

**SLOW ACCOUTUMANCE PROTOCOL FOR ANTITUBERCULOSIS DRUGS DELAYED
HYPERSENSITIVITY REACTION IN CHILDREN: ABOUT ONE CASE**N. Aarbaoui¹, F. Benbrahim¹, S. Benchekroun¹, Chafik Mahraoui¹ and Dr. Naima EL Hafidi*^{1,2}¹Pediatrics Department, Pediatric Allergology and Respiratory Diseases Division, Rabat Children's Hospital, Morocco.²Medical Biotechnology Laboratory (MedBiotech), Rabat Medical & Pharmacy School, Mohammed Vth University in Rabat, Morocco.

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ABSTRACT

Introduction: Antituberculosis drugs hypersensitivity reactions remains an unpredictable side effect, this occurrence may deprive patients of drug therapy, which subsequently need to be reinitiated as no better alternatives exist. **Case report:** We report a case of a seven years old boy, who was diagnosed with two tuberculosis localizations: caseous pneumonia and mediastinal lymphadenopathy. An associated HIV infection was ruled out and was started on a drug combination regimen of isoniazid, rifampicin, ethambutol, and pyrazinamide. After 20 days of therapy he developed a pruritus and generalized maculopapular exanthema, with fever, the blood test was normal. We considered this presentation as a drug toxidermia. The antituberculosis therapy was stopped, and we prescribed antihistaminic treatment. Three days later, the rash has completely disappeared and we achieved afebrile. An accoutumance protocol of antituberculosis drugs was started, we followed a slow protocol on 21 days. The time intervals between dose escalations of each drug were 24 hours. Subsequent drugs were sequentially added three days later when the preceding drug was tolerated. The tuberculosis treatment has been completed for six months by drug combination regimen, without any side effects, with improvement of clinical and radiological condition. **Conclusion:** Slow accoutumance in our patient is considered as an approach to the management of antituberculosis delayed hypersensitivity reactions. The literature lacks reported cases on antituberculosis drug accoutumance in children. The availability of validated protocols is crucial for the success of this procedure.

KEYWORDS : Antituberculosis, drugs hypersensitivity reactions, accoutumance to drugs, children.**INTRODUCTION**

Antituberculosis drugs hypersensitivity reactions remains an unpredictable side effect, this occurrence may deprive patients of drug therapy, which subsequently need to be reinitiated as no better alternatives exist. There have been many reports of desensitization to antituberculosis agents in adults but the experience is limited in children.

CASE REPORT

We report a case of a seven years old boy, presented with hemoptysis of low abundance for five month, without fever or weight loss, the chest X-ray shows ill-defined rounded opacity in right pulmonary hemifield, the rest of the lung appears to be normal (figure1). He was treated as pneumonia with an amoxicillin clavulanate in the onset of symptoms, but he continued to have hemoptysis and the X-ray shows the same radiological appearance. A chest computed tomography scan was done in front of the persistence of the symptom and radiological image; that showed an area of alveolar condensation with necrotic center in the right upper lobe, and mediastinal

lymphadenopathy.

He was diagnosed with two tuberculosis localizations: caseous pneumonia and mediastinal lymphadenopathy. An associated human immunodeficiency virus (HIV) infection was ruled out (negative ELISA test), and was started on a drug combination regimen of isoniazid (INH), rifampicin (RFP), ethambutol (ETB), and pyrazinamide (PZA). After 20 days of therapy he developed a pruritus and generalized maculopapular exanthema (figure 2), with fever. He did not have a history of hypersensitivity to drugs, but he is known to have asthma since the age of three years. The blood test was normal, especially liver and kidney functions, the full blood count does not show eosinophilia or other abnormalities. A viral infection, ricketiosis or others can be a possibilities of diagnosis, but the context is not in favor (no viral prodromes, normal blood tests). We considered this presentation as a drug toxidermia. The antituberculosis therapy was stopped, and we prescribed antihistaminic treatment. Three days later, the rash has

completely disappeared (figure 3) and we achieved apyrexia.

Following resolution of the rash, an accoutumance protocol was started. We followed a slow pattern adopted in adults in our context, the experience is limited in children. The time intervals between dose escalations of each drug were 24 hours. Subsequent drugs were sequentially added three days later when the preceding

drug was tolerated. Starting with ETB at full dose. PZA, INH and RFP was started at 1/6, 1/4, 1/3 of the final daily dose respectively, the full dose was reached on three days for each drug, by doubling dose daily (table 1). The tuberculosis treatment has been completed for six months by drug combination regimen (ERIP-K4®), without any side effects, with improvement of clinical and radiological condition (figure 4).

