Allopurinol hypersensitivity syndrome presenting as cutaneous lymphoma

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Abstract

Adverse cutaneous reactions to drugs are frequent (2 to 3 percent of hospitalized patients); although most are not severe, a few are related with high rates of morbidity and mortality. Rapid recognition of severe reactions is essential, such as Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity syndrome. The drugs most often responsible for the hypersensitivity syndrome are anticonvulsants, sulphonamides and allopurinol. Hypersensitivity syndrome induced by drugs in rare instances present clinical characteristics and even a histological picture indistinguishable from true cutaneous lymphoma. In these cases the differentiation between the two clinical entities although difficult is very important due to the natural therapeutic implications.

The authors present a 51 years-old patient with rapid onset of high fever and erythroderma. The histological findings of the cutaneous and lymph node biopsies were of cutaneous T-cell lymphoma with specific lymph node involvement. However, we were informed that the patient had been medicated with allopurinol, two weeks before the symptoms. The clinical and analytical characteristics and the clinical evolution, confirmed the diagnosis of allopurinol hypersensitivity syndrome.

Key words: hypersensitivity syndrome, cutaneous pseudolymphoma, allopurinol.

Introduction

The term drug-induced hypersensitivity syndrome refers to specific severe idiosyncratic reactions that typically include skin rash and fever, often with hepatitis, arthralgia, lymphadenopathy or hematological alterations (eosinophilia and atypical lymphocytosis).[1] They habitually appear 2 to 6 weeks after the start of drug administration, later than most other severe cutaneous reactions[1].

The cutaneous manifestations described in this syndrome include practically all the clinical types of cutaneous reactions to drugs, from morbilliform eruptions to toxic epidermal necrolysis. There is occasional atypical lymphoid hyperplasia and forms of cutaneous pseudolymphoma.[1] In the latter cases, the symptoms generally recede with suspension of the drug, but interestingly, cases of evolution to lymphoma have been described with hydantoin and carbamazepine after a transitional phase of pseudolymphoma.[2]

The pseudolymphoma that appear as reactions to drugs pose pertinent problems of differential diagnosis with lymphomas, since the histological profile of the two entities is practically the same, and it is only possible to differentiate between them by their evolution and clinical and laboratory manifestations.[3,4]

Anti-epileptic drugs and sulphonamides are the most frequent causes of drug-induced hypersensitivity syndrome; less often, it is found in association with captopril, gold salts and allopurinol.[1] The latter is the drug most often used in the therapeutic approach to hyperuricemia, and about 10% of patients that use it present side effects (rash or gastrointestinal complaints), which are habitually benign and self-limiting. Clinical symptoms of greater severity, such as hypersensitivity syndrome, are rare.

However, the authors describe an unusual clinical case of a patient with pulmonary tuberculosis, on antibacillary therapy for two months, who developed a high fever, erythroderma, lymphadenopathy, eosinophilia, atypical lymphocytosis and hepatitis,

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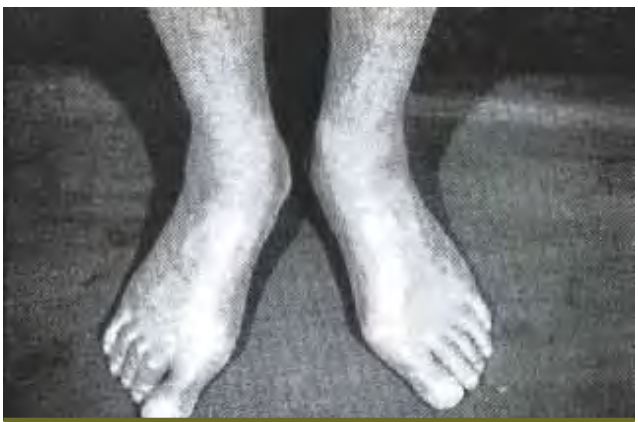
Generalized erythematous lesions.

FIG. 1



Violaceous lesions with follicular accentuation on the limbs.

FIG. 2

and in whom the histological examination of the cutaneous and ganglionary biopsies revealed cutaneous T-cell lymphoma (CTCL) with specific ganglionary involvement. However, it was later determined that the patient had been medicated with allopurinol two weeks before the start of the clinical symptoms. The clinical and laboratory features and the evolution of the disease confirmed the diagnosis of allopurinol hypersensitivity syndrome (AHS).

