Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome caused by first-line antituberculous drugs: two case reports and a review of the literature.

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Abstract

Background: Patients suffering from drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome caused by first-line antituberculous drugs often need to be re-treated rapidly. Patch tests prior to the re-introduction of antituberculosis drugs are rarely performed.

Objectives: We aim to highlight those drugs most often involved in DRESS from antituberculosis drugs, illustrate the potential value of patch tests to identify these culprit(s), and provide insights in how to rapidly re-treat these patients.

Methods: A detailed description of the work-up of two illustrative patients, together with a literature review of similar cases, is provided.

Results: All first-line antituberculosis drugs may cause DRESS syndrome, but rifampicin and isoniazid are most frequently involved. Patch tests can be performed sooner than usually advised in the context of DRESS syndrome and potentially in lower test concentrations, but false-negative results are possible. Sequential re-introduction of patch-test negative drugs is feasible, although the dose and order of drugs to be re-administered, as well as the use of concomitant systemic corticosteroids, remains a matter of debate.

Conclusion: Patch tests in the context of DRESS syndrome caused by antituberculous drugs, despite their shortcomings, may potentially guide rapid re-treatment of these patients.

1. Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, systemic adverse event mostly caused by anticonvulsants, sulfonamides, or non-steroidal anti-inflammatory drugs. We here describe two cases of DRESS syndrome induced by antituberculous drugs, and we review similar cases previously reported in the literature, thereby focusing on (i) those molecules most frequently involved, (ii) the possible usefulness of patch tests in the work-up, and (iii) how to rapidly re-treat these patients.

2. Case reports

2.1 Patient 1

A 56-year-old man, under treatment with a TNF-alpha inhibitor (golimumab; Simponi) for rheumatoid arthritis, developed pulmonary and lymph node tuberculosis. The immunosuppressive medication was interrupted and isoniazid, rifampicin, ethambutol, and pyrazinamide were started. After 6 weeks, he was admitted to the UZA department because of fever (38.5° C), an extensive maculopapular rash (> 50% body surface area [BSA]), pronounced facial and palmoplantar oedema (**Figure 1**) and disseminated peripheral lymphadenopathy. Laboratory tests revealed a high absolute blood eosinophilia (> 1000/µL; normal: < 500/µL) and elevated serum aminotransferases (aspartate transaminase [AST] and alanine transaminase [ALT]: both > 1200 U/L; normal: <35 for both). A DRESS syndrome from antituberculous drugs was highly suspected, and subsequently confirmed according to the International Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) system (1). Neither polymerase chain reaction (PCR) analyses for Epstein-Barr (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV)1-2, human herpes Virus (HHV)-6, and HHV-8 infection nor a skin biopsy were performed, as these investigations were considered not to have

additional diagnostic or therapeutic consequences. All drugs were immediately stopped, and potent topical corticosteroids were applied, which led to improvement. Systemic corticosteroid treatment could be avoided.

Three months later, after all skin lesions had resolved and blood values had normalized, patch tests (Allergeaze patch test chambers, SmartPractice, Calgary, Canada) were performed on the upper back. For ethambutol, pyrazinamide and rifampicin, commercially available drugs were used, whereas for isoniazid, raw material was used. Because of the severity of the rash, and the rather short time frame between resolution of all symptoms and performance of the patch tests (< 6 months), lower than usual test concentrations (i.e. "as is" or 30% pet.) were chosen: Myambutol (ethambutol) 3%, isoniazid 1%, Tebrazid (pyrazinamide) 3% and Rifadine (rifampicin) 3% all diluted in petrolatum (pet.). All tests were fixed with Fixomull stretch (BSN medical, Hamburg, Germany) for two days, after which they were removed and read according to ESCD criteria (2) on day (D) 2, D4, and D7. Positive reactions were observed to Myambutol (ethambutol) 3% pet. (D2++/D4++/D7++), isoniazid 1% pet. (D2++/D4++/D7++), and to Tebrazid (pyrazinamid) 3%. (D2++/D4++/D7++) whereas the patch tests with Rifadine (rifampicin) 3% remained completely negative (**Figure 2**). An additional patch test with Rifadine (rifampicin) 30% pet. remained negative as well. No other skin tests (prick or intradermal) were performed with Rifadine (rifampicin). Because Myambutol (ethambutol) tablets contain sodium lauryl sulfate (SLS) as excipient, an irritant potentially leading to false-positive patch test reactions, the manufacturer (Teofarma, Valle Salimbene, Italy) was contacted to provide us with the raw material of ethambutol, which, unfortunately, was denied. Patch tests with Myambutol (ethambutol) 3% pet. in 20 control patients did, however, not yield any positive reactions, thereby supporting a true contact allergic patch test response in our patient.

