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Evidence of a Monoclonal Peak in Clonality Assay during an Episode of Drug-Induced Eruption

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ABSTRACT

We describe the case of a patient presenting a drug-induced rash simultaneously associated with the discovery of a monoclonal T-cell proliferation (monoclonal peak revealed by clonality assay). The peak disappears with the rash after the responsible drug (pantoprazole) was withdrawn. Positive patch-test to pantoprazole confirmed the diagnosis of drug-induced rash. This case reports that a systemic monoclonal peak could then be the consequence of a drug-induced rash, and to our knowledge, it had never been described.

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INTRODUCTION

A drug-induced rash is an adverse drug reaction of the skin that disappears as the offending drug is withdrawn.

The most common appearance is the erythematous rash but we can sometimes face papulosquamous, bullous or lichenoid forms.

The frequency of such drug eruption is estimated around 2.2% (1) of hospitalized patients.

Some drugs are more likely than others to cause drug eruptions: anti-infective and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly suspected drugs in overall Cutaneous Adverse Drug Reactions (CADR). (2) NSAIDs are the second most important cause of hypersensitivity (3).

T-cell clonality assay provides molecular genetic evidence of clonality in malignant or suspect lymphoproliferations.

T-cell clonality can be proved either by detection of monotypic TCR molecule (indirect) or by PCR (direct). Here we used T-cell receptor (*TCR*) gene rearrangements using a PCR-based method.

The method is based on multiplex PCR techniques using multiple primers complementary to a consensus of TCR gene segments, in order to cover the T-cell repertoire. (4)

This clonality assay can be performed on blood but also on cutaneous samples.

CASE REPORT:

We describe the case of a 69-year old male patient with a medical history of psoriasis since the age of 14, treated by UV therapy.

Co-morbidities include alcohol (withdrawal 5 years ago), tobacco use (stopped 15 years ago), a stroke ten years ago, hypertension and benign prostatic hypertrophy.

His medical treatment was composed of Kardegic® (acetylsalicylate de lysine), Tahor® (atorvastatin) and Toviaz® (fésotérodinefumarate).

On October, 20th 2017 he consulted his doctor for left-knee ache and was prescribed nonsteroidal anti-inflammatory (Nabucox® = nabumétone) in order to relieve his pain, and also pantoprazole (proton pump inhibitor).

Within 2 days, he developed vertigo, hypotension (10mmHg systolic) and a rash characterized by a descendant erythema of the face, trunk, and limbs.

Clinical examination on October 25th showed that axillary skin was infiltrated and there was a serious flow from the intern part of thighs.

He also presented a few squamous patches on the chest, the thighs and the hands plus seborrhoeic dermatitis on the face. There was genital but no buccal lesions.

Concerning the biological check-up:

There was no hypereosinophilia (0.42 G/L) and neither renal nor hepatic disturbance.

CRP was elevated to 36 mg/L, there was hyperleukocytosis (16,47 G/L) and hyper IgE (1423 KUI/L for normal values ranging between 0 and 100 KUI/L) that we can relate to hypersensitivity. No Sezary cells were found on a blood smear.

Immunologic tests revealed the presence of parietal cell antibody, titer > 800. That could be related to an immunopathological an atopic background.

Thus the patient suffered B12 deficiency (160ng/L with normal values ranging between 197 and 771 ng/L). Serum protein electrophoresis did not show any abnormalities.

A cutaneous biopsy of the right thigh in the erythematous area and a biopsy of the back were performed on October, 26th.

Biopsy of the thigh revealed: “a very slightly spongiotic epidermis topped with cornea including a microabscess. No visible necrosis of keratin. The underlying dermis includes a very small perivascular lymphocytic infiltrates.”