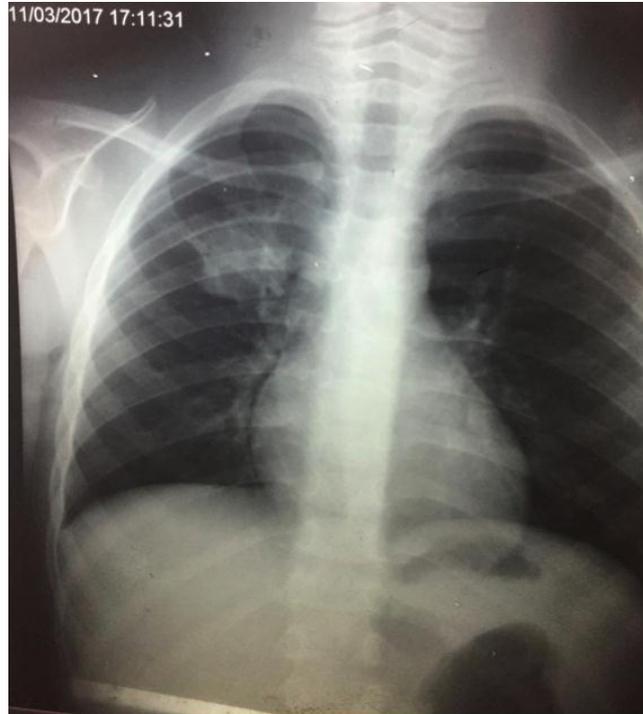


Fig. 1: Chest X-ray shows ill-defined rounded opacity in right pulmonary hemifield.



Fig. 2: Generalized maculopapular exanthema.



Fig. 3: Improvement of the rash three days after stopping antituberculosis drugs.

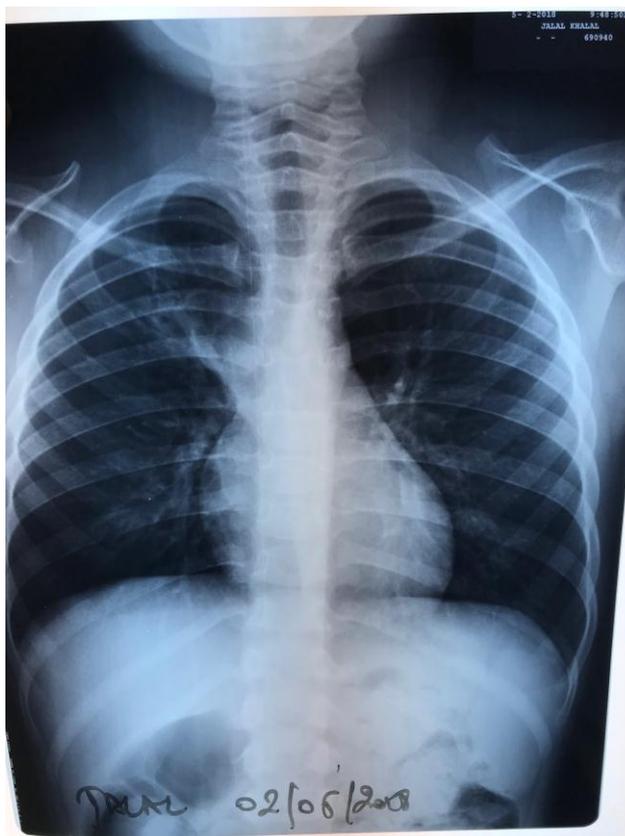


Fig. 4: Chest X-ray shows disappearance of the opacity.

Table 1: Antituberculosis reintroduction regimen in our patient (a weight of 22Kg).

Days	ETB (mg)	PZA (mg)	INH (mg)	RFP (mg)
D1 - D3	500	-	-	-
D4	500	125	-	-
D5	500	250	-	-
D6	500	500	-	-
D7 - D10	500	750	-	-
D11	500	750	50	-
D12	500	750	100	-
D13 - D16	500	750	220	-
D17	500	750	220	100
D18	500	750	220	200
D19 - D21	500	750	220	300

Key: ETB – ethambutol; PZA – pyrazinamide; INH – isoniazid; RFP – rifampicin.

DISCUSSION

Antituberculosis drugs can induce toxidermia of varying severity.^[1-4] All molecules can be responsible and their combined use, makes it difficult to identify the culprit, the date of synchronous introduction of the molecules making identical the intrinsic accountability of each.^[1-2,5-7]

Certain factors seem to promote the occurrence of toxidermia: women are more frequently involved than men,^[8-9] maximum risk is in the first two months,^[9] a particular HLA typing; immunosuppressed, in particular infected with HIV,^[9]

Note that viral infections can lead to skin eruptions and mimic drug hypersensitivity reaction if a drug (mostly an antibiotic) is taken at the same time.^[10-11] Although they are the leading cause of skin eruptions in children, viral infections can also interact with drugs, leading to mild eruptions in the case of the ‘ampicillin rash’ linked to the Epstein-Barr virus (EBV) infection^[10,12] and severe reaction during drug reaction with eosinophilia and systemic symptoms (DRESS) that is related to the human herpes virus (HHV)-6.^[10,13-15]

Our patient is presented with a maculopapular exanthema which is a form of delayed cell-mediated reactions.

