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CASE REPORT

Azathioprine hypersensitivity syndrome, a drug reaction mimicking sepsis

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Abstract

A 55-year-old male was admitted to hospital and later to the ICU with refractory distributive shock thought to be sepsis of unknown origin. Two days after discharge the patient was readmitted to the ICU with a generalised skin eruption and multiple organ dysfunction syndrome. Extended microbiological testing and CT scans were negative for an infection. Azathioprine hypersensitivity syndrome, characterised by systemic symptoms such as fever, nausea, vomiting, diarrhoea, arthralgias, myalgias, liver and/or renal involvement and even shock, was thought to be the most likely diagnosis. Early recognition of this syndrome and the discontinuation of azathioprine seems vitally important to prevent morbidity or even mortality.

Background

Making the correct diagnosis is crucial in deciding the most effective treatment in life-threatening conditions but can be challenging in patients with rare diseases. Azathioprine hypersensitivity syndrome (AHS) is a rare and unknown entity and might be confused with sepsis or severe cutaneous adverse drug reactions (SCARs). This case report presents a patient with azathioprine hypersensitivity, describes the pathophysiology, clinical presentation and treatment, and reviews the recent literature. AHS is compared with azathioprine-induced Sweet's syndrome (AISS) and the differential diagnosis of severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP) and drug rash with eosinophilia and systemic symptoms (DRESS), is briefly discussed from an educational point of view and more specifically with regard to our case.

Case presentation

A 55-year-old male patient presented to the emergency department (ED) with complaints of fever, headache, coughing, shivering and night sweats which started two weeks ago. Six months previously, the patient was diagnosed with granulomatosis with polyangiitis with renal involvement (biopsy proven, serum creatinine 426 μmol/l), and started treatment with cyclophosphamide 150 mg daily, prednisone 12.5 mg daily, plasmapheresis and trimethoprim/sulfamethoxazole (TMP/SMX) 960 mg three times a week as prophylaxis for Pneumocystis jiroveci pneumonia. Six weeks before presentation the patient was seen by a dermatologist with generalised and itchy erythematous papular lesions thought to be induced by amoxicillin and successfully treated with topical steroids. The amoxicillin, given for acute otitis media, was withdrawn. Due to oral mucositis, cyclophosphamide 150 mg daily was switched to maintenance therapy with azathioprine 175 mg seven days before presentation to the ED as it was considered to be a possible side effect of cyclophosphamide and he was given prednisone 12.5 mg daily. Two days before presentation he went to the dentist for excision of his right upper third molar without antibiotic prophylaxis. Besides some swelling in the right submandibular region and shivers, physical examination revealed no other findings and more specifically no lymphadenopathy and no skin lesions. The patient did not show any abnormalities on his mucous membranes on presentation to the ED. His blood pressure was 80/40 mmHg, heart rate 100 beats/min and his temperature was 39.6 °C.

The patient was admitted to the general medical ward with the diagnosis of sepsis of unknown origin and treated with a single dose of gentamycin 400 mg IV, ceftriaxone 2 g IV twice daily, metronidazole 500 mg three times a day and hydrocortisone 200 mg per 24 hours, as continuous infusion, and the azathioprine was discontinued. That night the patient was admitted to the intensive care unit (ICU) because of refractory distributive shock. In the absence of an abdominal focus the metronidazole was stopped, TMP/SMX reintroduced, erythromycin added to cover a possible

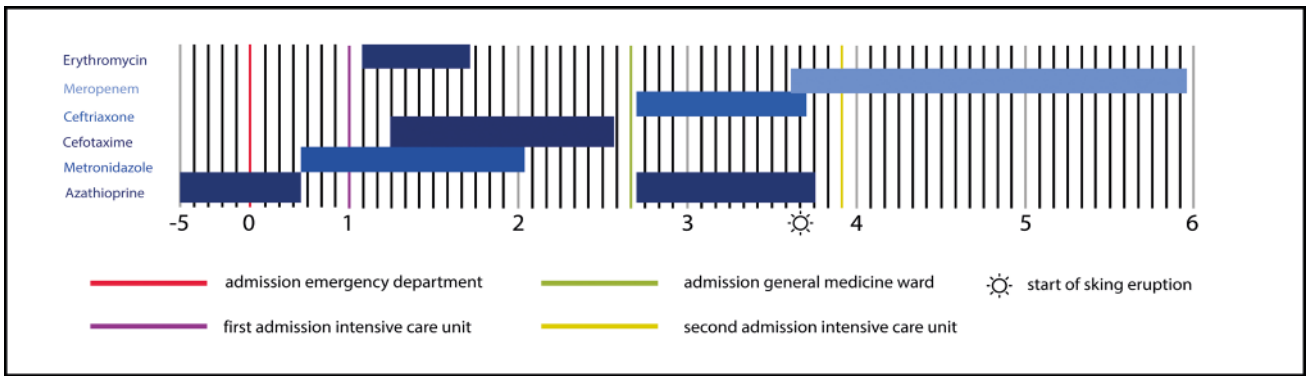

Figure 1. Time relation between drugs administered and specific events during admission.
X-axis shows time in days. Y-axis shows the drugs administered during the admission with the bars indicating start and stop of that specific drug