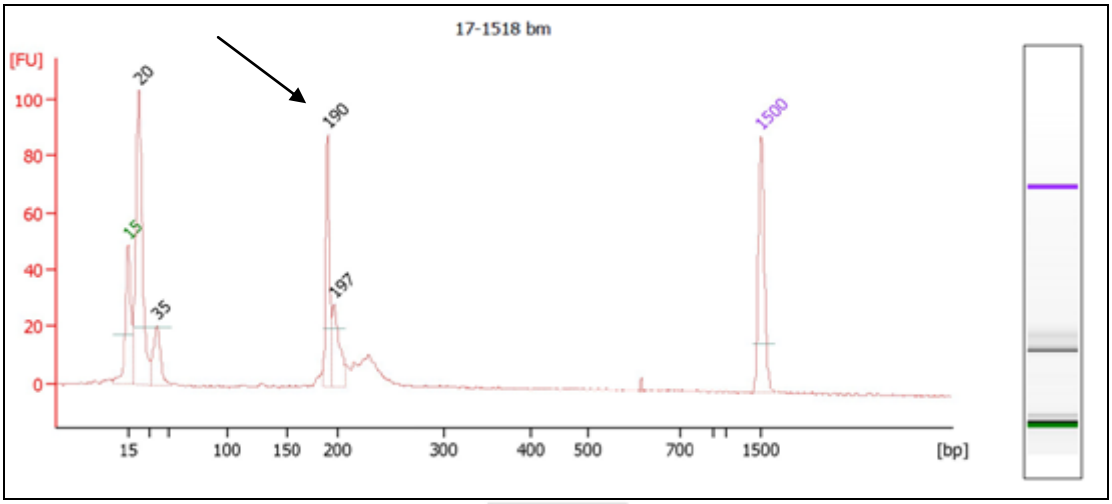
The pathological anatomy report stated that the histologic change was minor and lacked in specificity.

Provided the doubtful characteristics of the skin eruption, several hypotheses were mentioned: recurrence of psoriasis, T cutaneous lymphoma … That explains why numerous

tests were launched including T clonality assay, which would not have been performed if the skin damages had clearly evoked toxidermia.

During his hospitalization, a clonality assay was ordered and performed on a blood sample collected on October 27th (5 days after the eruption) and showed a clear monoclonal peak, meaning there was evidence for a systemic monoclonal population of T-phenotype (189 base pair in gammaB tube, clear/sharp peak).

Flow cytometry analysis was not performed at this time.



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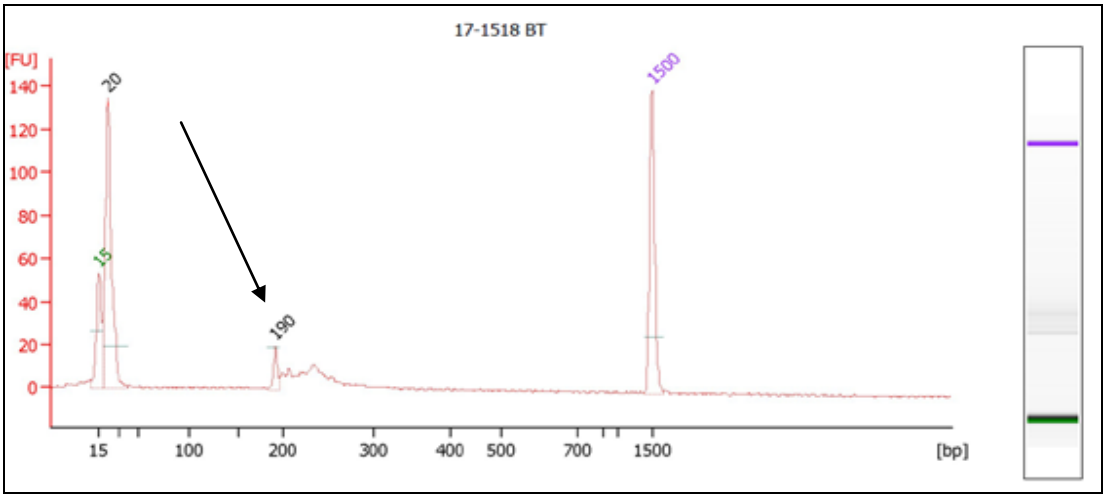


B

Figure 1: A shows evidence of the monoclonal peak in tube B for our patient (see arrow), 189 base pair, October 27th

B: shows the persistence of monoclonal peak after heteroduplex analysis, October 27th

One of the hypothesis being a drug-related eruption, pantoprazole and nabumetone were withdrawn and a rapid decline of the skin lesions and pruritus was observed, and finally ended with desquamation. The patient was treated by topical corticosteroid, but then developed furunculosis for which he received local and oral antibiotics. He also received antihistaminic to stop pruritus.

