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Generalized drug toxic dermatitis secondary to ethambutol: exceptional case

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ABSTRACT

The antibacillary have an undeniable effect but their poor tolerance is often la ransom their therapeutic success. The knowledge of anti-tuberculosis side effects is important to identify the offending drug and to take a practical approach to such situation. Ethambutol may rarely be responsible for immunologic skin manifestations and unusually for generalized drug toxic dermatitis. We report an exceptional case of generalized drug toxic dermatitis to Ethambutol in a young 34 years old patient occurred on treatment of relapse for pulmonary positive TB smear. We discuss through this observation the medical behavior in front of generalized drug toxic dermatitis of immunologic origin.

KEYWORDS

Ethambutol;
Tuberculosis;
Toxic dermatitis;
Immunoallergy.

INTRODUCTION

Tuberculosis is an infectious disease curable with well identified treatment. The antibacillary have an undeniable effect but their poor tolerance could influence their therapeutic success. The knowledge of anti-tuberculosis side effects is important to identify the offending drug and to take a practical approach to such situation.

The Rifampicin, Isoniazid, Pyrazinamid and the Ethambutol are the major antibacillary currently involved in all treatment protocols of tuberculosis not resistant.

Immunologic reactions to anti-tuberculosis are a major problem in their consequences, the complexity of diagnosis and in their treatment. These reactions are reported in literature in 4 to 5% of the population exposed[1] and 25% in the persons living with HIV[2].

The Ethambutol is a bacteriostatic antimycobacterial drug, which rarely causes immunologic cutaneous manifestations and exceptionally generalized Toxico-dermatitis. We report through this observation, a case of generalized immune allergic toxidermitis secondary to Ethambutol occurring in a young immunocompetent woman.

This case illustrates the different measures for diagnosis and therapy front of an immunoallergic reaction secondary to an antibacillary.

OBSERVATION

This is a young 34 years old Moroccan woman,, already treated for pulmonary tuberculosis smear positive in 1996 and placed under the anti-TB regimen contain a 2 months attack phase (Association of streptomycin, Rifampicin Isoniazid and Pyrazinamid) and a maintenance phase of 4 months (combination of Isoniazid and Rifampicin) with declaration of healing at the end of treatment. Moreover, the patient does not have

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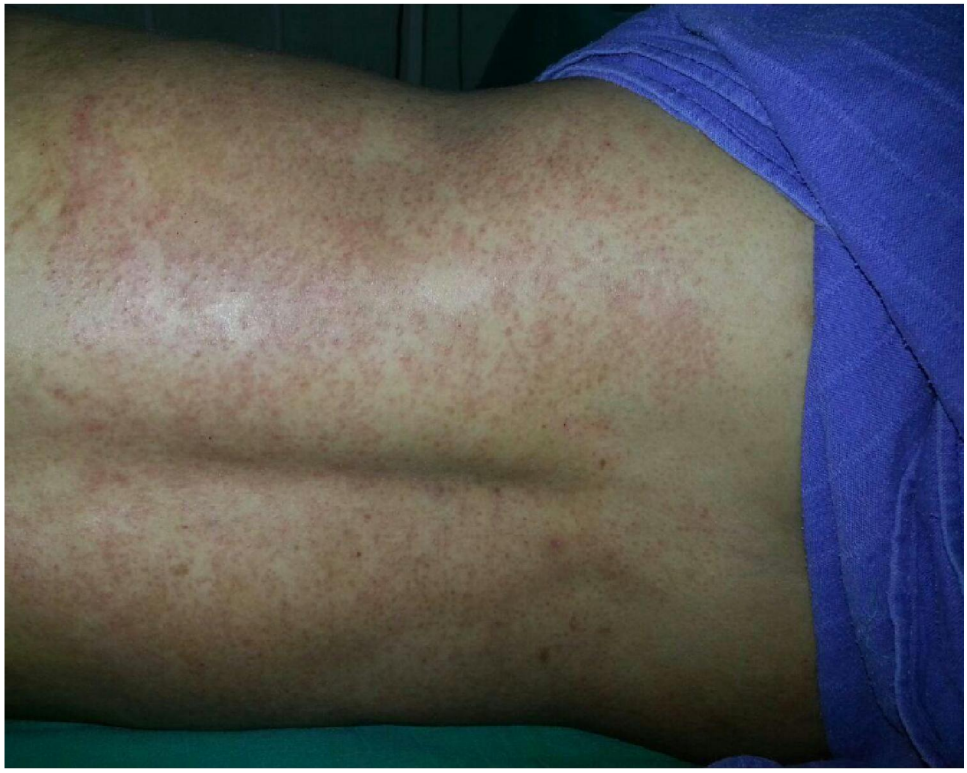

