Tiapride Associated Toxic Epidermal Necrolysis in an HIV-Infected Patient

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Abstract

Toxic epidermal necrolysis is a rare but severe and often fatal adverse cutaneous drug reaction. Early diagnosis and prompt discontinuation of the culprit drug is of the utmost importance, making drug causality assessment the mainstay when managing this condition. We present the first reported case of toxic epidermal necrolysis induced by tiapride, in a 43-year-old male Caucasian with a history of liver cirrhosis and HIV infection. This case report should raise awareness on the medical community to a potentially fatal reaction to a frequently prescribed drug in alcoholic patients. It also underlines the importance of further research regarding HIV infection, immune deregulation and adverse cutaneous drug reactions.

Keywords: Tiapride; HIV; Toxic epidermal necrolysis

Abbreviations: TEN: Toxic Epidermal Necrolysis; SJS: Stevens-Johnson Syndrome; BSA: Body Surface Area; SMX/TMP: Sulfamethoxazole/Trimethoprim; MHC: Major Histocompatibility Complex; HAART: Highly Active Antiretroviral Therapy; CMV: Cytomegalovirus; HSV: Herpes Simplex Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus

Introduction

Toxic epidermal necrolysis (TEN) is a severe adverse cutaneous drug reaction characterized by mucosal erosion and epidermal detachment [1]. It is usually distinguished from Stevens-Johnson Syndrome (SJS) by the extent of affected body surface area (BSA): SJS when less than 10% of BSA is affected, TEN when BSA affected is more than 30% and when 10 to 30% of BSA is affected as SJS-TEN overlap [1,2]. TEN is a rare condition, with an estimated incidence of 0.4 to 1.9 per million people annually [3-5]. Reported incidence in HIV infected patients is higher, as much as 1 per 1000 people annually [6]. Some of the most frequently implicated drugs are anti-infective sulfonamides, phenytoin, carbamazepine, phenobarbital and allopurinol [7]. We present the first reported case of TEN attributable to tiapride, a neuroleptic drug mainly used in alcoholic withdrawal syndrome.

Case Report

A 43-year-old male Caucasian was admitted to the emergency room of our tertiary care hospital with a two day history of fever, headache and malaise, followed by bilateral conjunctivitis, oral enanthem and a maculopapular exanthema distributed to the face, neck, trunk, limbs, hands and feet, including the palms and soles and sparing the scalp and perineum. Laboratory results were the following: haemoglobin 11.4 g/dL, white blood cell count 35×10⁹/L, thrombocytes 42×10⁹/L, albumin 25.9 g/L, AST 51 U/L, ALT 48 U/L, total bilirubin 8.3 mg/dL, urea 1.8 mg/dL, creatinine 7 mg/L, aPTT 37 sec, PT 13.7 sec and C-reactive protein 48 mg/L. His CD4+ T lymphocyte count was 71/mm³ and HIV viral load was 633,000 copies/mm³. He was admitted to the Infectious Diseases Ward with a diagnosis of suspected TEN associated to tiapride and all medication was discontinued. On D2 after admission, due to cutaneous tenderness and dorsal bullae, the patient started intravenous corticosteroids. On D4, diffuse bullae formation was observed and positive Nicholsky sign localized to the dorsum was elicited. A skin biopsy was performed on D5, confirming epidermal necrosis and detachment as well as discrete inflammatory infiltrate in the superficial dermis. Blood, sputum and urine cultures were all negative. Serological testing revealed past infection by CMV, HSV1, Mycoplasma pneumoniae and Chlamydia pneumoniae and no prior contact with HSV2, HBV, HCV, Treponema pallidum or Toxoplasma gondii. Serum cryptococcal and CMV antigens were negative. Peripheral blood polymerase chain reaction for HSV1 and 2, CMV, Mycoplasma pneumoniae and Chlamydia pneumoniae were negative. Clinical worsening ensued with sheet like epidermal sloughing which eventually covered about 90% of total body surface (Figures 1 and 2). On D7 corticosteroids were discontinued. The patient was transferred to the Burn Unit where hemodynamic stability was maintained with undetectable blood HIV viral load and a CD4+ T lymphocyte count of 312/mm³.