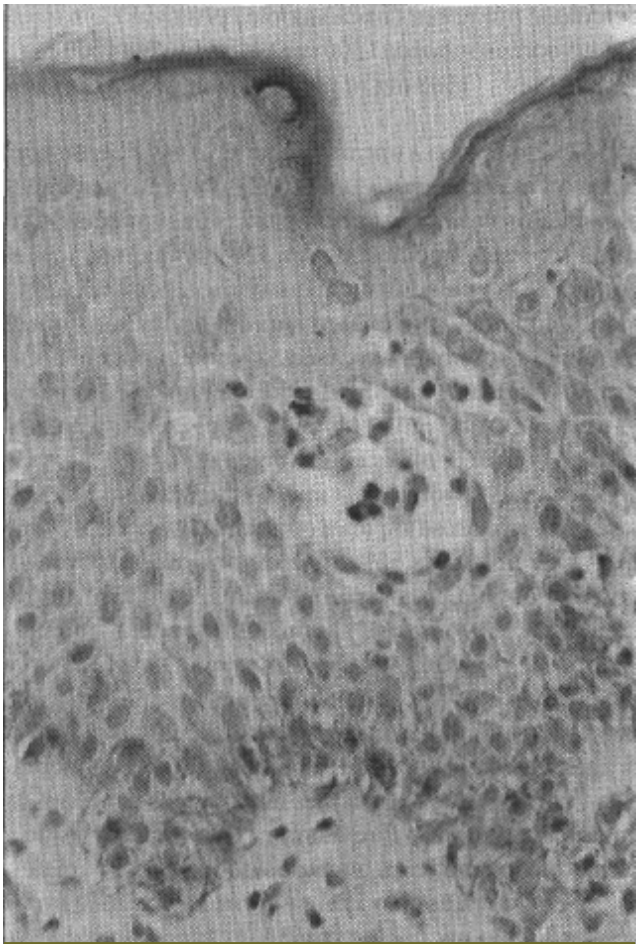
Case report

A 51-year-old patient, Black, married, born in Cape Verde and a resident of Carcavelos for 30 years, admitted to the Dermatology Unit due to symptoms with sudden onset, with one week of evolution, high fever (40ºC), and erythroderma, accompanied by odynophagia and mild coughing. The patient had pulmonary tuberculosis (positive bacilloscopy), and had been under treatment with isoniazid (300 mg), rifampicin (600 mg), pyrazinamide (1500 mg) and pyridoxine for two months.

The main findings of the physical examination upon admission were: patient in reasonable general state; feverish (40ºC); with conjunctivitis and hyperemia of the oropharynx; adenomegalies of the cervical and axillary chains; and hepatomegaly. The patient presented erythematous lesions occupying almost all the cutaneous tegument, which coalesced to cover the trunk, upper limbs, face and scalp, with follicular accentuation and violaceous coloration of the lower limbs, multiple vesicles in the palmoplantar regions, and edema of the face, hands and feet (*Fig. 1 and 2*).

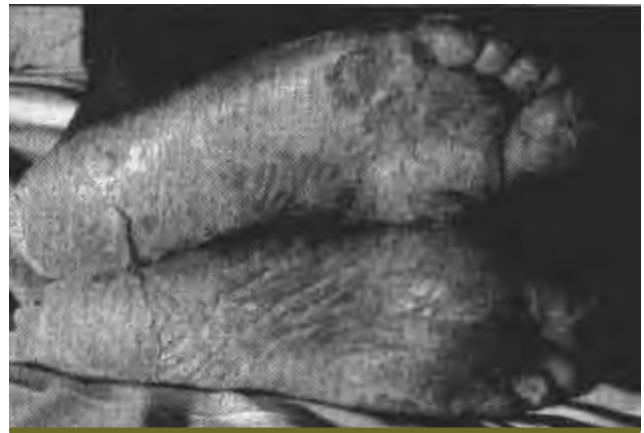
The initial laboratory tests showed: leukocytosis with atypical lymphocytosis and eosinophilia (leucocytes 29000 per mm^3, lymphocytes 55%, half of which were activated, eeosinophils 8%), normal renal function (urea 29 mg/dL, creatinine 1.01 mg/dL), alterations in hepatic function (prothrombin time 45%, glutamic-oxaloacetic transaminase 103 U/L, glutamic-pyruvic transaminase 164 U/L, gamma-glutamyl transpeptidase 404 U/L), lactate dehydrogenase 861 U/L and sedimentation rate 43 mm in the 1st hr. The histological examinations of the cutaneous and ganglionary biopsies revealed "epidermotropism and follicle tropism, with Pautrier's microabscesses in the epidermis, aspects that are compatible with cutaneous T-cell lymphoma (mycosis fungoides type) and specific ganglionary involvement" (*Fig. 3*). In view of this diagnosis and the potential need for chemotherapy, the patient was transferred to the Medicine Unit on the 3rd day.

