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NET induced by fluconazole in an HIV-positive patient

Net induzida por fluconazol em paciente HIV positivo

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ABSTRACT

Toxic Epidermal Necrolysis (TEN) is a rare disease that was first described in 1956 by Lyell.l Its incidence is around 0.4 to 2 cases per 1 million people per year (LEWERENZ, V. et al., 2006) (DE MENDOZA-SABILLÓN et al., 2017). Although rare, it has a significant mortality, reaching 25% in adults. It is characterized by peeling of the skin, erythema, necrosis and the formation of easily displacement blisters both on the skin and mucous membranes. Symptoms also include body aches, fever, chills, cough and keratoconjunctivitis. The lesions may also be localized in the respiratory, digestive, and urinary tracts, but less frequently.

Keywords: Toxic Epidermal Necrolysis, HIV, Skin lesions.

1 INTRODUCTION

Toxic Epidermal Necrolysis (TEN) is a rare disease that was first described in 1956 by Lyell.l Its incidence is around 0.4 to 2 cases per 1 million people per year (LEWERENZ, V. et al., 2006) (DE MENDOZA-SABILLÓN et al., 2017). Although rare, it has a significant mortality, reaching 25% in adults. It is characterized by peeling of the skin, erythema, necrosis and the formation of easily displacement blisters both on the skin and mucous membranes. Symptoms also include body aches, fever, chills, cough and keratoconjunctivitis. The lesions may also be localized in the respiratory, digestive, and urinary tracts, but less frequently (POR, J.; BENEDETTI., 2023) (TSENG, J.; MAURER, T.; MUTIZWA, M. M., 2015) , (TSENG, J.; MAURER, T.; MUTIZWA, M. M., 2016).

An important differential diagnosis of NET is Stevens-Johnson Syndrome (SSJ), which also presents cutaneous, mucosal and systemic involvement. What differentiates the two diseases is the extension of the skin lesions, because while in the SSJ the involvement is less than 10%, in the NET its extension is greater, characterized by more than 30% (MONASTIRLI, A. et al., 2008) (OFOMA, U. R.; CHAPNICK, E. K., 2009) (GEORGE, J. et al., 2012) (TSENG, J.; MAURER, T.; MUTIZWA, M. M., 2016) (ISLAM, S.; SINGER, M.; KULHANJIAN, J., 2014). Both are considered severe drug reactions by the World Health Organization (WHO), due to their need for hospitalization, their great morbidity and disability, and the threat to life (DE MENDOZA-SABILLÓN et al., 2017).

The most important cause of NET is medication, corresponding to up to 80% of cases. In this scenario, more than 100 drugs are involved, the main ones being the following: sulfonamides, allopurinol, phenytoin, phenobarbital, carbamazepine, lamotrigine, nonsteroidal anti-inflammatory drugs and nevirapine. A drug also involved in triggering the disease, however, less commonly is Fluconazole (DE MENDOZA-SABILLÓN et al., 2017) (ISLAM, S.; SINGER, M.; KULHANJIAN, J., 2014) (OFOMA, U. R.; CHAPNICK, E. K., 2009).

Fluconazole is a synthetic antifungal used mainly for the treatment of mycoses, including superficial and systemic infections caused by Candida, as well as some types of meningitis and, empirically, in patients with the Human Immunodeficiency Virus (HIV) in critical conditions. It is a medication that is usually well tolerated, including in children, with few adverse effects, but when they occur, the most common are nausea, headache, vomiting and mild gastrointestinal symptoms. Dermatological reactions caused by this substance are rare (AZON-MASOLIVER, A.; VILAPLANA, J., 1993) (GEORGE, J. et al., 2012) (MONASTIRLI, A. et al., 2008) (OFOMA, U. R.; CHAPNICK, E. K., 2009).

Patients with HIV are more susceptible to rare adverse drug reactions, including skin reactions. The risk of the incidence of NET in HIV carriers who use fluconazole increases by up to 1000 times, compared to the general population (AZON-MASOLIVER, A.; VILAPLANA, J., 1993) (ISLAM, S.; SINGER, M.; KULHANJIAN, J., 2014) (OFOMA, U. R.; CHAPNICK, E. K., 2009) (TSENG, J.; MAURER, T.; MUTIZWA, M. M., 2015).

2 OBJECTIVE

This article aims to report a rare case of NET in an HIV-positive patient due to the use of fluconazole.