At the emergency room (D1) the patient presented fever (38.8°C), tachycardia (110 hbpm) and tachypnea (24 cpm), as well as oral enanthem, bilateral conjunctivitis and a non-pruriginous coalescent maculopapular exanthema distributed to the face, neck, trunk, limbs, hands and feet, including the palms and soles and sparing the scalp and perineum. Laboratory results were the following: haemoglobin 11.4 g/dL, white blood cell count 35×10⁹/L, thrombocytes 42×10⁹/L, albumin 25.9 g/L, AST 51 U/L, ALT 48 U/L, total bilirubin 8.3 mg/dL, urea 1.8 mg/dL, creatinine 7 mg/L, aPTT 37 sec, PT 13.7 sec and C-reactive protein 48 mg/L. His CD4+ T lymphocyte count was 71/mm³ and HIV viral load was 633,000 copies/mm³. He was admitted to the Infectious Diseases Ward with a diagnosis of suspected TEN associated to tiapride and all medication was discontinued. On D2 after admission, due to cutaneous tenderness and dorsal bullae, the patient started intravenous corticosteroids. On D4, diffuse bullae formation was observed and positive Nicholsky sign localized to the dorsum was elicited. A skin biopsy was performed on D5, confirming epidermal necrosis and detachment as well as discrete inflammatory infiltrate in the superficial dermis. Blood, sputum and urine cultures were all negative. Serological testing revealed past infection by CMV, HSV1, Mycoplasma pneumoniae and Chlamydia pneumoniae and no prior contact with HSV2, HBV, HCV, Treponema pallidum or Toxoplasma gondii. Serum cryptococcal and CMV antigens were negative. Peripheral blood polymerase chain reaction for HSV1 and 2, CMV, Mycoplasma pneumoniae and Chlamydia pneumoniae were negative. Clinical worsening ensued with sheet like epidermal sloughing which eventually covered about 90% of total body surface (Figures 1 and 2). On D7 corticosteroids were discontinued. The patient was transferred to the Burn Unit where hemodynamic stability was maintained with undetectable blood HIV viral load and a CD4+ T lymphocyte count of 312/mm³.

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weeks ahead the onset of reaction, tiapride was the only one to which he had never been exposed to before. Since cutaneous testing or re-introduction was not done, as they were deemed unnecessary risks, drug causality was assessed using the ALDEN algorithm, with a result of “probable” [11]. Several mechanisms have been proposed to explain increased incidence of TEN and SJS in HIV infected patients [6]. Genetic predisposition seems to play an important role in adverse drug reactions, as is the case in the association between abacavir hypersensitivity and the presence of class I major histocompatibility complex (MHC) allele HLA-B5701 [12]. Other possible explanations include viral infection and reactivation, increased use of certain drugs, immune reconstitution, elevated serum IgE levels, a Th2 type of cytokine pattern, slow acetylation and decreased anti-oxidant levels [13-16]. Our case report seems to contradict some of these hypotheses. This patient had no acute viral infection or reactivation, HAART had not been started and, therefore, no immune reconstitution occurred. Type 1 hypersensitivity responses are not attributable to the sulfonamide functional group. However it is not known whether T-cell-mediated TEN is related to the sulfonamide moiety [17]. Our clinical report suggests that the immune determinant for TEN may also be different from the sulfonamide functional group because our patient was later treated with SMX/TMP without any adverse effect. Though we cannot advance a completely satisfactory overall explanation, it is worth noticing that in this case report TEN occurred during severe immune suppression, due to exposure to an unsuspected drug and not while the patient was on HAART, with increasing CD4+ cell count and exposed to “high-risk” drugs such as SMX/TMP [7,11].

Conclusion

This is the first reported case of TEN attributable to tiapride. As it is a frequently used medication in alcoholic patients the medical community as a whole should be aware of this occurrence. Adverse cutaneous drug reactions in HIV infected patients are yet to be thoroughly understood, though the pathophysiologic mechanism seems to be multifactorial.

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References