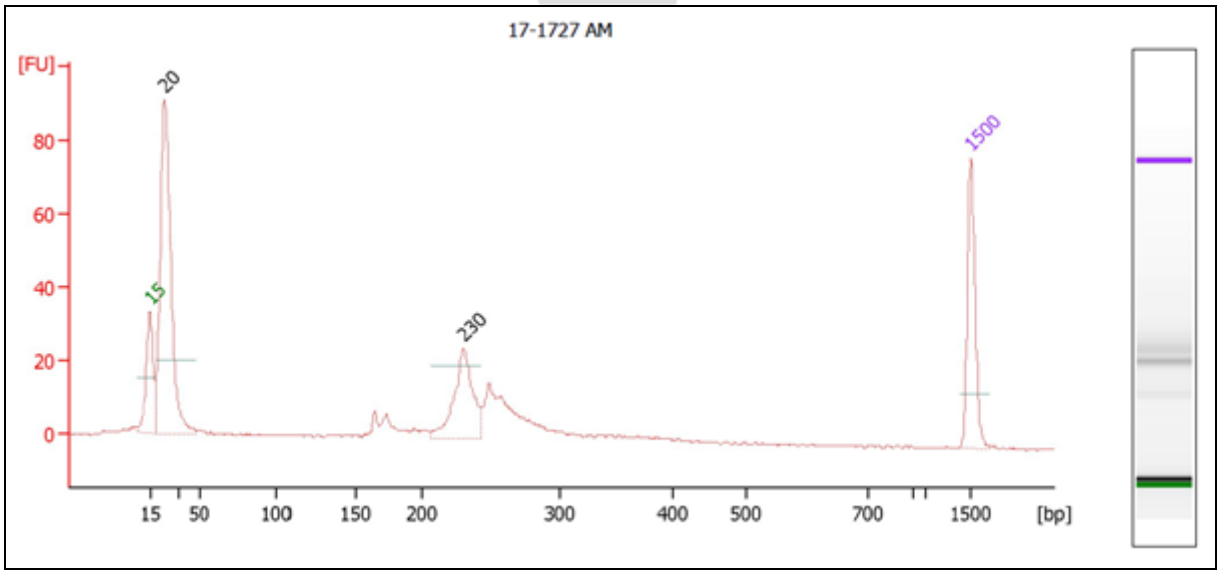
Since we were facing a discrepancy between a clinical presentation and evolution suggestive of toxidermia and this evidence of monoclonality, we decided to double-check the clonality assay.

The analysis was performed again 9 days later (December, 5th).

The clonality assay now showed the same profile but the peak was under threshold meaning the patient now presented a polyclonal T cell population.

Our hypothesis is that the peak disappeared in parallel with the toxidermia.

This time flow cytometry on blood sample was performed and showed that HLA-DR-expressing CD8+ T cells lymphocytic population were above the normal range (29%).



