CASE REPORT

Allopurinol-induced DRESS syndrome presented as a cholecystitis-like acute abdomen and aggravated by antibiotics

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SUMMARY

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a potentially life-threatening adverse drug reaction characterised by generalised skin rash, fever, lymph node enlargement and haematological abnormalities, in addition to multiorgan involvement. However, diagnosis can be challenging, with rare cases presenting as an acute abdomen.

Its aetiopathogenesis is not fully understood but inefficient drug detoxification, deregulated immune responses, reactivation of host viruses and genetic predisposition appear to be important. Furthermore, it has been recently recognised that antibiotics may act as promoters of DRESS syndrome caused by another drug. We report the case of a 48-year-old man, receiving allopurinol, who developed DRESS syndrome, initially presenting with a cholecystitis-like acute abdomen that was triggered by antibiotics. This report also emphasises the utility of performing patch skin tests to establish drug imputability.

BACKGROUND

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome typically presents with fever, rash and lymph node enlargement, in addition to multiorgan involvement, the liver being the most commonly affected. To the best of our knowledge, this is the second case report of DRESS syndrome with gallbladder involvement.

CASE PRESENTATION

A 48-year-old Caucasian man was admitted to the emergency department with fever (39.5°C), acute abdominal pain in the right hypochondrium and positive Murphy sign. Relevant medical history included hypertension and recurrent gout attacks for which he had been prescribed allopurinol 4 weeks prior to admission.

Blood tests showed slightly elevated C reactive protein (4.91 mg/dL), creatinine (1.24 mg/dL), alkaline phosphatase (206 IU/L) and γ -glutamyl transpeptidase (337 U/L) and a marked increase in aspartate aminotransferase (AST: 205 IU/L) and alanine aminotransferase (ALT: 575 IU/L), but a normal complete blood count.

Abdominal ultrasound showed slight perihepatic fluid, gallbladder with thickened (12 mm) and layered wall, but not stretched and with no signs of lithiasis. The patient was submitted to laparoscopic cholecystectomy that revealed a perforated gallbladder with subserous oedema but without inflammation on histopathological examination. This finding along with negative bacterial culture was inconsistent with the diagnosis of cholecystitis.

Intravenous piperacilin-tazobactam was initiated after surgery but stopped within 48 hours due to a rash. Dermatological examination revealed a maculopapular exanthema that progressed to an intensely pruritic exfoliative erythroderma with facial involvement, including the ears (figure 1), and enlarged lymph nodes.

Figure 1 Maculopapular exanthema with follicular accentuation (A,B), progressing to exfoliative erythroderma involving the face and ears (C).

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Figure 2 Histopathology of the fifth day of exanthema, showing diffuse epidermal spongiosis, vacuolar degeneration of the basal layer and lymphohistiocytic infiltrate of the superficial dermis, mostly perivascular (A), with numerous eosinophils (B). H&E, (A) $\times 100$, (B) $\times 200$.

At this point, biochemistry panel and complete blood counts showed worsening of renal and liver function (creatinine 2.5 mg/dL, AST 361 IU/L, ALT 1022 IU/L) and an elevated white cell count $26.800/\text{mm}^3$ with frank eosinophilia of $5300/\text{mm}^3$.

INVESTIGATIONS

A skin biopsy showed mild spongiosis, vacuolar degeneration of the basal layer and a predominantly perivascular lymphohistiocytic infiltrate with many eosinophils consistent with a drug eruption (figure 2).

Serologies for Epstein Barr virus, cytomegalovirus, hepatitis B and C, and HIV were negative as well as serum DNA for human herpes virus 6 (HHV-6), anti-nuclear antibodies and human leukocyte antigen (HLA)-B*58:01.

According to The European Registry of Severe Cutaneous Adverse Reactions to Drugs criteria for the diagnosis of DRESS, the patient was diagnosed as having DRESS, meeting all the diagnostic criteria, except for atypical lymphocytosis.

Patch tests performed later with allopurinol at 10% pet and an antibiotics' series, including piperacilin-tazobactam, revealed a positive patch test only to cefoxitin 10% pet (+ +). Histological examination of the positive patch skin reaction showed a dermal lymphohistiocytic perivascular infiltrate with mild lymphocytic exocytosis and vacuolar degeneration of the basal layer. A review of the pharmacological history revealed a single administration of cefoxitin before surgery.