Figure 1 : Diffuse macular skin lesions without papules or vesicles associated two days after the arrest of the antibacillary treatment

other medical history or concept of personal or familial atopy. On the 11 of May 2013, the patient were placed under an antibacillary treatment for relapse smear positive with an Association of (Ethambutol, Isoniazid, Rifampicin and Pyrazinamid), she came one week after starting the treatment with generalized Toxico-dermatosis showed as diffuse macular skin lesions all over the body without papules or vesicles, and associated with edema of the eyelids and lips without shortness of breath (Figure 1). The patient was admitted to our phtisiology department for suspicion of serious side effects. The antituberculosis treatment was stopped. Biological assessment on admission was not associated with objectified hypereosinophilia or leukocytosis. The sedimentation rate was elevated to 60mm, the C reactive protein (CRP) was at 40mg/l and the serology of HIV and hepatitis B and C came back negative. Clinical evolution on antihistamine therapy was marked by a total regression of skin lesions after 4 days without scars. Toxico dermatosis of immunologic origin was diagnosed. We started to introduce the anti- tuberculosis one by one with three-days interval starting with the least offending drug in the following order: first Ethambutol, Pyrazinamid, Isoniazid and Rifampicin. Each drug was reintroduced on progressive doses (one third of the daily dose on the first day, two thirds of the day 2 and full dose on day 3). Skin test was not made due to the non-availability of injectable anti-tuberculosis. The evolution was marked by the appearance of erythematous skin lesions all over the trunk, the back and upper limbs after 4 hours of reintroducing third of the daily dose of Ethambutol. It was stopped definitively. The reintroduction of other anti-tuberculosis was uneventful. Treatment was adjusted with the combination of streptomycin, rifampin, Isoniazid and Pyrazinamid for the first two months, the combination of Rifampicin, Isoniazid and Pyrazinamid for the month after and then the association of Rifampicin and Isoniazid for 8month. The outcome was favorable with declaration of complete healing at the end of treatment.

DISCUSSION

Drug allergies may be defined as a drug-induced outlet linked to an immunological pathological reaction[3]. The hypersensitivity to anti-tuberculosis is one of the unpredictable side effects that appears in 4-5% of the exposed population and in 25% of HIV-positive subjects[1,2] cutaneous allergic manifestations of antibacillary are varying from a simple skin reaction to life-threaten-

ing reactions.

Our observation illustrates a rare case of immunoallergic dermatosis due to Ethambutol. In literature, Mattes and al. reports that Isoniazid was responsible of 2% of urticarial skin rash and streptomycin was responsible in 5% of cases[4]. Tan and al. identified 5.4% of cutaneous effects attributed to Pyrazinamid in 2.4% of cases, streptomycin in 1.4% of cases, Ethambutol in 1.4% and Rifampicin in 1.2% of cases[5]. Severe dermatosis were exceptionally observed with Ethambutol, and noted especially with Rifampicin and streptomycin.

In our case, the immunoallergic reaction appears seven days after the beginning of the treatment. Generally, these reactions occur between 7 to 21 days after treatment initiation. The risk is major during the first two months[6]. Immunologic manifestations may occur in general in any patient but are more common in certain pathological conditions including infections by human immunodeficiency virus[7].

The Risk factors are many: advanced age could be a factor due to changes in the pharmacokinetics of drugs in aged people[8] - female gender plays a promoting role by some authors[9] - history of tuberculosis, - Genetics predisposing could be an important factor in potential drug allergies[10] - immunodepression[11] - intramuscular injection: more immunogenic, is responsible for severe reactions compared to oral intake. - And personal atopy may be a risk factor of immunoallergic accidents. In our case, only two risk factors are identified: sex and antibacillary treatment history.

In our case, the diagnosis was firstly suspected on the compatible clinical history with an allergy and on the disappearance of the cutaneous manifestations after the arrest of the antibacillary treatment and finally confirmed on the re-appearance of the symptoms after the test of re-introduction of the Ethambutol.

The various stages of definitive diagnosis of an allergic immune response to anti-tuberculosis are as follows[12] : The presence of a compatible clinical history with an allergy, validated positive skin tests and provocation positive test. The interrogation is the first step of diagnosis to clarify the mode of start, clinical symptomatology, the chronology of symptoms, risk factors, a concomitant drug taking and signs of severity.

The laboratory tests in the exploration of drug allergies are still limited. However, these explorations sometimes used to assess the severity of the reaction, such as the histaminemia or the tryptasemia, but cannot help to identify the responsible drug[13]. The place of biological tests in the diagnostic approach to antibacillary allergy yet to be defined[14]:

- For the Rifampicin: dosage of IgE by ImmunoCAP Pad is not marketed
- For the Isoniazid: dosage of specific IgE is not validated
- For the Pyrazinamid and Ethambutol: the presence of the immunoglobulin E (IgE) has never been demonstrated in skin tests, prick tests and intra-dermal reaction of the major antibacillary are not validated. The patch tests are not standardized especially also on the concentration of the molecule.