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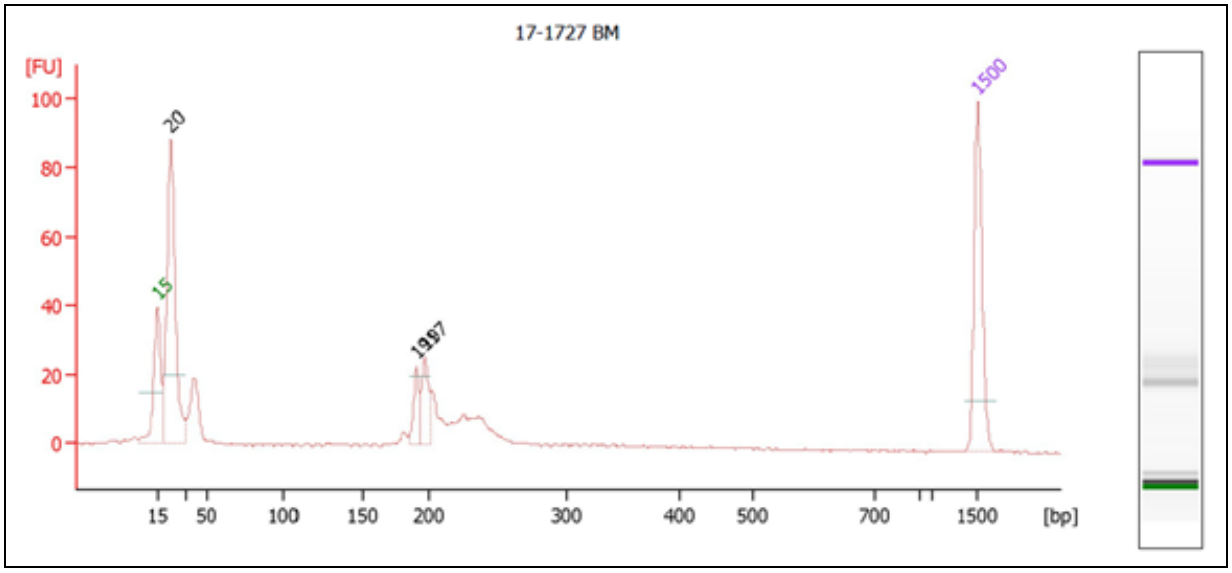

B

Figure 2: A is the profile on tube A PCR (December, 5th): no evidence of monoclonal peak, B: is the profile on tube B PCR (December, 5th): no evidence of monoclonal peak

The patient was controlled on January, 4th, he had no more skin lesion except for psoriasis.

On January, 15th 2018, allergy tests (Patch test type) to pantoprazole and nabumetone were performed. For both drugs, there were 3 different dilution trials: 30%, 50% and pure. The test was negative for nabumetone and positive after 48 and 72 hours for pantoprazole and also for fragrance mix 8%.

Lifelong contraindication to further use pantoprazole and derived molecules (such as esomeprazole, omeprazole) was stated, whereas nabumetonecould be reintroduced along with antihistaminics.