Legionella infection and, following local practice, the ceftriaxone was switched to cefotaxime. Intravenous noradrenaline was started and during the next 38 hours of admission the noradrenaline could be weaned off and finally the patient was discharged to the general medical ward. As the urinary antigen test for *Legionella* was negative, the erythromycin was discontinued and the cefotaxime was again switched to ceftriaxone.

Three days after admission the azathioprine was reintroduced and 20 hours later the patient developed itchy papules on his arms and feet *(figure 1)*. Seven hours later the patient started shivering, had a high fever (temperature 40 °C) and within hours developed an erythematous and pustular rash without mucous membrane involvement and mainly on the extremities, thorax and abdomen (*figure 2*). The patient was evaluated by a dermatologist. The differential diagnosis at that moment was sepsis or an azathioprine- or antibiotic-induced drug reaction. The antibiotics were switched to meropenem, an extra dose of prednisone 50 mg IV was given and the azathioprine was stopped. Subsequently, the patient was admitted to the ICU with refractory distributive shock, developed oedema of the face and neck and an emergency cricothyrotomy was performed.

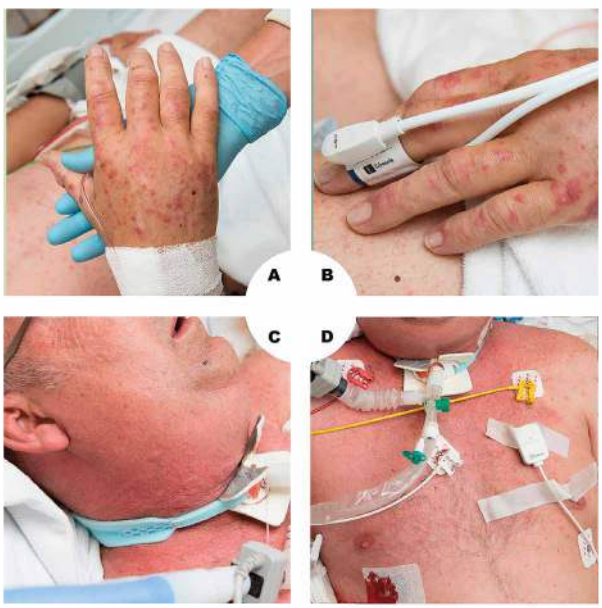

Figure 2. A: Pustules covering hands of patient. B: Close-up of pustules on hands. C: Side view of swollen neck and tracheostomy. D: Front view of thorax and abdomen

The hydrocortisone was switched to prednisone 25 mg IV three times a day, a single dose of dexamethasone 200 mg IV was given and clemastine 1 mg IV twice daily was started. Due to a refractory distributive shock, noradrenaline and milrinone infusion was started, as well as renal replacement therapy (RRT) for acute kidney injury. During ICU admission the patient received mechanical ventilation with minimal support. As the microbiology results were all negative, all the antibiotics, the noradrenaline and milrinone were stopped 48 hours after admission, and three days later the RRT was discontinued

Investigations

Laboratory tests in the emergency department showed a CRP of 181 mg/l, leukocytes 10.7/nl, neutrophils 9.5/nl, eosinophils 0.0/nl, basophils 0.0/nl, lymphocytes 0.0/nl, monocytes 0.0/nl, lactate 2.5 mmol/l and a negative dipstick urinalysis. All cultures of blood, urine and sputum were negative as were the PCR multiplex assay for respiratory pathogens and urinary antigen tests for both *Legionella pneumophila* serogroup 1 and *Streptococcus pneumoniae*. A total body CT scan showed no findings except some perirenal stranding on both sides and enlarged mediastinal lymph nodes.