Thereupon, and in view of the negative patch tests to Rifadine(rifampicin) , it was decided to change his tuberculostatic therapy to second-line tuberculostatics, that is, IV amikacin (1g) and oral moxifloxacin (400 mg), together with a stepwise, 7-day reintroduction of Rifadine (rifampicin) in ascending doses. Given the severity of the drug eruption, the consideration that the patch test to Rifadine (rifampicin) might have been false-negative, and in accordance with the treating infectiologists, this reintroduction was, as precaution, performed under prophylactic therapy with systemic corticosteroids (methylprednisolone 64mg 1 day, 32mg 3 days, 16mg 3 days, 8 mg 3 days). The reintroduction schedule of Rifadine (rifampicin) was as follows: 0.6mg in two doses (D1), 12mg in two doses (D2), 150mg in three doses (D3), 300mg in two doses (D4-5), 300mg in one dose (D6-7), followed by 600mg/day every day. Unfortunately, after 7 days, the patient developed a generalized, itching erythema and a mild recurrence of blood eosinophilia, which necessitated the withdrawal of Rifadine (rifampicin). The skin eruption was treated with potent topical corticosteroids, and, taken into account that (i) the patient needed timely re-treatment whilst minimizing the risk of bacterial resistance, (ii) a literature research suggested that no-cross-reactivity occurs between rifampicine and rifabutin in cases of DRESS syndrome (3)**,** and (iii) the fact that no hard data favour slow increasing doses or concomitant corticosteroid treatment (see below), the latter was administered uneventfully and immediately at full dose (300 mg), without re-installing systemic corticosteroids.

2.2 Patient 2

A 21-year-old female, suffering from pulmonary tuberculosis for which the same quadruple therapy had been initiated 3 months earlier, presented with lethargy, fever (39,5°c), abdominal and neck pain, as well as a maculopapular skin eruption of 60 % of the BSA (**Figure 3**), and

edematous swelling of all extremities. Generalized lymphadenopathy and hepatosplenomegaly were also present. Laboratory tests revealed an elevated C-reactive protein (CRP) level (86mg/L; normal: <5mg/L), anemia (Hemoglobin (Hb): 8,6g/dL; normal: 13.0-18.0 g/dL), hypereosinophilia (1830/µL; normal: < 500/µL), thrombocytopenia (126.000/µL; normal 140.000-400.000/µL) and altered liver tests (AST: 250 U/L, ALT: 182 U/L, GGT: 120 U/L; normal: 9-36 U/L). PCR analyses were negative for EBV, CMV, HSV1-2, HHV-6, and HHV-8 infection. A skin biopsy showed spongiotic dermatitis with subepidermal oedema. A dermal perivascular lymphohistiocytic infiltrate with scattered eosinophils and activated lymphocytes was also present (**Figure 4**). The clinical, laboratory and histological findings, and also the RegiSCAR criteria as in Case 1, supported a diagnosis of DRESS syndrome. The antituberculosis treatment was discontinued, and in this case, IV corticosteroids were administered (methylprednisolone 40mg/day), followed by 20 days of oral corticosteroid therapy in decreasing doses. Complete clinical and biological remission was observed 15 days after stopping corticosteroids. In order to prevent a too long withdrawal from antituberculosis treatment, patch tests were rapidly performed with all four commercialized drugs. Nicotibine (isoniazid), Tebrazid (pyrazinamide) and Myambutol (ethambutol) were patch tested ”as is”, as well as diluted 30%, in saline and petrolatum, whereas Rifadine (rifampicin) was tested ”as is”, and 30%, only in saline. The patch test materials used were IQ Ultra Chambers (Chemotechnique Diagnostics, Vellinge, Sweden) covered on the upper back with Fixomull stretch (BSN medical). All tests were removed after two days and read at D2, D4, and D7 according to ESCD criteria and a clear positive reaction was observed only for Nicotibine (isoniazid) ”as is” aq. (D2+/D4+/D7+), 30% aq. (D2-/D4?+/D7+), ”as is” pet. (D2+/D4++/D7++), and 30% pet. (D2+/D4+/D7+) (**Figure 5**). A doubtful reaction was noted to Myambutol (ethambutol) on D2 and D4, which turned negative on D7. The patch tests with Rifadine (rifampicin) and Tebrazid (pyrazinamide) remained

