Drug Rash with Eosinophilia and Systemic Symptoms to antituberculosis treatment

Syndrome de DRESS secondaire aux antituberculeux

Sonia Toujani [1], Ahmed Zaiem [2], Meriem Mjid [1], Yacine Ouahchi [1], Nozha Ben Salah [1], Bechir Louzir [1], Nadia Mehiri [1], Jouda Cherif [1], Majed BEJI [1].

1- Service de pneumo-allergologie, CHU La Rabta, Université de Tunis El Manar, Faculté de Médecine de Tunis
2-Centre de pharmacovigilance- Université de Tunis El Manar, Faculté de Médecine de Tunis

RÉSUMÉ

Le syndrome de DRESS ou éruption cutanée avec éosinophilie et symptômes systémiques est une réaction d'hypersensibilité médicamenteuse grave. Les anticonvulsivants sont les médicaments les plus incriminées. Ce syndrome est rarement due aux antituberculeux et il est parfois difficile d'identifier l'agent responsable. Nous rapportons le cas d'une femme de 45 ans qui est sous traitement antituberculeux (RHZE) pour une tuberculose ganglionnaire. La patiente a présenté une fièvre, une dyspnée, une éruption cutanée, une hyperéosinophilie et une atteinte viscérale (hépatique). Après la disparition des symptômes et la normalisation des anomalies biologiques, les antituberculeux ont été réintroduits un par un. Malheureusement, les mêmes symptômes sont réapparus avec les quatre médicaments anti-tuberculeux. L'évolution clinique était favorable sous les antituberculeux de seconde ligne.

Mots-clés

Hypersensibilité médicamenteuse, DRESS, effets indésirables, antituberculeux

SUMMARY

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome reflects a serious hypersensitivity reaction to drugs. This syndrome is an uncommon adverse reaction due to antituberculosis drugs and is sometimes difficult to identify the culprit agent. We report a case of a 45-year-old woman who received combined anti-tuberculosis drugs (RHZE) for lymph node tuberculosis. Clinical manifestations included fever, dyspnea, rash, hypereosinophilia and visceral involvement (liver involvment). After symptom resolution and biology normalization, anti-tuberculosis drugs were reintroduced successively one after another. Systemic symptoms reappeared with the four anti-tuberculosis drugs. The clinical outcome was favorable with second line antituberculosis treatment.

Key-words

Drug Hypersensitivity, DRESS, adverse effects, anti-tuberculosis treatment

Tuberculosis is an infectious disease which can be complety cured by combining anti tuberculosis (Tb) treatment. However, adverse reactions (ADRs) are observed in 9% of patients treated with antituberculosis drugs (1). Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) is uncommon, but lead to interruption of treatment for long periods, systemic corticosteroid use and resumption of treatment with less effective regimens (1-3). The identification of the culprit drug is sometimes difficult. Management of these ADRs remains controversial.

CASE REPORT

A 45-year old woman, with no history of asthma or rash, nor any known allergies, was treated for lymph nodes tuberculosis with combined anti tuberculosis treatment (RHZE: a fixed-dose, single-tablet combination of rifampin, isoniazid, pyrazinamide, and ethambutol: 4 tablets per day). On the 34th day, she developed generalized rash involving upper and lower limbs, trunk and face. The lesions didn't improve with antihistaminic. Four days later, rash had worsened and the patient was referred to our respiratory unit. On physical examination, she had fever at 38.2 C° and dyspnea at 24 cycles/min, with otherwhise normal vital signs. Pruriginous maculopapular erythema was observed in her face (Figure 1), trunk and limbs (Figure 2). Laboratory analysis revealed leukocytosis (14,500/mm³), lymphocytosis (5000/mm³), eosinophilia (2500/mm3), erythrocyte sedimentation rate: 72 mm/h, C-reactive protein: 35 mg/l and hepatic cytolysis (alanine transaminase ALT: 141IU/l; and aspartate transaminase AST: 111IU/l), without cholestasis. Viral hepatitis B and C viruses and human immunodeficiency virus were negative. Serological tests for EBV and HHV6 were negative. Abdominal ultrasound revealed intra-abdominal lymphadenopathy. Clinical features highly suspected DRESS syndrome to anti-Tb drugs (RHZE). The later were discontinued.