In the Medicine Unit, the patient continued to present persistent high fever (39-40ºC), with the skin lesions evolving through periods of exacerbation with accentuation of the inflammatory characteristics, followed by generalized peeling, more intense and coarse in the extremities and palmoplantar regions (*Fig. 4*). The characteristics of the leukogram (leukocytes 33000 per mm^3, eosinophils 14%, lymphocytes 46%), remained the same. There was significant exacerbation of hepatic function (glutamic-oxaloacetic transaminase 930 U/L, glutamic-pyruvic transaminase 580 U/L, total bilirubin 2.3 mg/dl, with conjugated



Epidermotropism with Pautrier's microabcesses in the epidermis.

FIG. 3



Accentuated desquamation, in layers, in the extremities.

FIG. 4

bilirubin of 1.3 mg/dL, prothrombin time 44%) and impairment of renal function (urea 54 mg/dL, creatinine 1.88 mg/dL).

Staging examinations (bone marrow examination, bone biopsy, thoracoabdominal compression technique - TAC) were performed with negative results. Viral serology tests (hepatitis B and C and Epstein-Barr viruses, V1H1 and 2, HTLV1) were also negative. Of the immunological alterations found, we emphasize: total IgE 1047 UI/mL (N10), cel LE 1+, Waller Rose 1/64.

At this stage, and after an exhaustive investigation of the drugs prescribed to the patient, it was determined, together with the attending physician that the patient had started to take allopurinol (300 mg/day) two weeks before the onset of the fever, due to asymptomatic hyperuricaemia. This new aspect made allopurinol hypersensitivity syndrome a pertinent diagnosis, despite the specific histological diagnosis of CTCL.

During the 2nd and 3rd weeks of hospitalization, the patient continued to present high fever, erythroderma and marked prostration. With the appearance of a profile of hepatitis, the health professionals scheduled a liver biopsy that was not immediately feasible by the percutaneous route, due to insufficient parameters (prothrombin time 45%), or by the transjugular route due to technical unavailability. The biopsy was only performed in the 5th week of hospitalization, when there was found to be an improvement in the coagulation values (prothrombin time 73%).

Histological examination of the liver biopsy revealed "extensive hepatocellular necrosis, with moderate inflammatory process consisting of plasmocytes and eosinophils from the portal spaces" (*Fig. 5*). These aspects later favored a hypothesis of allopurinol hypersensitivity syndrome. Also, the abrupt onset of fever two weeks after the start of allopurinol administration, with severe hepatic impairment, and peripheral blood alterations (eosinophilia and lymphocytosis), although with cutaneous lesions with histological alterations indistinguishable from CTCL, were in favor of the diagnosis of hypersensitivity syndrome. To this effect, the patient was sent to the Hematology Clinic of Hospital dos Capuchos, where the blood count was repeated, revealing 10% Sezary type cells and reinforcing the admission diagnosis, whereupon the introduction of corticotherapy was proposed.

Hepatocellular necrosis, inflammatory infiltrate composed of plasmocytes and eosinophils in the portal spaces.

FIG. 5

The patient was then submitted to therapy with prednisolone (60 mg/day), with reports of rapid apyrexia and progressive improvement of the cutaneous lesions; tuberculostatic drugs, which had been suspended since the start of the complaints, were reintroduced at the same time.