completely negative. Although sometimes discouraged in cases of severe cutaneous drug reactions, an additional intradermal test with rifampicin 10% aqueous solution (aq.), prepared by using the commercialized IV solution of Rifadine (rifampicin), was performed in this case, and also remained negative.

Rifadine (rifampicin) and Tebrazid (pyrazinamide) were thus reintroduced, in this case immediately at full dose, together with a second-line tubcerculostatic drug, that is, moxifloxacin. Unfortunately, also in this case, a mild recurrence of symptoms was observed which again necessitated withdrawal of the drugs. Thereupon it was decided, as in Case 1, to perform a sequential reintroduction of these drugs, and under prophylactic therapy with oral corticosteroids (methylprednisolone 12 mg/day), again with the aim to prevent a more severe re-challenge reaction. First, moxifloxacin was re-administred, followed by Tebrazid (pyrazinamide) which caused a rapid serum aminotransferase elevation leading to definite cessation of the latter drug; it was successfully replaced by amikacin 1g/day IV. Thereafter, Rifadine (rifampicin) was also progressively reintroduced, i.e. at 150mg/day for 7 days, then 300mg/day for 3 days, and finally 600mg daily, without any further adverse reaction. The corticosteroids were succesfully tapered and stopped after a few weeks.

3. Discussion

DRESS syndrome, also known as drug-induced hypersensitivity syndrome (DIHS), is a drug-induced skin eruption, often presenting with marked facial and/or palmoplantar edema, and associated with fever, lymphadenopathy, eosinophilia, and systemic organ involvement, such as hepatitis. It is considered a severe drug reaction with an estimated death rate of 10-20% (4).

The most frequently incriminated drugs in DRESS syndrome are aromatic antiepileptic drugs, allopurinol, sulfonamides, antiretroviral drugs (abacavir, nevirapine), and minocycline. Previous studies have already addressed antituberculosis drugs as rather exceptional, but potentially underestimated, causes of DRESS syndrome. A 10-year (1998-2008) retrospective review documented that two of 60 reported cases (3%) of DRESS syndrome were associated with antituberculosis drugs (5). Online supplemental **Table 1** summarizes 37 published cases of DRESS syndrome associated with antituberculosis treatment where an allergological work-up was performed.

Rifampicin and isoniazid appear to be the most frequently involved molecules, identified as the culprit agent in 19 cases (our Case 1 and 18 cases in Online supplemental **Table 1** (3, 6-12) and 18 cases (our Case 1 and 2 and 16 cases in Online supplemental **Table 1** (3, 6-8, 11, 13-18), respectively. This equally applies to tuberculosis patients concomitantly infected with HIV (19). Pyrazinamide and ethambutol seem to be less frequently involved: pyrazinamide was implicated in 11 cases (i.e, the two present clinical reports, as well as in 9 cases in Online supplemental **Table 1** (3, 6-9, 11, 13, 20). The only two cases where pyrazinamide was successfully re-challenged are (10, 17) (Online supplemental **Table 1**). Ethambutol produced a positive skin test in only 3 cases (our Case 1, and two cases in Online supplemental **Table 1** (14, 21)), a negative skin test in two patients (Online supplemental **Table 1**) (7, 18), and was responsible for a doubtful skin test result in our Case 2. Ten other patients presented a reaction when re-challenged with ethambutol (Online supplemental **Table 1;** (6-8,10-13, 16). When ethambutol is implicated, it is usually responsible for the drug reaction together with one or more other first-line antituberculous drugs. Overall, in spite of rifampicin and isoniazide being the usual suspects, all first-line antituberculous drugs should initially be suspected.