Figure 1 : Macular exanthema of the face without mucosal involvement

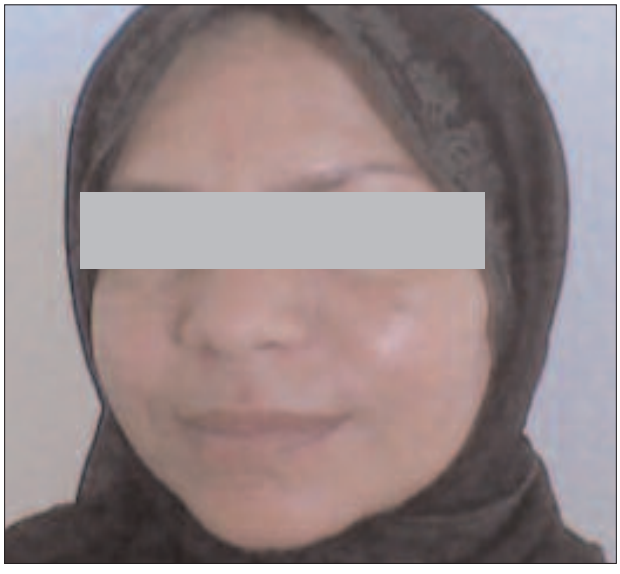
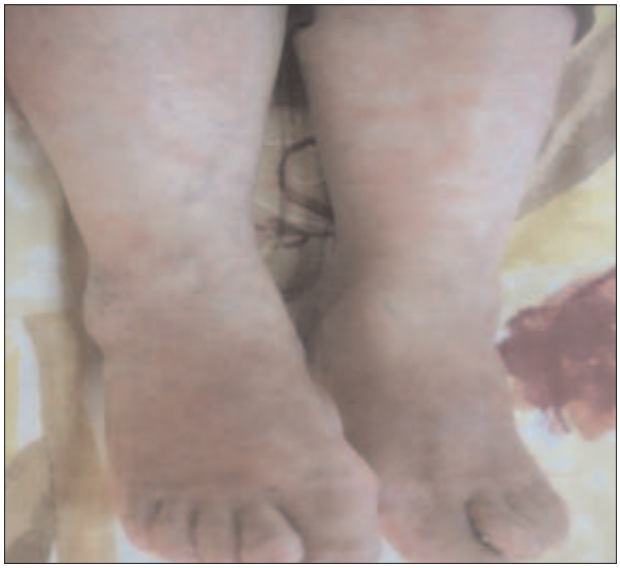


Figure 2 : Diffuse exanthema of the limbs



New antituberculosis drugs (streptomycin and ciprofloxacin) were initiated and antihistaminic and silver sulfadiazine cream for local application were given for symptoms relief. The skin lesions improved progressively. However, cytolysis and eosinophilia increased (in the 5 day after drug withdrawal). Thus, corticosteroids on IV were prescribed. The follow-up was marked by disappearance of skin lesion and normalization of blood counts and liver function tests four weeks after anti-tubercular drugs withdrawal. One month later, rifampicin, isoniazid, ethambutol and pyrazinamide were reintroduced separately and sequentially. Intervals left between each treatment are summarized in the table 1.

Table 1: Drug challenge tests

Drugs Interval after withdrawal (d)	Doses	Clinical/laboratory findings	Time of symptoms reappearance	Time of symptoms resolution	REGISCAR Score
Rifampicin (28)	600 mg	Rash , Eo: 2300/mm , ALT: 400IU/l; AST: 320IU/l	7days	20 days	5: probable
Isoniazid (21)	200 mg	Generalized rash; pruritus Eo: 1800/mm	7 days	12 days	2-3: possible
Ethambutol (12)	1200 mg	Maculopapular rash	6days	10 days	1: no case
Pyrazinamide (10)	1500 mg	Eosinophilia 1200/mm ALT: 220IU/l; AST: 180IU/l	3days	12 days	2: possible

Eo; Eosinophilia; AST: aspartate transaminase; ALT: alanine transaminase

Rifampicin was the first reintroduced drug. Systemic symptoms reappeared at each reintroduction (rash, eosinophilia, cytolysis with rifampicin; rash, eosinophilia with isoniazid; rash with ethambutol and eosinophilia, cytolysis with pyrazinamide). The time to onset of symptoms was variable (7 days (d): rifampicin; 7 d: isoniazid; 6 d: ethambutoland 3 d: pyrazinamide). The interval left before drug reintroduction was: 28 d for rifampicin; 21 d for isoniazid; 12 d for ethambutol and 10 d for pyrazinamide. (plus de précision chronologique) The outcome of tuberculosis was favorable when treated with ethionamid, streptomycin and ciprofloxacin. The patient is going well after 18 months of second line therapy and 24 months follow up.

DISCUSSION

Drug eruptions are the most frequent target of drug reactions (2,4). About 80% of cases are related to drug hypersensitivity (2). The clinical presentation of "drug eruptions" is highly variable. DRESS, is an adverse drug reaction initially reported to the anticonvulsant drugs (5). It was first reported in 1996 by Bocquet and co. (6). It includes a severe skin eruption, fever, hematologic abnormalities with eosinophilia and/or atypical lymphocytosis, multi-visceral involvement and/or generalized lymphadenopathy (6,7).