In the convalescence period, there was an episode of fever, lumbago and acute renal failure (urea 106 mg/dL, creatinine 8.0 mg/dL), which was attributed to interstitial nephritis secondary to rifampicin. With its suspension, complete normalization of renal function was achieved without the need to resort to haemodialysis, continuing the therapeutic approach with isoniazid, pyrazinamide and ethambutol with total tolerance. The patient remained under corticosteroid therapy for 4 months, with complete normalization of the clinical symptoms and laboratory alterations. After the suspension of the corticotherapy, epicutaneous tests and lymphoblastic transformation tests were performed with negative results. The patient remained asymptomatic for a year, under outpatient follow-up.

Discussion

In this case, the differential diagnosis was somewhere between the CTCL suggested by the cutaneous and ganglionary biopsies and allopurinol hypersensitivity syndrome with expression of cutaneous pseudolymphoma, from the time when, as mentioned previously, the use of this drug was confirmed by the attending physician, who had introduced it two weeks before, due to asymptomatic hyperuricaemia related to pyrazinamide. The clinical and laboratory aspects, as well as the histopathological findings, made it possible to rule out other diseases, either of the infectious kind, or other types of adverse cutaneous drug reactions.

While the patient's history of allopurinol administration was not known, the histological aspects observed (epidermotropism, follicle tropism and Pautrier's microabscesses) were of much value as they were highly specific to cutaneous lymphoma, serving as a basis for the entire therapeutic strategy, not allowing the use of corticotherapy, even after the diagnosis of allergic reaction to allopurinol has been admitted. In fact, pseudo-lymphomas have been classically attributed to anticonvulsant drugs such as hydantoin and carbamazepine, and are only described very infrequently for allopurinol (just 1 case),[5] with no cases related to the tuberculostatic drugs being found. However, some clinical and laboratory aspects allowed the hypothesis of allopurinol hypersensitivity syndrome (AHS) to gradually gain more consistency. The sudden onset of the state of fever and erythroderma, as it occurred in the patient described here, is much more frequent in severe drug reactions than in cutaneous lymphomas, which generally have a more insidious onset and indolent course. The clearly systemic nature of the initial symptoms; high fever (40°C), deterioration (albeit slight) of renal function, and hepatitis with marked cytolysis, are also much more common in AHS.[6,7] In mycosis fungoides, on the other hand, hepatic impairment seldom occurs (microscopic infiltration is found in 31% of the patients) and when it does, it occurs only in the terminal stage, rarely with evident clinical or laboratory translation.[8] The liver biopsy, although only possible at a late stage due to the lack of coagulation parameters, revealed extensive hepatocellular necrosis and moderate infiltration of the portal spaces with plasmocytes and eosinophils, substantially reinforced the hypersensitivity sAs referred to above, epicutaneous tests were carried out two months after the suspension of corticotherapy, including allopurinol in concentrations of 1 and 0.5% in Vaseline, with negative results, which is frequent in toxidermia. The lymphoblastic transformation tests were conducted later on and produced negative results, which was not considered relevant since these tests have very low sensitivity for drug hypersensitivity reactions.[1]

The excellent clinical evolution recorded with

the suspension of the drug, and with the corticotherapy (continued for four months) and the one-year follow-up, led us to confirm a diagnosis of AHS with certainty.

The pathogenic mechanisms involved in this syndrome are not fully clarified, admitting, as probable, immunological factors (the deposition of circulating immune complexes predominates, although there are also alterations of cellular immunity), genetic predisposition (more frequent in patients with purine nucleoside phosphorylase deficiency) and accumulation of the drug (of its main metabolite, oxypurinol, whose excretion is dependent on renal function).[9,10]

Treatment of AHS includes immediate suspension of the drug, generally with complete regression of the clinical symptoms, although this process may be slow, while the cutaneous lesions may persist or even worsen for several weeks (as in this case). Corticotherapy is frequently used in the improvement of the symptomatology and laboratory alterations. It habitually requires prolonged use (the treatment time was four months in this patient) and a very gradual decrease of the doses, due to the frequent reappearance of symptoms.[11] Despite the therapeutic approach, mortality is high (26% in a series of 38 patients), the most frequent causes of death, in these cases, being hepatic failure and sepsis.[7,11]

Finally we draw your attention to the need for the judicious use of allopurinol, reminding readers that its use in asymptomatic hyperuricaemia is controversial and often unnecessary, and that it is essential to adjust the dose in patients with altered renal function. ■

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