3 METHODOLOGY

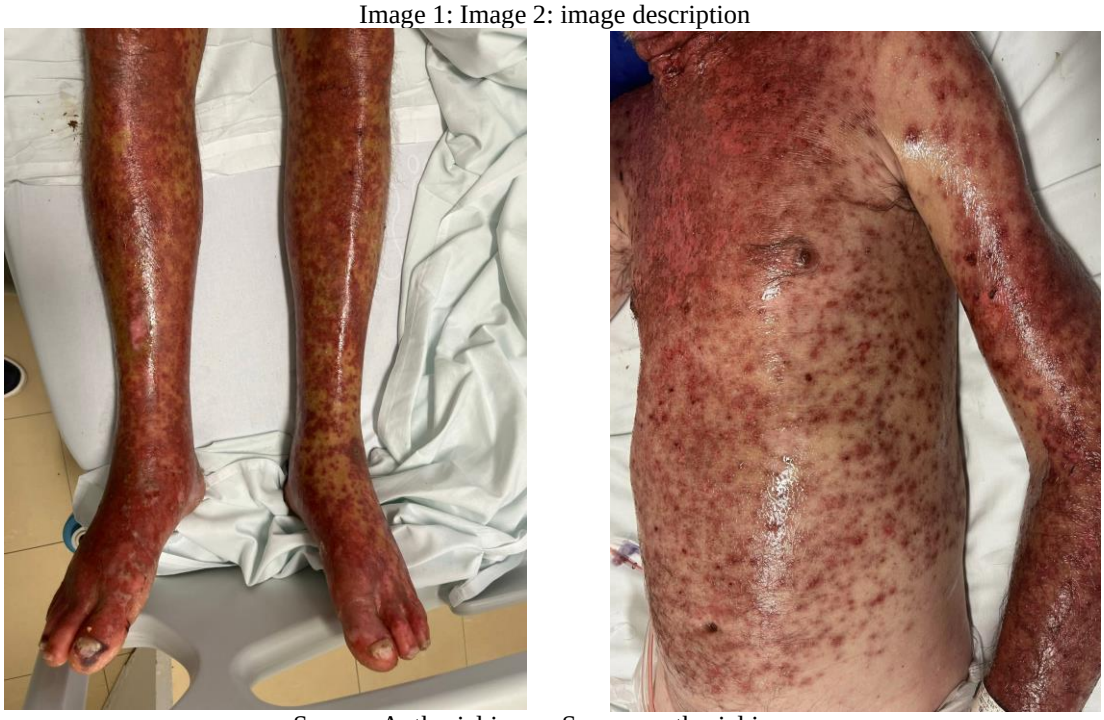
The information reported here was collected through a thorough review of medical records, interviews with the patient, photographs, complementary exams and literature review, for scientific basis, on the subject in the database National Library of Medicine (PubMed) e Biblioteca Virtual de Saúde (BVS).

4 CASE REPORT

Male patient, 53 years old, homeless, chronic drinker – ingestion of 3 liters of distillates per day, under follow-up at the CAPS, and carrier of the Human Immunodeficiency Virus (HIV) for 33 years, having ceased use of Antiretroviral Therapy (ART) for 1 year. In continuous use of Sertraline, Thiamine, Carbamazepine and Diazepam. He was admitted to the hospital medical service in a regular general condition, complaining of multiple papules and purpuric and painful plaques, initially on the trunk and face that progressed to the lower limbs and back, pruritus in the hands and feet, pain, hyperemia, and desquamation throughout the body, including in the external genitalia. In addition, he had significant asthenia, fever and general malaise.