In our case, with regard to cutaneous rash, eosinophilia, thrombopenia and hepatic dysfunction two diagnosis were evoked: induced systemic lupus erythematous and drug-induced eosinophilia. However, Lupus erythematous does not fulfill for ACR criteria mainly because immunological tests were negative. The diagnosis of DRESS was retained with a probable Regiscar of 5: (a) enlarged lymph nodes, (b) skin rash> 50%, (c) hypereosinophilia ≥ 1500 and (d) visceral involvement (hepatitis).

The pathophysiology of DRESS has not been fully elucidated. Both immunological and non-immunological mechanisms were discussed (8-10). In our case, DRESS syndrome was not associated with viral reactivation, since serogical tests for EBV, CMV and HHV6 were negative. DRESS syndrome has been reported to be associated with a limited number of drugs mainly anticonvulsants: phenytoin, carbamazepin, phenobarbital, dapsone, allopurinol, minocycline, ranitidine and sulphasalazine (5-12). Antituberculousis are rarely responsible of DRESS syndrome (13,14). After an exhaustive review of the literature, 40 cases of DRESS syndrome with anti Tb drugs have been reported (3,15-18).The responsibility of one related drug was retained in 26 cases and more than one drug in the remaining cases. Rifampicin and Isoniazid were the most often associated with DRESS. However, Pyrazinamide and Ethambutol were the more tolerated (3). A cause effect relationship is difficult to establish when multiple drugs are concomitantly administrated such as seen in anti TB regimen. Patch testing can be helpful to confirm the imputability of a drug in several patterns of cutaneous adverse drug reactions where delayed hypersensitivity mechanisms are involved (19-22). Positive patch tests occur more frequently in maculopapular exanthema, acute generalized exanthematous pustulosis and fixed drug eruptions. Whereas, in DRESS patch reactivity depends highly on the culprit drug. Santiago et al conclude that patch testing is useful in patients with antiepileptic drug induced DRESS, where the proportion of relevant and specific positive patch tests is high. Patch testing has no value when allopurinol is the suspected drug (23). Although, there are no large studies evaluating the utility of patch testing in patients with DRESS induced by antituberculosis, theses tests can be helpful when they are positive as reported by Zaiem et al (23). But, they are not fully standardized with a lack of both sensitivity and specificity (24, 25). To confirm the responsible agent in DRESS, rechallenge with the suspected drug considered as the 'gold standard' in other drug eruptions, is not advised due to the risk of a life-threatening reaction. But rechallenge with antituberculosis could be justified because alternative treatement are less tolerated, less effective also more expensive and rarely available in our country. The reintroduction of the culprit drug should be administered cautiously. In our case, because of the lack of data about skin tests, we decided to proceed with challenge tests with intensive clinical and laboratory monitoring. The imputation scores of rifampicin, izoniazid and pyrazinamide were evaluated as probable (I3), because: (a) suggestive delay after starting treatment- (b) favorable evolution after drug withdrawal and mainly successive positive rechallanges of rifampicin, izoniazid and pyrazinamide. As it concern ethambutol, the imputation score was valued as possible (I2) mainly because rechallenge did not reproduce DRESS (table 1 REGISCAR score: 1 no case). Another particularity of our case was recurrence of symptoms with different drugs. Recurrent ADRs could be explained by multidrug hypersensitivity (MDH) defined as a predilection to react to different chemically and structurally unrelated drugs with no evidence of cross reactivity. Besides, the interval left between every reintroduction could be insufficient. In fact, Rodríguez and co have left and interval of at least one month between one challenge and the next to ovoid false positive (17). The authors reported that the cross reactivity between isoniazid, rifampicin, ethambutol and pyrazinamide cannot be explained by chemical structure. In our case we had left 4 weeks and 3 weeks to reintroduce rifampicin and isoniazid but respectively 12 and 10 days for ethambutol and pyrazinamide. Treatment of DRESS syndrome remains empirical (5,12). The suspected drug should be discontinued immediately when this syndrome is being considered. Delaying this measure may be associated with a poor outcome. Systemic corticosteroid administration is classically reported in the case of organ- or life-threatening disease (26). In our case, corticosteroids were administrated for important cytolysis and eosinophilia, which is thought to account for organ involvement. No randomized controlled trials of corticosteroids in the treatment of DRESS syndrome are available.

CONCLUSION

Through this case of DRESS syndrome induced by antituberculosis drugs and confirmed by challenge tests, we highlight the potential of such ADRs of these drugs and underline the usefulness of provocation tests in the identification of the causative drug. The management of anti Tb drugs reintroduction is difficult particularly when more than one drug is suspected to be responsive. So, besides the prompt withdrawal of causative drug as standard of care, further studies are needed to recommend specific treatment guidelines in DRESS induced by anti TB drugs.