In the cases of DRESS induced by antituberculosis treatments, it is important to rapidly identify the culprit drug(s), in order to keep treatment interruption as brief as possible. So, treating physicians may skip allergological work-up, and rely immediately on some kind of re-challenge procedure, or, if time allows, are tempted to perform skin tests (patch tests) quite rapidly, that is, once the allergic symptoms have subsided. However, in general, the most appropriate timing for performing patch tests with drugs as a potential cause of DRESS is, although still a matter of debate, ranging from 4-6 weeks to 6 months following complete remission of DRESS syndrome (25, 26). With regard to antituberculosis drugs and DRESS the delay for testing is usually much shorter, but not always specifically mentioned in the cases reported. It generally varies from 4 to 5 weeks after drug withdrawal, and always following complete remission of the skin lesions.

Concerning the most appropriate vehicles (petrolatum vs. aqua/saline vs. others), comparative studies are needed, taking into account the solubility of the molecules. In our experience petrolatum and/or saline seemed to perform well, with the former vehicle potentially being more reliable when testing isoniazide.

Note that in many cases no data on skin and/or re-challenge tests are available, and, if they are performed, these are not always clearly detailed. If allergological work-up is performed, some patients, are apparently investigated by prick and intradermal tests (with late readings), or, more often, even immediately through re-challenge tests, despite recommendations to relatively avoid such high-risk procedures in case of a severe adverse skin reaction such as DRESS syndrome (26). Patch tests seem to be performed only rarely, that is, in only 16 of 39 cases (our Cases 1 and 2; Online supplemental **Table 1** (3, 7, 14, 17, 18, 21, 27)).

False-negative reactions may occur, for example due to patch tests being performed too early (25), as evidenced by the experience with rifampicine in our first case, and pyrazinamide in our second patient. Indeed, in both patients a relapse was observed upon reintroduction of

these particular molecules, in spite of negative patch tests, and in spite of a (precautionary) adjuvant treatment with systemic methylprednisolone. In the second case, besides a true false-negative test result, an aspecific ("non-allergic") flare-up reaction of DRESS might need to be considered as well, as this might occur with early administration of (even chemically unrelated) drugs in this setting; theoretically, new drug sensitizations in the course of DRESS syndrome can probably not be excluded either. Nevertheless, although a risk of true false-negative patch test reactions should be kept in mind, this should not be used as an argument to avoid the early performance of these tests. Indeed, when patch tests do become positive for a certain drug, clinicians will most likely not re-introduce that particular drug.

Doubtful or irritant, potentially false-positive patch test reactions, might also occur, particularly with Myambutol®, the commercialized drug containing, besides ethambutol, also SLS as an excipient (26, 28). This does however not explain the reactions observed in the two cases reported here: besides a morphologically contact-allergic rather than contact-irritant patch test reaction being observed in both our cases, also 20 control patients did not show any doubtful or positive reactions to Myambutol® 3%pet.

So, besides patch tests not frequently being performed, and, whenever performed, potentially resulting in false-negative test reactions, in part explained by the sometimes (too) short time interval between resolution of skin lesions and performance of these tests, they can still be of value. Indeed, as suggested by our cases, and by similar cases from the literature, patch tests might point towards one or more potential culprit antituberculosis drugs as a cause of DRESS syndrome, and this may be useful to guide the subsequent reintroduction process. However, as patch test-positive drugs are usually not re-administered, the exact relevance and positive predictive value of these patch tests remains difficult to evaluate. However, as a precaution, many (if not all) clinicians will not re-introduce these drugs, and it remains thus debatable

whether some of these drugs, eventually aided by the use of systemic corticosteroids, might still be tolerated by a given patient.