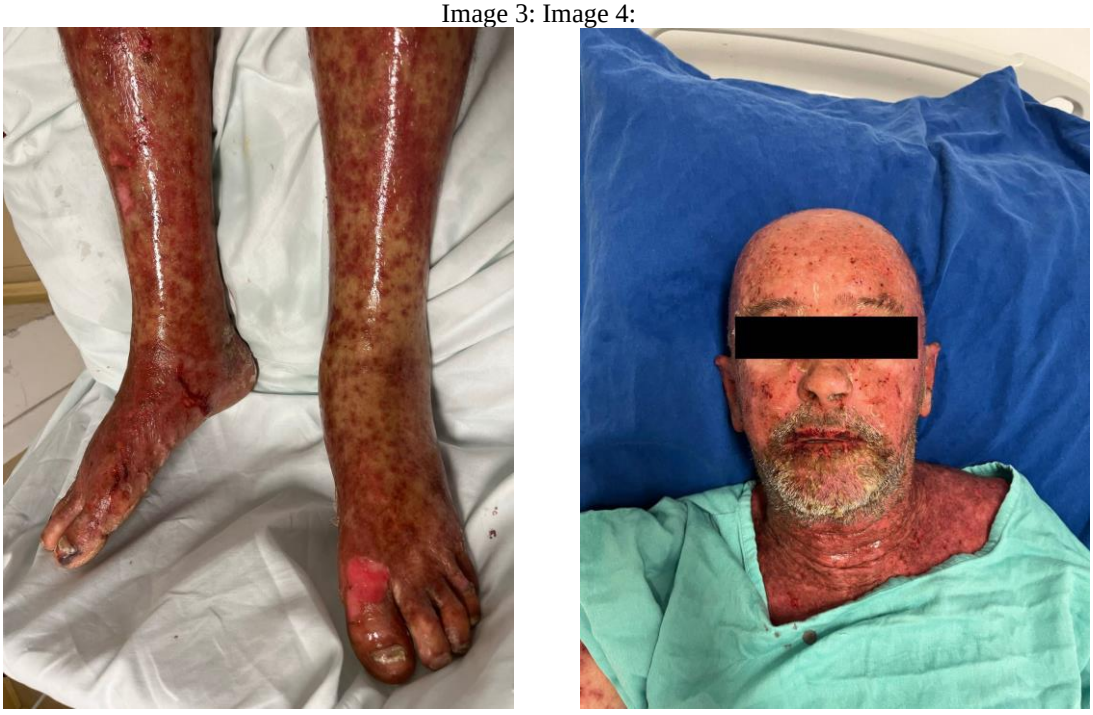
The condition started seven days after the use of fluconazole for the treatment of onychomycosis in the right foot. He was then admitted to a ward bed for treatment and support. In the days following hospitalization, the lesions spread and the papules evolved to blisters and areas of desquamative necrosis with involvement of about 70% of the body surface, including skin and mucosa. The images referring to the beginning of hospitalization are illustrated in Figures 1, 2, 3 and 4 and show classic signs of NET, such as target lesions and Nikolsky's sign, which corroborates the predisposition to secondary infections.

Image 1: Image 2: image description



Source: Authorial image Source: authorial image

Image 3: Image 4:



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Approximately 1 month after hospitalization, the diagnostic hypothesis of meningococcemia was raised, which was ruled out after lumbar puncture for anatomopathological study. After that, the diagnosis Toxic Epidermal Necrolysis (TEN) was established, analyzing the

clinical and epidemiological aspects of the patient. With the diagnosis established, supportive treatment and infectious surveillance were initiated.

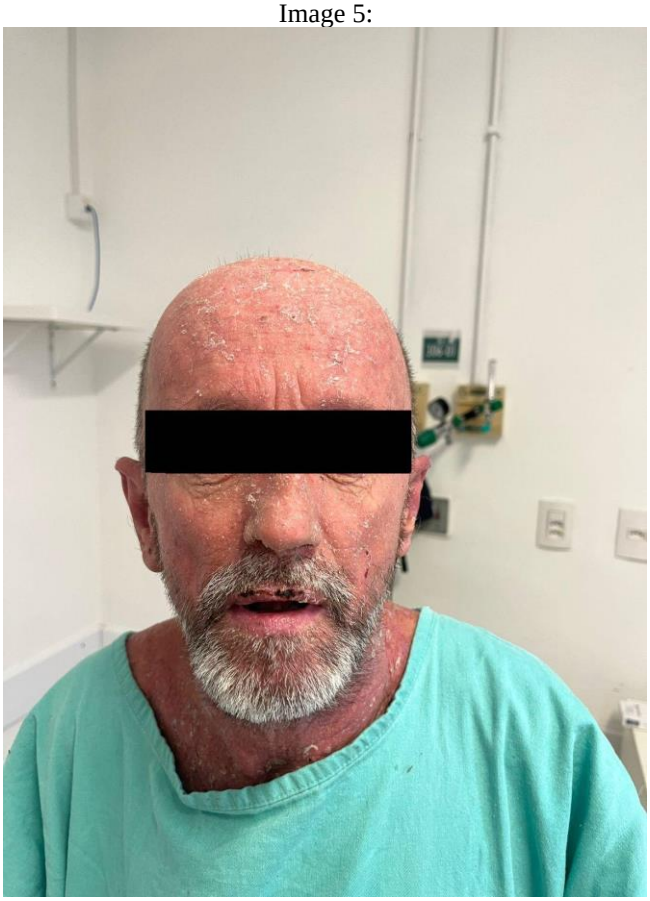
4.1 CONDUCT

The result of the blood culture performed at the beginning of hospitalization showed *Acinetobacter baumannii* (AB), leading to the start of antibiotic therapy, both by the finding of the exam and by the immunocompromise of the patient. To this end, he used the following antibiotics in sequence: Piperacillin-Tazobactam, Ceftriaxone and Imipenem, without therapeutic success, leading to the administration of the association of Meropenem, Ampi-Sulbactam and Polymyxin. After 15 days, a new blood culture was performed and showed no growth of microorganisms.

