chen et. al observed that the central and proximal parts of long bones were primarily affected in their VIP cases. Similarly, in our patient, the pathologies were predominantly located in the central parts of the body, such as the ribs, sternum, scapula, acetabulum, and bilaterally in the upper and lower extremity bones. Historically, patients with VIP developed clinical symptoms between six weeks to three years after starting voriconazole, with a median onset time of six months. Our patient’s symptoms appeared in the fourth month of therapy.

Notably, as in previously reported cases, our patient exhibited a marked elevation of ALP, which likely served as a pivotal clue in diagnosing VIP. In patients with a known drug history, an elevated blood ALP level combined with generalized body pain could suggest VIP.

In this instance, the voriconazole trough level was not evaluated. Assessing blood drug levels could be invaluable in elucidating the relationship between VIP and dosage. However, prior studies on this topic suggest that VIP manifestations are independent of voriconazole levels.

Consistent with all previously reported VIP cases, our patient’s symptoms resolved rapidly and completely within three days of discontinuing voriconazole.

SOT remains a successful treatment option for end-stage organ failure, with survival rates rising in recent years. Advances in surgical techniques, medical procedures, immunosuppressive drugs, and antimicrobial medications have contributed to this success. However, every medical intervention carries potential metabolic, chemical, and functional side effects that warrant caution. It is crucial to monitor transplant recipients not only for graft function but also for medical complications and side effects of all concurrent medications.

**Informed Consent**
Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

**Conflicts of interest**
There are no conflicts of interest.

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Authorship Contributions

References