After the second admission to the ICU the patient became progressively dyspnoeic with rapid swelling of his face and neck (*figure 2*). A CT scan of the neck and thorax showed soft tissue swelling of the oropharynx, a swollen epiglottis and swollen submandibular glands. Afterwards, an emergency cricothyrotomy was performed. The microbiology results were all negative (influenza A and B, respiratory syncytial virus,

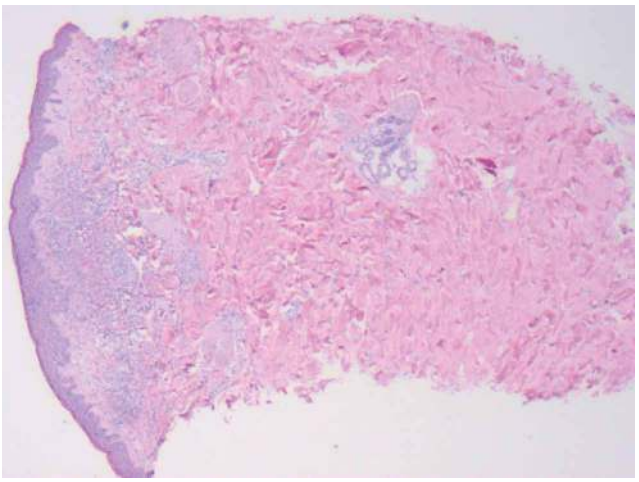

Figure 3. A: Skin biopsy shows widespread intra-epidermal and intradermal neutrophilic infiltration with oedema without the presence of septic emboli or microorganism

human metapneumovirus, human parainfluenza virus, coronavirus, rhinovirus, enterovirus, adenovirus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Chlamydia psittaci* and *Legionella pneumophila*, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, parvo virus B19 and Coxsackie virus and tuberculosis) as were the blood, urine and sputum cultures. Skin biopsies showed a widespread intra-epidermal and intradermal neutrophilic infiltration with oedema without the presence of septic emboli or microorganism (*figure 3*). Furthermore, fluid from the pustules was negative for herpes simplex, varicella zoster virus, bacteria, yeast and fungi.

Laboratory tests from the second ICU admission showed a CRP 295 mg/l, leukocytes 23.4/nl, eosinophils 0.07/nl, polymorphonuclear neutrophils 13.4/nl, band neutrophils 8.5/nl, lymphocytes 0.20/nl, haemoglobin 4.4 mmol/l, thrombocytes 81/nl, ferritin 10,457 μg/l, triglycerides 4.3 mmol/l, d-dimer >5000 μg/l, fibrinogen 6 g/L, sIL-2R >7500 U/ml, lactate dehydrogenase 336 U/l, urea 13 mmol/l and creatinine 321 μmol/l. Three months after discharge the patient underwent skin patch testing for azathioprine (0.1, 1 and 5% in petrolatum), metronidazole (30% in petrolatum), cefotaxime (30% in petrolatum), ceftriaxone (30% in petrolatum), meropenem (10 and 30% in petrolatum) and erythromycin (10 and 30% in petrolatum), with negative results.

Differential diagnosis

Drug-induced Sweet's syndrome

First described by Dr Robert Sweet in 1964, Sweet's syndrome is characterised by painful erythematous plaques, dense dermal neutrophilic infiltrate, which may be associated with fever, neutrophilia, leukocytosis and a dramatic response to systemic corticosteroids.[1]

Although the development of Sweet's syndrome in patients is only partially understood, it is thought to be caused by a hypersensitivity reaction stimulating the production of cytokines that cause neutrophil activation and infiltration of the skin. Sweet's syndrome can be divided into three subtypes based upon their underlying cause: (1) classical Sweet's syndrome defined as Sweet's syndrome without associated malignancy or drug exposure, (2) malignancy-associated Sweet's syndrome mostly caused by haematological malignancies and (3) drug-induced Sweet's syndrome developing within two weeks after exposure to a recently started drug. Neutrophilic infiltration of other organs than the skin is rare. However, these symptoms can be severe and might lead to serious morbidity or even mortality (such as renal failure, encephalitis, systemic inflammatory response syndrome).[2] Patients with Sweet's syndrome (i.e. the classical and malignancy-associated type) fulfil two major criteria and two out of four minor criteria. The major criteria are abrupt onset of painful erythematous plaques or nodules and histology with a predominantly neutrophilic dermal infiltrate without leukocytoclastic vasculitis. The four minor criteria are fever and nonspecific symptoms (such as weight loss, pain and malaise), leukocytosis, good response to systemic corticosteroids and the association with malignancy (for malignancy-associated Sweet's syndrome), inflammatory disorder, pregnancy or preceded by an infection or vaccination. For diagnosis of drug-induced Sweet's syndrome five specific criteria are required: abrupt onset of painful erythematous plaques or nodules, dense dermal neutrophilic infiltrate without leukocytoclastic vasculitis, fever and constitutional symptoms, temporal relationship between drug ingestion and clinical presentation and temporally related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids.[2]