The patient was submitted to computed tomography (CT) of the chest without contrast, since the systemic picture of the main hypothesis may present with pneumocystosis, which showed: "Bilateral axillary lymph node enlargement and mediastinal lymph nodes in greater number than usual, some prominent, nonspecific. Discrete bilateral pulmonary opacities, which may be related to an inflammatory/infectious process." Cranial CT was also submitted to rule out a possibility of meningoencephalitis, which demonstrated "Slight degree of diffuse brain volume reduction", a result that corroborated the discarding of the hypothesis. Other complementary tests, collected at the beginning of therapy: Hemoglobin: 13.9g/dL; Hematocrit: 39.0%; Leukocytes: 3850/mm3; segmented: 68%; lymphocytes: 14%; platelets: 156000/mm3. Total bilirubin: 0.46mg/dL. CRP: 8.58mg/L. Potassium: 3.7mmol/l. Sodium: 134mmol/l. AST: 28U/L. ALT: 30U/L. Lactate dehydrogenase: 190U/L. Creatinine: 0.5mg/dL. Viral load prior to admission: 463,557 and CD4: 77.

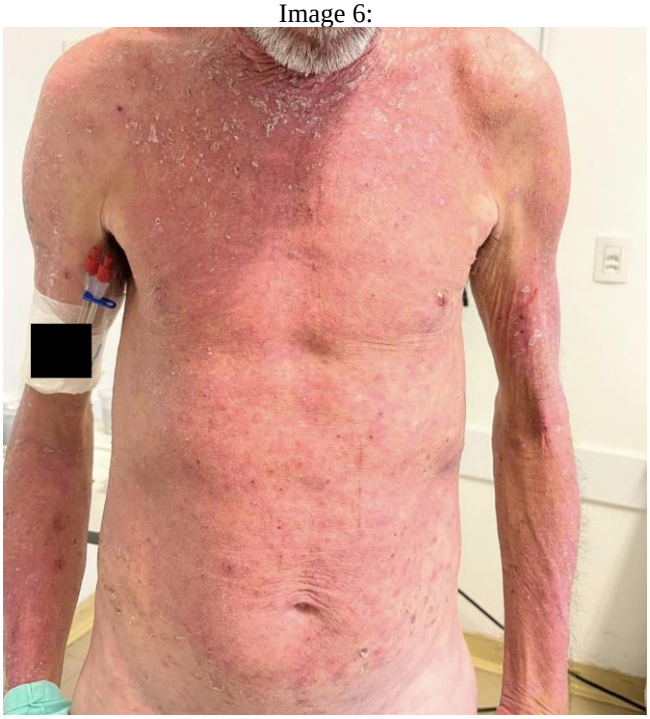
The remission of the disease occurred 28 days after the beginning of the aforementioned treatment, as can be seen in the images below:

Image 5:



Source: Copyright image

Image 6:



Source: Copyright image

5 DISCUSSION

The adverse reaction to a given drug is characterized as a harmful, unintentional response occurring after drug administration, either for prophylactic purposes or for treatment (OFOMA, U. R.; CHAPNICK, E. K., 2009).

The adverse skin reaction is considered as severe when the response due to the use of the drug causes changes in the structure and/or function of the skin, appendages or mucous membranes, which can cause hospitalization, disability and even death. Classic patterns of severe drug reactions include angioedema, exfoliative dermatitis, SSJ, and NET (OFOMA, U. R.; CHAPNICK, E. K., 2009).

While SSJ can be caused by medications and infections, NET is most often triggered by drugs. The pathophysiological mechanisms of both SSJ and NET are not yet properly understood, however, studies indicate that there is an alteration resulting from an innate or acquired defect in phase 2 of detoxification enzymes and in the growth of cytochrome P450 isoforms, which performs the processing of the drug responsible for the reactive metabolites. These metabolic peculiarities can lead to an increase in the levels of compounds that will serve as possible immunogens or cause a direct toxic effect on the cell (OFOMA, U. R.; CHAPNICK, E. K., 2009). In addition, it is believed that a T-cell-mediated response occurs, with activation of CD8+ T lymphocytes, leading to apoptosis of keratinocytes (LEWERENZ, V. et al., 2006).