DIFFERENTIAL DIAGNOSIS

Sepsis, acute viral infections and other severe cutaneous adverse reactions to drugs such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) should be considered in the differential diagnosis of DRESS syndrome. In our patient, negative viral serologies and blood cultures excluded an infectious cause and, in turn, the longer latency period from exposure to the drug and the presence of eosinophilia favoured DRESS syndrome instead of SJS or TEN. A DRESS syndrome induced by allopurinol and aggravated by cefoxitin was presumed.

TREATMENT

The patient received treatment with oral methylprednisolone (0.75 mg/kg/day). Since an infectious aetiology had been excluded, antibiotherapy was interrupted. Allopurinol, the probable main culprit, had already been stopped on admission.

OUTCOME AND FOLLOW-UP

Within a few days after starting methylprednisolone, marked clinical improvement was observed with resolution of the fever and disappearance of the erythroderma. Nonetheless, a residual maculopapular exanthema still persisted, with slow improvement.

There was also a progressive improvement of hepatic and renal function that subsequently became normal.

Methylprednisolone therapy was slowly tapered for 5 months, as eosinophilia and pruritus recurred on dose reduction. However, the skin changes resolved without sequelae after approximately 1 month of oral steroid treatment.

DISCUSSION

DRESS is a potentially fatal adverse drug reaction characterised by a generalised rash, fever, enlarged lymph nodes, haematological changes and multiorgan involvement. The liver is the most frequently affected organ with only one reported case of DRESS syndrome concerning a possible involvement of the gallbladder.¹

Our patient presented with a cholecystitis-like acute abdomen and was not immediately recognised as having an adverse drug reaction, mainly because it was followed by an exanthema only 2 days after admission, and eosinophilia and enlarged lymph nodes appeared after 5 days.

As previously reported,² renal dysfunction, which impairs allopurinol excretion, is typically associated with allopurinol-induced DRESS, and this was also the case of our patient.

Imputability tests to allopurinol, namely patch skin test and HLA-B*58:01 were negative. HLA-B*58:01 positivity, although strongly associated with severe cutaneous adverse reactions to allopurinol, is not mandatory.³ Also, negative patch test results with allopurinol are found commonly,⁴ and a negative test does not exclude the imputability of a drug.

DRESS flare-ups may occur with drugs other than the culprit and patch skin tests can be used if there is uncertainty regarding the offending drug.

Antibiotics may aggravate DRESS by enhancing HHV6 proliferation within infected lymphomononuclear cells in target organs⁵ or by a co-sensitisation phenomenon.

Antibiotic-induced exanthema occurs more frequently in conditions with previous immune activation, like in infectious mononucleosis, and a percentage of these patients become permanently sensitised to the drug. This may also occur in DRESS where, apart from the culprit drug, we find frequent positive patch tests to antibiotics that are maintained in time.⁶

This seems to be the case for our patient as well, who used two different antibiotics and presented with an exanthema 2 days after surgery.

He had received one single dose of cefoxitin and was under therapy with piperacilin–tazobactam. The positive patch test to cefoxitin with histopathology compatible with a drug eruption in our patient favours co-sensitisation to cefoxitin and not to piperacilin-tazobactam.

This report of DRESS induced by allopurinol is unusual for its initial presentation, mimicking an acute cholecystitis and reminds us that an acute abdomen, in the context of likely drug exposure, can be caused by an intense systemic inflammatory response in the setting of a DRESS syndrome. As oral rechallenge is contraindicated in DRESS, it also highlights the utility of performing patch skin tests with all drugs used by the patient to establish potential culprit drugs, as these individuals may become sensitised to concurrent drugs other than the main culprit.

Learning points

- ▶ Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome can present as an acute abdomen.
- ▶ It should be considered in patients with multiorgan involvement and a history of likely drug exposure.
- ▶ A detailed review of drug exposure is mandatory to establish the potential culprit.
- ▶ DRESS flare-ups may occur with drugs other than the main culprit and patch skin tests can be useful to establish drug imputability and even co-sensitisation.

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