As a word of caution, it should be noted that in a recent prospective study, the authors showed that patch tests with antituberculous drugs, in tuberculosis patients co-infected by HIV, may result in generalized, systemic reactions, rather than localized reactions to the patch-test area. However, these reactions, which have not been observed in HIV-negative patients, generally do not seem to be life-threatening and are probably explained by the immune dysregulation in HIV-positive patients, and by the short time interval between the initial skin reaction and the test procedure (29). Likewise, another retrospective study supports that HIV infection is a specific risk factor, associated with more cutaneous adverse drug reactions and re-introduction reactions (19).

Of note, isoniazid and pyrazinamide, both being derivatives from a common precursor molecule, that is, nicotinamide, share structural similarities and this raises the question of potential cross-reactivity between these drugs. Indeed, simultaneous responsibility of both molecules has been observed, in both clinical cases reported here, and in 6 additional cases (Online supplemental **Table 1;** 6-8, 11, 13), although primarily through re-challenge tests.

Cross-reactivity between the rifamycins also remains unclear (3). However, in some cases of DRESS syndrome, occurring in HIV co-infected TBC patients, rifabutin has succesfully replaced rifampicin (3). However, in spite of the successful administration of rifabutin in our first (HIV negative) patient, the absence of such cross-reactivity remains to be confirmed in larger groups of patients, also with regard to other (severe) drug eruptions. In any case this information can be valuable, for example when allergy tests are really not feasible to guide any reintroduction.

With regard to the most frequent antituberculosus drugs as a cause of DRESS, and the application of patch tests in the work-up, similar observations have been made in a recent review of 67 cases in France (30): also in this series rifampicin and isoniazid were the most frequently involved culprits, and, skin tests, including patch tests, were rarely performed. Moreover, discrepancies indeed existed between the result of epicutaneous tests and the outcome of reintroduction. Nevertheless, also these authors argued for a drug allergy evaluation, including patch tests, to guide the reintroduction of drugs in order to rapidly optimize the treatment of patients (30).

In vitro tests, such as the lymphocyte transformation test (LTT), might also be valuable in the work-up of these patients (25, 31). According to some authors the LTT might be a more reliable, and also safer, alternative to patch tests. For example, Ye YM et al. (32) demonstrated specific T-cell responses to isoniazid and rifampicin in patients with antituberculosis drugs-induced DRESS syndrome or maculo-papular exanthema. However, the apparent limited sensitivity of the LTT does not allow it to replace drug provocation tests at this moment, although its good specificity might aid in incriminating a particular drug (33). Besides questions regarding its sensitivity, the LTT is also a time-consuming test and not readily available, especially in those countries where tuberculosis is very prevalent nowadays.

Concerning rapid tuberculosis re-treatment, several authors suggest withdrawing all antituberculous agents whenever DRESS syndrome occurs, to start topical and/or systemic corticosteroid therapy, the latter even in spite of the concomitantly active tuberculosis infection, and, once resolution is obtained, to perform, if time allows, an allergological work-up.

A reintroduction of course requires that the patient is effectively suffering from tuberculosis, with microorganisms sensitive to the antibiotics that will be re-introduced, without any existing therapeutic alternatives, and rechallenges should, in any case, be performed in a

hospital setting. Usually a sequential reintroduction of different antituberculous drugs (e.g. one drug every 3 to 5 days), in increasing doses, is attempted (3); some authors suggest a (temporary) bridging therapy with second-line antituberculous drugs, such as aminoglycosides and quinolones (3, 19, 29). This fairly rapid re-introduction of potentially DRESS-causing drugs should not be considered a desensitization, which, in fact, is contraindicated in DRESS syndrome (34), but rather constitutes a 'careful re-administration', or, a 'diagnostic reintroduction'. As shown by our cases, and similar published reports, such sequential reintroduction of drugs can be guided by the results of patch tests, that is, with a reintroduction of patch-test negative drugs. However, the dose (immediately full dose or progressively ascending doses) and the order of drugs to be re-administered, as well as the use of concomitant systemic corticosteroids, remain debated.