Several mechanisms are involved but the specific T cell appears to be at the center of this type of toxidermal reaction. The specific involvement of T lymphocytes is suggested by a positive response in late readings of intracutaneous tests and/or patch tests. The cytotoxic functions of CD4 or CD8 lymphocytes are predominant in type IV reactions. Some studies have shown that the number of CD25+ CD4+T cells increases significantly after desensitization, although the number of CD8+ cells decreased during desensitization, suggesting that CD4+ and CD25+ regulatory T cells may have a suppressive effect on the effector function of CD8+ T lymphocytes.^[16]

Practical management plan for antituberculosis delayed hypersensitivity is not consensual to date. Although according to published cases we can propose the following steps. The first one consists of verifying, in view of the dermatological presentation and the precise chronology of the drugs taken by the patient, if possible synthesized on a frieze 'drug frieze', the intrinsic imputability of the antituberculosis drugs and the absence of other drugs.^[1,17] The second one, Concomitant with the first, it begins by assessing, the severity of the toxidermia (dermatological manifestations, general signs or systemic manifestations), the patient's field and the severity of his tuberculosis, a blood test will also be carried out to look for signs of severity or complication: liver and kidney functions, the full blood count in search of eosinophilia.^[1,17-20]

The main question whether or not it is possible to continue antituberculosis treatment under close dermatological and biological surveillance.

In the absence of signs of severity and if the patient can be seen daily by a doctor with experience of toxidermia, the treatment can be continued and a sequential reintroduction every three days, molecule by molecule, under clinical supervision, without prior allergological tests, can then be considered.^[1,8]

If there are signs of clinical or biological severity, antituberculosis treatment should be discontinued. The type of toxidermy must be specified (severe maculopapular exanthema, generalized acute pustulosis (PEAG), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, toxic epidermal necrolysis) and this should be treated without delay.^[1,8]

The third stage is based on performing allergy tests. Wich is an essential element in the decision to reintroduce or not interrupted treatments, performed remotely from the toxidermia (six weeks) and if possible within six months.^[1,8]

Only patch tests will be performed. After analysis of the literature,^[1,21] it did not note that the prick tests or intradermal tests significantly increased the sensitivity of

the tests in maculopapular exanthema, whereas they remain discussed in severe toxidermia.

After reading the patch tests, an oral reintroduction of the negative molecules into the patch tests is proposed for maculopapular exanthema, PEAG and DRESS. In the current state of knowledge, we do not recommend these reintroductions in cases of Stevens-Johnson syndrome or toxic epidermal necrolysis.^[1,8,22]

The accoutumance to drugs is defined as the induction of a temporary state of tolerance that continues as long as the drug is consumed daily and then disappears when it is stopped. It is different from desensitization wich permanent.^[23,24]

The rate of reintroduction will depend on the patient's HIV status, due to the risk of reactivation of toxidermia by patch tests in this field.^[1,25] In HIV-infected patients, the patch tests are carried out separately and the reintroduction is done molecule by molecule per week.

In patients not infected with HIV, all patch tests are performed at the same time and the reintroduction will be done molecule by molecule, every three days in case of maculopapular exanthema, and every seven to eight days in case of PEAG or DRESS.^[1,25]

Several accoutumance protocols have been described, it's depends on the mechanism of the induced reaction: S.Aniked et al.^[26] and L.P. Pur Ozyigiet et al.^[27] have described a rapid habituation protocol in adult patient. J-H. Kim et al have reported a case of oral rapid accoutumance in a child.^[28] A.Ben Mansour et al have reported a slow accoutumance in a series of 20 adult patients.^[29]

Slow accoutumance is considered as an approach to the management of patients with antituberculosis delayed hypersensitivity reactions.^[30] Its indication and its realization must be posed by a team experienced in this practice. It remains confined to mild demonstrations.

CONCLUSION

Accoutumance to drugs is a high-risk procedure and should be performed in selected patients, while no others alternatives exist. Despite the diversity of protocols reported, the literature lacks reported cases on antituberculosis drug accoutumance in children. The availability of validated protocols is crucial for the success of this procedure.

FINANCIAL DISCLOSURES

None reported.

CONFLICT OF INTEREST

The authors report no conflicts of interest relevant to this manuscript.

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