HIV infection is a well-known risk factor for the development of SSJ and NET, however, although the immunological disorder is certainly involved, the exact mechanisms by which these patients present a greater predisposition are not clear (TSENG, J.; MAURER, T.; MUTIZWA, M. M., 2015).

However, the literature associates the increased incidence of TEN identified in patients with HIV/AIDS (Acquired Immunodeficiency Syndrome) with glutathione deficiency, an important detoxification pathway (OFOMA, U. R.; CHAPNICK, E. K., 2009). In addition, patients with HIV/AIDS have an increased number of abnormal B-cell polyclonalities that are improperly activated to secrete immunoglobulins, forming circulatory and autoimmune immune complexes. These mechanisms justify why HIV-infected patients are more susceptible to drug-induced NET. Therefore, in cases of NET by drugs, HIV infection needs to be ruled out always (GEORGE, J. et al., 2012).

In this sense, fluconazole acts as an inhibitor of cytochrome P450, especially in the isoenzymes CYP1A2, 2C19, 2C9 and 3A4 (AZON-MASOLIVER, A.; VILAPLANA, 1993). . In general, the adverse effects of fluconazole are hematological, neurological, metabolic, hepatic,

gastrointestinal, endocrine and cutaneous. However, the cutaneous effects usually presented are mild, such as pruritus, maculopapular eruptions, alopecia, exfoliative dermatitis, angioedema and purpura, unlike what occurred in the case of the reported patient, in which approximately 70% of the body surface was affected, with skin and mucosa involvement, characterized as NET, a rare complication after the use of fluconazole.

NET, in general, begins between one week and two months after the use of the drug, the most common being its occurrence in the first two weeks (LEWERENZ, V. et al., 2006). Therefore, it is proven in the case reported that TEN was induced by the use of fluconazole, because the patient began to present the lesions 7 days after its use. The hypothesis that NET was caused by carbamazepine, a drug that also presents itself as a triggering factor, was discarded, considering that long-term use never resulted in any adverse reaction.

In the treatment of NET there is no defined therapy, however, discontinuing the causative drug is an indispensable action. The support measures, in general, are the same as those offered to burn victims (hydration, correction of hydroelectrolytic disturbances, temperature control, monitoring of inflammatory parameters and treatment of secondary infections). There are controversies regarding the use of glucocorticosteroids, but some authors state that they can be used at the beginning of the disease, at first with a high dose, but with subsequent dose reduction (LEWERENZ, V. et al., 2006).

The broad-spectrum antibiotics administered to the patient were performed in order to treat the secondary infection by *Acinetobacter baumannii*, which affected him due to his high viral load and the cessation of ART. According to YANG, J. et al. 2018, immunosuppressed patients with severe underlying diseases, as well as undergoing invasive procedures and/or broad-spectrum antibiotics, are susceptible to AB infection.

NET is a disease that carries an increased risk for the development of sepsis, and for this reason, some immunosuppressive drugs such as cyclosporine A and cyclophosphamide can be administered under intensive medical care. In addition, there are reports of successful treatment with the use of plasmapheresis, hemofiltration and intravenous immunoglobulins (LEWERENZ, V. et al., 2006). In view of the case described, the patient did not use these medications, but obtained a positive outcome after discontinuation of fluconazole, supportive measures and treatment of the infection associated with the use of antibiotics.

6 CONCLUSION

In view of the case reported and the findings in the literature, TL induced by fluconazole is rare and its correlation with patients with HIV may be correlated with the hypothesis of glutathione deficiency and immune response to antigens, as these are mechanisms that justify the adverse reaction to the drug. Thus, fluconazole is a useful drug that offers safety, as reviewed in the literature, in addition to presenting few serious adverse events, but it is necessary to pay attention and use with caution in HIV patients.

It is known that the treatment was carried out in a timely manner and it is important to emphasize the importance of the correct diagnosis and initiation of appropriate therapy for a better prognosis of the condition. In this sense, it is also worth mentioning the importance of detecting dermatological signs and symptoms, correlating them with systemic ones, since some pathologies such as NET can rapidly evolve to fatal conditions, which corroborates the importance of early diagnosis and treatment.

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