Case report

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Voriconazole induced Stevens-Johnson syndrome: a case report

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ABSTRACT

Stevens-Johnson syndrome is a life-threatening skin disorder which is known to occur associated with a variety of medications. One of these classes of medications is antifungals and the mechanism is known to be mediated through altering gene expression of cytochrome P450 (CYP) 26 isoforms. To the best of our knowledge, this is the first reported case of Stevens-Johnson syndrome induced by voriconazole.

Key words: *Stevens-Johnson syndrome, voriconazole, antifungal.*

RESUMEN

El síndrome de Stevens-Johnson es un trastorno cutáneo potencialmente mortal que se sabe que está asociado con una variedad de medicamentos. Una de estas clases de medicamentos son los antifúngicos y se sabe que el mecanismo es mediado a través de la alteración de la expresión génica de las isoformas del citocromo P450 (CYP) 26. Hasta donde sabemos, éste es el primer caso reportado de síndrome de Stevens-Johnson inducido por voriconazol.

Palabras clave: *Síndrome de Stevens-Johnson, voriconazol, antifúngico.*

INTRODUCTION

Stevens-Johnson syndrome (SJS) is a rare severe adverse cutaneous drug reaction involving the skin and mucous membranes. The incidence is less than 2-6 cases per million people per year. It has a mortality rate of 1-5% and is considered a medical emergency. Pharmaceuticals account for the vast majority of cases, but cases from *Mycoplasma pneumoniae* and herpes simplex virus infections have been reported, as well as bone marrow transplants, and certain vaccinations, including smallpox, anthrax, and tetanus.[1] The most commonly associated drugs are anticonvulsants, sulfonamides, other antibiotics, nonsteroidal anti-inflammatory drugs, retinioids, antifungals, antimalarials, and allopurinol. There is also genetic susceptibility. Diagnosis is made based on clinical signs combined with the histological analysis of skin biopsies which reveal typical full-thickness epidermal necrolysis due to extensive keratinocyte apoptosis. Differential diagnosis includes linear IgA dermatosis and paraneoplastic pemphigus, pemphigus vulgaris and bullous pemphigoid, acute generalized exanthematous pustulosis, disseminated fixed bullous drug eruption and Staphylococcal scalded skin syndrome. Treatment is based on identification and discontinuation of the causative drug, supportive care in an intensive care unit, and consideration of immunomodulating agents such as high-dose intravenous immunoglobulin therapy.[2]

CASE REPORT

A 51-year-old caucasian female with a history of pulmonary aspergillosis infection presented to the Emergency Department as directed by her pulmonologist for severe hemoptysis and worsening clinical presentation. The patient had a significant pulmonary history including three episodes of right pneumothorax, pleurodesis in 2003 with complication of *Mycobacterium avium* complex infection,

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and right lobectomy with removal of rib six in 2008. The patient suffered from chronic, recurrent pulmonary infections including pseudomonas, staphylococcus, and streptococcus which were previously treated with cefixime. Once diagnosed with pulmonary aspergillosis, voriconazole treatment was initiated to which she developed Steven-Johnson syndrome. Chest X-ray demonstrates the right apical cavitary lesion consistent with the aspergillosis infection and associated pulmonary aspergilloma «Fungus Ball» (Figure 1). Chest CT scan with contrast further revealed the right cavitary mass with right paratracheal lymph node enlargement, consistent with fungal mass and infection (Figure 1). On a subsequent admission, she was successfully treated for this fungal infection with micafungin with no observed adverse reaction.

DISCUSSION

Fungal infections remain a significant cause of morbidity and mortality despite advances in medicine and the emergence of new antifungal agents. Immunocompromised patients are particularly at risk of developing these infections. These can be severe and Aspergillosis carries a 100% mortality rate if left untreated. Historically, amphotericin B has been the drug of choice for the treatment of systemic infections caused by *Aspergillus* and *Candida spp*. However, the high incidence of toxicity associated with amphotericin B had limited its use in many patients. Fluconazole and itraconazole are triazole antifungal agents used in the treatment of fungal infections. They have both intravenous and oral formulations and favorable safety profiles. However, the triazoles' spectrum of activity is somewhat limited. Fluconazole is active mainly against *Candida albicans* and *Cryptococcus neoformans*. Itraconazole is most active against *Aspergillus spp.* and has greater activity than fluconazole against resistant strains of *Candida spp.* other than *C. albicans*.[3]

Voriconazole is the most recent pharmaceutical agent for use against fungal infections. It is a triazole antifungal with a structure related to that of fluconazole and a spectrum of activity comparable to that of itraconazole. Voriconazole was approved by the Food and Drug Administration in May 2002 for the treatment of invasive