References

1. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med 2003; 167(11):1472–7.
2. Aouam K , Chaabane A , Loussaïef C, Ben Romdhane F, Boughattas N.-A, ChakrounM . Les effets indésirables des antituberculeux : épidémiologie, mécanismes et conduite à tenir. Med Mal Infect 2007 ;37 :253-261.
3. Palermo D, Castagnino J, Musella RM, Mosca C, Montaner PG, de Casado GC. Difficult clinical management of anti-tuberculosis DRESS syndrome. Int J Tuberc Lung Dis 2013;17:76-8.
4. Fekih L, Fenniche S, Boussofara L, Hassen H et al. Manifestation d'hypersensibilité aux antituberculeux. Rev Mal Respir 2010; 273-78.
5. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, Roujeau JC. The DRESS Syndrome: A Litterature Review.Am J Med 2011; 124:588-597.
6. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophiliaand Systemic Symptoms: DRESS). Semin Cutan Med Surg 1996; 15:250-7.
7. Walsh SA, Creamer D. Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking. Clin Exp Dermatol. 2011;36(1):6-11.
8. Camous X, Calbo S, Picard D, Musette P. Drug Reaction with Eosinophilia and Systemic Symptoms: an update on pathogenesis. Curr Opin Immunol 2012;24:730-5.
9. Alfirevic A, Pirmohamed M. Drug Induced Hypersensitivity and the HLA Complex Pharmaceuticals 2011;4:69-90.
10. Criado PR, Avancini J, Santi CG, Medrado AT, Rodrigues CE, de Carvahlo JF. Drug reaction with eosinophilia and systemic symptoms (DRESS): a complex interaction of drugs, viruses and the immune system. Isr Med Assoc J 2012;149: 577-82.
11. Picard D, Janela B, Descamps V, D'Incan M, Courville P, Jacquot S et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. SciTransl Med 2010;2:46-62.
12. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. Dermatology 2003; 206: 353-6.
13. Kim JH, Jang SH, Kim DH, Park S, Kim DG, Jung KS. A case of DRESS syndrome induced by the antituberculosis drugs, prothionamide and para-aminosalycilic acid. Ann Allergy Asthma Immunol 2013;110 :118–9.
14. Atadokpede F, Sehonou J, Vigan J, Adégbidi H. DRESS syndrome induit par l'isoniazide et hépatite fulminante à virus B. Ann Dermatol Venereol 2011;138 : 202–3.
15. Joo Ho Lee, Hye-Kyung Park, Jeong Heo, Tae Oh Kim,Gwang Ha Kim, Dae Hwan Kang et al. Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome induced by celecoxib and antituberculosis drugs. J Korean Med Sci 2008;23:521-5.
16. Khammassi N, Ben Sassi M, Mohsen D, Hamza M.DRESS syndrome caused by Pyrazinamide. Egyptian Dermatology online Journal 2010; 6:2-6.
17. Rodríguez R, Jover V, Orozcol, Domenech J. DRESS Syndrome in a 19-Year-Old Patient Following the Administration of First-Line Antituberculosis Drugs. J Investig Allergol Clin Immunol 2012; 22: 380-1.
18. Moubachir H, Idahmed I, El Ataouna K, Bourkadi JD, Iraqi G. DRESS syndrome aux antituberculeux. Rev fr allergol 2013;53 :605–7.
19. Felicidade S, Margarida G, Ricardo V, S´onia Coelho and Am´erico F. Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). Contact Dermatitis 2010: 62: 47–53.
20. Barbaud A, Gonc¸alo M, Bruynzeel D, Bircher A. European Society of Contact Dermatitis. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. Contact Dermatitis 2001: 45: 321–8.
21. Lammintausta K, Kortekangas-Savolainen O. The usefulness of skin tests to prove drug hypersensitivity. Br J Dermatol 2005: 152: 968–74.
22. Strauss RM, Green ST, Gawkrodger DJ. Rifampicin allergy confirmed by an intradermal test, but with a negative patch test. Contact Dermatitis. 2001;45:108.
23. .Zaiem A, Toujani S, Hamza I, Lakhoua G, Daghfous R, Mami B, El Aidli S. DRESS associé aux antituberculeux avec test épicutané positif a` l'isoniazide Rev fr allergol 2013 ;53 :361–371.
24. Santiago F, Gonçalo M, Vieira R, Coelho S, Figueiredo A. Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). Contact Dermatitis 2010;62:47-53.
25. Birnbaum J. Réactions aux antituberculeux : prise en charge allergologique à propos de quatre cas. Rev fr allergol 50 (2010) 32–35.
26. Uhara H, Saiki M, Kawachi S,Ashida A, Oguchi S, Okuyama R.Clinical course of drug-induced hypersensitivity syndrome treated without systemic corticosteroids. J Eur Acad Dermatol Venereol 2013; 27:722.