Out of precaution, many clinicians, as in the illustrated cases, will eventually opt for careful dose-increasing regimens. A case-by-case evaluation, in cooperation with the infectiologist, is often necessary in this regard. Indeed, many (also non-dermatological) variables need to be taken into account (e.g. the severity of the infection, the risk of bacterial resistance, the time available to re-install treatment, and so on). The same applies to the question whether systemic corticosteroids should be concomitantly administered or not: one can argue that corticosteroids may be regarded as a risk-minimizing strategy, to avoid a (potentially) worse flare of the DRESS, but, on the other hand, they might mask and just delay a potential (severe) flare-up.

In many cases the objective is to keep at least 1 or 2 first-line drugs, preferably isoniazid and/or rifampicin, as these appear to be most required to achieve a successful outcome of the tuberculosis infection. Although both drugs are often prioritized and -whenever feasible- preferentially re-installed in re-introduction schemes, they are also most often implicated in

the occurrence of tuberculostatics-associated DRESS; as such, one might argue, in the context of DRESS, to rather start a reintroduction scheme with pyrazinamide and ethambutol.

Usually second-line antituberculosis drugs, notably quinolones (levofloxacin (6) but also ofloxacin, moxifloxacin and ciprofloxacin) and aminoglycosides (amikacin, streptomycin, kanamycin) are added to the treatment regimen. Ethionamide, prothionamide, linezolid, cycloserine, rifabutin, and para-aminosalicylic acid may also be used, although some of these (e.g. para-aminosalicylic acid) have also been reported to have caused DRESS syndrome (24). As mentioned above, rifabutin could be a valuable alternative in rifampicin-associated DRESS (3).

Conclusion

Notwithstanding the existence of many "unmet needs" and potential research in this area, our observations, and similar experiences in the literature, do point towards a potential added value of patch tests in the work-up of DRESS syndrome caused by antituberculous drugs. Indeed, if, in view of the infection and the urgency involved, patch tests are considered feasible, they might, taken into account their shortcomings, be useful to at least guide the reintroduction process of these particular drugs. Early patch testing is feasible, and in any case sooner than a sometimes advised 6 months following resolution of DRESS (35). Moreover, lower patch test concentrations than those usually applied in the work-up of drug eruptions might be considered (e.g. 1% of the raw material, 3% of the commercialized drug), and , although sometimes discouraged in the case of a serious cutaneous adverse drug reaction, such as DRESS, a re-challenge (not: desensitization) of patch test-negative drugs, by means of a careful reintroduction, is feasible. The order of drugs to be re-administered, and at which dose (immediately at full dose or via careful dose-escalation), and whether concomitant administration of systemic corticosteroids should be considered, all remain matters of debate.

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Figure legends

Figure 1: Case 1 presenting with DRESS syndrome from tuberculostatics; note the characteristic facial edema.

Figure 2: Positive patch tests reactions (++) on Day 4 to Myambutol® 3% pet., isoniazid 1% pet., and Tebrazid® 3% pet. but not to Rifadine® 3% pet.

Figure 3: Case 2 presenting with DRESS syndrome from tuberculostatics; note the maculopapular eruption on the legs.

Figure 4: left: HE20x. Spongiotic dermatitis with subepidermal edema (and red cell extravasation).

right: Dermal perivascular lymphohistiocytic infiltrate with scattered eosinophils (green arrows) and activated lymphocytes (red arrows).

Figure 5: Positive patch tests reactions on Day 4 to isoniazid ‘as is’ aq. (+), 30% aq. (?-), ‘as is’ in pet. (++) and 30% pet. (+).