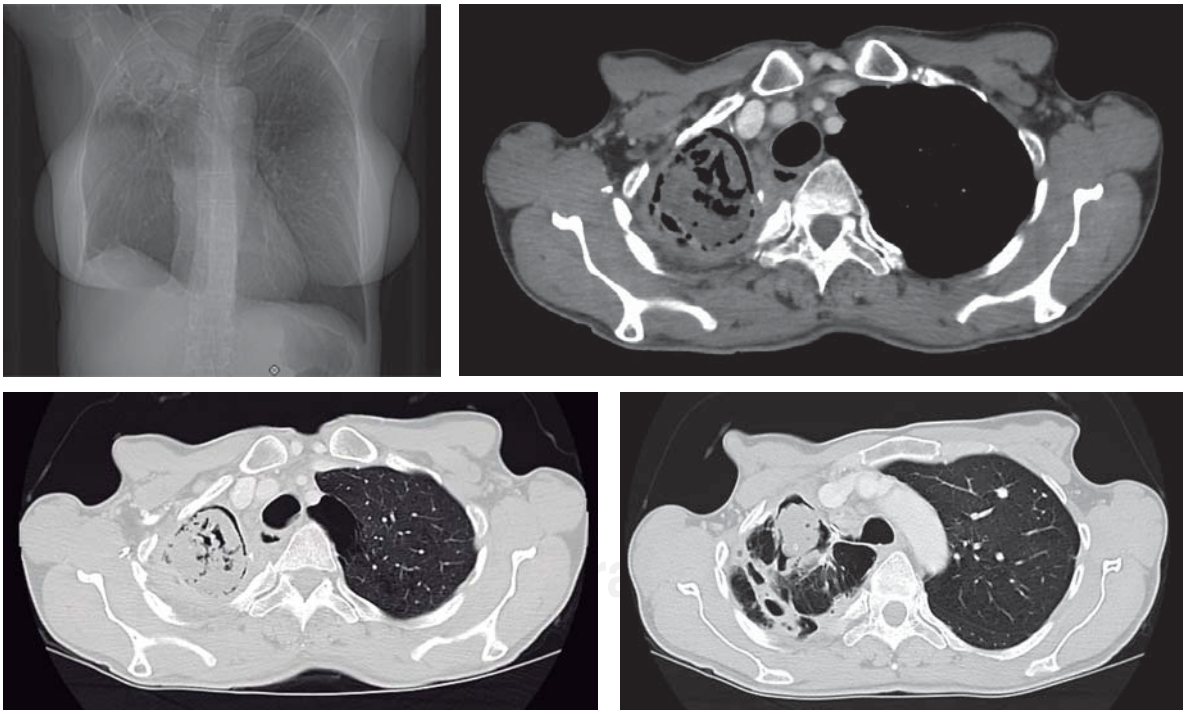

Figure 1. *Anterior-posterior chest radiograph shows evidence of right apical cavitary lesion (top left) and chest CT with contrast demonstrates emphysematous changes of the lung parenchyma with multiple calcified granulomas scattered throughout bilaterally, large cavitary lesion filled with low attenuation opacity within right apex measuring up to 6.3 × 4.7 × 6.6 cm with adjacent pleural thickening, and an enlarged mediastinal lymph node in right paratracheal stripe measuring 1.8 × 1.1 cm (top right, bottom left, bottom right).*

aspergillosis and refractory infections of *Scedosporium apiospermum* and *Fusarium spp*. This was the first broad spectrum antifungal with an acceptable safety profile that is available in both intravenous and oral formulations. Like the other triazole antifungals, voriconazole exerts its antifungal activity by inhibition of 14-alpha-lanosterol demethylation, which is mediated by fungal cytochrome P450 enzymes. It is generally well tolerated, with visual disturbances, fever, rash, hepatic abnormalities, nausea, vomiting, abdominal pain, and headache being the most commonly reported adverse effects.[3]

Antifungal agents include the azoles of fluconazole, itraconazole, ketoconazole, miconazole, posaconazole, and voriconazole and the echinocandins ofanidulafungin, caspofungin, and micafungin.[4] All antifungals have on effects on cytochrome P450 enzymes. SJS induced by antifungals has been determined to be mediated through alteration of gene expression of cytochrome P450 (CYP) 26 isoforms.[1] However, the pathophysiology is incompletely understood. Three pathogenic mechanisms causative of drug adverse reactions are considered to exist: immune, non-immune and idiosyncratic mechanisms. Non-immune mechanisms include drug adverse effects (e.g., mucositis with chemotherapeutic agents), cumulative effects (e.g., hepatic toxicity with methotrexate), and the effect of delayed toxicity, drug interactions and drug metabolism alterations.[5]

SJS as a consequence of Voriconazole treatment has not been independently reported previously. However, it has been mentioned as a concern in a few reports that detailed all potential side effects with comments on dermatologic manifestations.[6-8] A detailed analysis of these reports reveals that there has been a single case in the world's literature, and this case was on combined therapy.[9] In this report, the patient was simultaneously treated with antileukemic therapy (Phase IIB) and Voriconazole was given as secondary prophylaxis. This case of SJS was more likely related to antileukemic therapy than Voriconazole since there has been over 46 SJS and 37 Toxic epidermal necrolysis (TEN) cases associated with 18 and 22 anticancer drugs in the literature.[10]

On the contrary two cases of TEN have been reported with voriconazole.[11,12] Both TEN and SJS are rare but severe adverse cutaneous drug reactions that predominantly involve the skin and mucous membranes. They are characterized by mucocutaneous tenderness and typically hemorrhagic erosions, erythema and more or less severe epidermal detachment presenting as blisters and areas of denuded skin. Currently, TEN and SJS are considered to be separate conditions of two ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions.[2]

CONCLUSION

The severity of TEN is much greater than SJS and incidence of both remain low. While the pathophysiology is incompletely understood it is clear that medications in the same class share risk. Because of the serious life-threatening consequences, it is important that clinicians are aware of the presentation, diagnostic criteria, and treatment options.

Conflicts of interest: None.

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