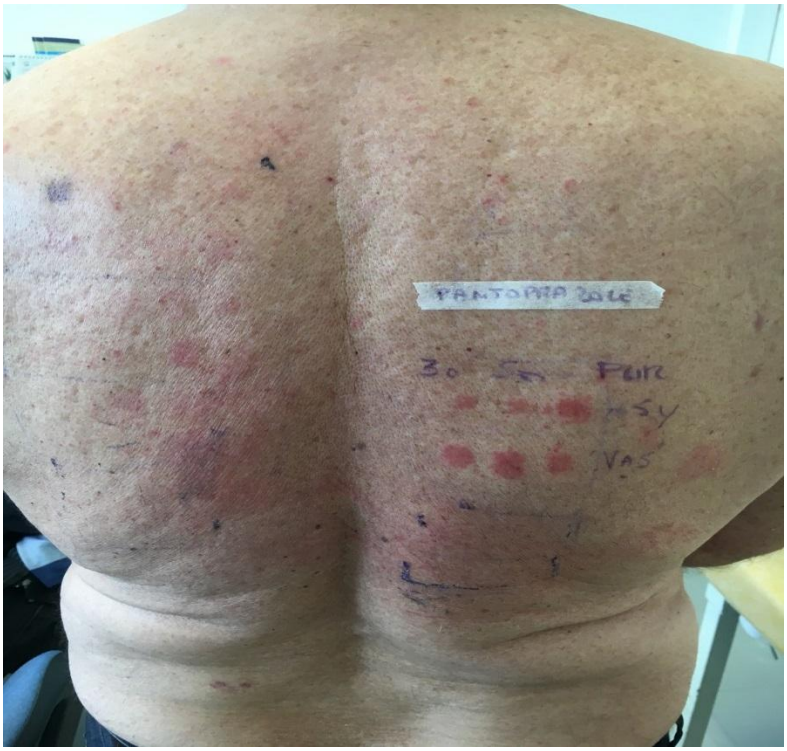

Figure 3: Shows positive patch test to pantoprazole

Many studies suggest that Patch tests may be a useful, safe and valuable procedure to demonstrate evidence of drug imputability in CADR. For (3) although oral rechallenge is considered the gold standard for confirming drug imputability in CADR, patch testing could be suggested as a first choice in the study of non-immediate reactions(5).

The significant correlation was found between the patch test result and the clinical probability of a CADR according to the imputability score of the drug. With this high specificity, we can say that patch test confirmed the diagnosis of Pantoprazole-induced toxidermia.

DISCUSSION

To our knowledge, it is the first time that a blood monoclonal peak is described as a concomitant with toxidermia in its appearance and disappearance.

However, reports have already shown that drug toxicity can result in abnormal T-cell proliferation such as pseudolymphoma.

“Dominant T cell clonality in pseudolymphomatous drug eruption: a case report” (6) states how hard it is to differentiate pseudolymphomatous drug eruption from frank lymphoma.

Drug eruptions are a common cause of cutaneous T-cell pseudolymphoma and might be wrongly suspected of being malignant.

It might be the same with clonality blood assay that should always be interpreted carefully with the global analysis of patient history including possible drug hypersensitivity. In case of doubt, clonality assay should be re-performed after regression of cutaneous eruption.

The presence of such proliferation during infectious or inflammatory diseases is well known in cutaneous biopsy but it is the first time that systemic atypical proliferation is described. However in 2016 in "Intralymphatic CD30+ T-cell proliferation during DRESS: a mimic of intravascular lymphoma" (7) was described intralymphatic proliferation. A patient who developed DRESS syndrome had a biopsy that revealed atypical, partially CD30+, intralymphatic T cell proliferation.

Taxidermy is known to cause local disorders, it was recently shown that a regional atypical proliferation is possible (7). This case report lets us think that a drug-induced eruption might also cause systemic disorders such as monoclonal T-cell proliferation in blood.

Atypical lymphocytic infiltrates are often observed in skin biopsy specimens from patients with altered immune function (8), this is the case of our patient who suffers from psoriasis (systemic immune dysregulation state) since the age of 14. Evidence of parietal cell binding antibody also confirms the underlying perturbations in immune function.

Some drugs like anticonvulsants, antidepressants or benzodiazepines have immune dysregulating properties since they are able to depress T suppressor function, but pantoprazole is not known to perturb lymphoid function. (8)

In a study (8), T cell clonality on FFPE is present in 14% (2 of 14) of lymphomatoidhypersensitivity cases. In other studies, evidence of T cell clonality in tissues ranged between 0 and 6%. But again, they did not investigate systemic clonality.

In their study, the clinical course was the same as with our patient: when the drug was discontinued all patients experienced complete resolution of skin lesions.

Now, what is the mechanism that enables some drugs to cause atypical cutaneous lymphocytic infiltrates? For Magro and Crowson(9), the drug may be able to induce an

aberrant immune response to an antigen that could be the drug itself. The antigen could block or stimulate receptor-mediated lymphocyte function. (8)

Thus pharmacological agents may be able to let a clone emerge by dysregulating T-cell function either by depressing the T-suppressor function or by antigenic stimulation.

When we face a cutaneous reaction concomitant with the discovery of a monoclonal peak, we should think of the eventuality that a real allergic response could be responsible for this abnormality. We should look for newly introduced drugs that could explain the situation and always perform a control of the clonality assay a few weeks later when the skin lesions have disappeared. We should also always take into account the medical history of the patient since an immune dysregulated background could explain why some patients develop atypical lymphoid reactions while others do not.

CONFLICTS OF INTEREST: none

ACKNOWLEDGMENT

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