The provocation test is the test with maximum sensitivity, but it can only be done under high supervision[15]. It should be done far from the episode with the drug and ways of administration initially caused the reaction, it should not be performed if the suspected drug is not widely used or when the reaction is severe (extensive maculopapular rash with fever, DRESS syndrome, acute erythematic generalized pustulosis).

What to do in front of a drug skin reaction of immunologic origin depends on the severity of the clinical symptoms and the drug involved. Stopping antibacillary treatment in generalized eruption should be done firstly once the regression of the lesion is there we carefully reintroduce with an escalating dose one drug after another starting with the drug least suspected. This test will identify the involved molecule and in some cases provide the realization of a drug tolerance. The therapy of induction of tolerance is to get the patient accustomed to antituberculous and consists in progressive reintroduction of involved medication so as to force its tolerance. Its practice is not standardized and is done on a variable time from some hours to some days. The effects are temporary and there is no specific immunotherapy. This induction therapy must be performed inside a hospital with a respect of the contraindication.

In our case, given the possibility of adjusting the treatment with alternative regimen, we did not realize the therapeutic of induction of tolerance. So, we decided to arrest definitively the Ehambutol and to extend the duration of the second phase of treatment. The out-

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come was favorable with obtaining complete healing at the end of treatment.

CONCLUSION

Ethambutol should be suspected in front of toxicodermatitis under antibacilliary treatment. All diagnoses means must be used to prove the involvement of the drug by a comprehensive examination, skin tests and if possible provocation test outside contraindications. It is imperative to inform patients of the existence of allergic reactions and recommend a consultation in the occurrence of these events.

CONFLICT OF INTEREST

All authors declare no conflicts of interests

CONTRIBUTIONS OF THE AUTHORS

All the authors have contribute on the diagnosis of the case and the writing this article.

REFERENCES

[1] L.P.Pur Ozyigit, C.Galera, C.Defrance, Z.Kilicaslan, P.Demoly; Allergy to antituberculosis drugs, a pragmatic approach: Tolerance induction to Rifater®. Rev Fr Allergo., **51**, 446-448 **(2011)**.

[2] C.Kuaban, R.Bercion, S.Koula-Shiro; Current HIV seroprevalence rate and incidence of adverse skin reactions in adults with pulmonary tuberculosis receiving thiacetazone-free antituberculosis treatment inYaounde, Cameroon. Cent Afr J Med., **44(2)**, 34–7 **(1998)**.

[3] L.Imbart Comte; P.Demoly; Tolerance to medicines. Rev Fr Allergol Immunol Clin, **44**, 308-314 **(2004)**.

[4] T.Matz, L.C.Borish, J.M.Routes, L.J.Rosenwasser; Oral desensitization to Rifampicin and Ethambutol in mycobacterial disease. Am J Respir Crit Care Med., **149(3 Pt 1)**, 815-7 **(1994)**.

[5] W.C.Tan, C.K.Ong, S.C.Kang, M.A.Razak; Two years rewiew of cutaneous adverse drug reaction from first line anti-tuberculous drugs. Med J Malaysia., **62(2)**, 143-6 **(2007)**.

[6] J.C.Roujeau; Toxic epidermal necrolysis and Stevens-Johnson syndrome. Rev Prat.,15, **57(11)**, 1165-70 **(2007)**.

[7] S.A.Coopman, R.A.Johnson, R.Platt, R.S.Stern; Cutaneous disease and drug reactions in HIV infection. N Engl J Med.,10, **328(23)**, 1670-4 **(1993)**.

[8] R.Gruchallar; Understanding drug allergies.J.Allerg., **105(6 Pt 2)**, S637-44 **(2000)**.

[9] S.Cheze, M.Leporrier; Immuno-allergic cytopenias. Rev Prat., **51(14)**, 1564-70 **(2001)**.

[10] A.Covic, D.J.Goldsmith, L.Segall, C.Stoicescu, S.Lungu, C.Volvat, M.Covic; Rifampicin-induced acute renal failure: a series of 60 patients. Nephrol Dial Transplant., **13(4)**, 924-9 **(1998)**.

[11] S.Bevilacqua, C.Rabaud, T.May; HIV-Tuberculosis coinfection. Ann Med Intern., **153(2)**, 113-8 **(2002)**.

[12] W.Aberer, A.Bircher, A.Romano, M.Blanca, P.Campi, J.Fernandez, K.Brockow, W.J.Pichler, P.Demoly; Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy., **58(9)**, 854–63 **(2003)**.

[13] P.Demoly, B.Arnoux; Laboratory diagnosis of drug allergies.J.Allerg.,03., 009 **(2004)**.

[14] J.Birnbaum; Reactions to antituberculosis drugs : management of allergic reactions in four cases. Rev Fr Allergol., **50(1)**, 32-35 **(2010)**.

[15] D.Messaad, H.Sahla, S.Benahmed, P.Godard, J.Bousquet, P.Demoly; Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. Ann Intern med., **140(12)**, 1001 6 **(2004)**.