Azathioprine hypersensitivity syndrome

Azathioprine hypersensitivity syndrome (AHS) is a syndrome with systemic symptoms such as fever, nausea, vomiting, diarrhoea, arthralgias, myalgias, liver and/or renal involvement. As one third of the patients with AHS present with shock and half of the patients with AHS have no cutaneous manifestations, this syndrome is often confused with sepsis or exacerbation of the underlying condition for which azathioprine was prescribed. Rapid recurrence of the symptoms after a rechallenge with azathioprine (hours) and negative microbiological tests must alert clinicians to AHS. AHS is a dose-independent hypersensitivity reaction to azathioprine with the development of symptoms within four weeks after starting azathioprine and resolution of symptoms within five days after discontinuation. The cutaneous findings in AHS are diverse and comprise AGEP, erythema nodosum, Sweet's syndrome, leukocytoclastic vasculitis or nonspecific eruptions. A neutrophilic dermatosis seems to be a dominant histological feature in patients with AHS. Azathioprine can also induce Sweet's syndrome (AISS); due to very similar clinical findings it is difficult to differentiate between AHS and AISS.[3,4]

Stevens-Johnson syndrome and toxic epidermal necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) belong to a heterogeneous group of severe cutaneous

adverse reactions (SCARs) with severe morbidity and mortality. SJS and TEN are two entities of the same disease with an incidence of 1.2 per million person-years.[5] In SJS, skin detachment occurs over less than 10% of the total body surface area, while in TEN more than 30% of the skin is involved. Mortality in SJS and TEN is ranging between 1-5% and 25-30%, respectively.[6] The pathogenesis of SJS/TEN is thought to be immune-triggered as rechallenging the patient with the culprit drug can result in a rapid eruption of SJS/TEN. Histology shows confluent apoptosis of keratinocytes with subepidermal blistering leading to full-thickness necrosis of the epidermis. The sequelae of TEN and to a lesser extent SJS include ocular lesions, lesions of the integumentary system, pulmonary, dental or genitourinary complications and complications of the gastrointestinal system.[7] The onset of the disease is usually 1 to 4 weeks after the start of the culprit drug.[8] For example, co-trimoxazole is a known culprit drug for SJS/TEN. Mockenhaupt et al. found that despite co-medication with corticosteroids the risk of developing SJS/TEN in patients treated with co-trimoxazole was increased, even after 8 weeks of treatment with the drug.[9]
In the absence of a painful blistering skin rash, no mucosal involvement, no ophthalmological or genitourinary involvement, the acute onset of the skin eruption, rapid recovery and the lack of epidermal necrosis in the biopsy specimen, neither SJS nor TEN were considered as a possible diagnosis.

Drug reaction with eosinophilia and systemic symptoms
Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe multi-organ hypersensitivity reaction caused by an extended number of causative drugs. Typically, DRESS starts with a progressive maculopapular rash on more than 50% of the body surface area and in some cases with purpura or pustules. Half the patients have facial oedema with or without focal non/erosive mucous-membrane involvement. The histological features are dermal oedema with dense diffuse or perivascular lymphocytic infiltration and eosinophils are usually present.[10-12]
The most characteristic feature of DRESS is its delayed onset with symptoms developing 2 to 12 weeks after the start of the culprit drug and lasting more than 15 days with a waxing-and-waning recovery. Symptoms may, however, develop more swiftly and be more severe after re-exposure, developing in hours to days.[11,13] DRESS is characterised by fever, rash, hepatitis, lymphadenopathy, leukocytosis and eosinophilia. Less frequently, renal involvement and impaired pulmonary function can be found. In the absence of a typical rash, liver involvement, eosinophilia, lymphadenopathy at two or more sites, rapid recovery within 15 days without flares and no suggestive drug in the typical time frame, DRESS was not considered a possible diagnosis.

Acute generalised exanthematous pustulosis
Acute generalised exanthematous pustulosis (AGEP) presents with a widespread erythema including non-follicular sterile pinhead-sized pustules with intertriginous accentuation often associated with fever. AGEP is a T-cell mediated disease and after these drug-specific T-cells are activated, they proliferate and migrate into the dermis and epidermis where they induce apoptosis of keratinocytes leading to tissue destruction.[14,15] Skin biopsy of AGEP shows inter-epidermal and subcorneal pustules with perivascular infiltration of neutrophils and eosinophils. AGEP presents within two days after exposure to culprit antibiotics and within 11 days in all other associated drugs.[15] Upon discontinuation of the causative agent, resolution of the cutaneous features typically occurs within 4 to 10 days with desquamation of the affected areas.[16] Mucous membrane involvement is rare, but if present mostly limited to the mouth or lips. Internal organ involvement is less common than with DRESS.[14,16] In short, AGEP was not considered a possible diagnosis as our patient did not show the typical cutaneous and histopathological pattern.

Generalised fixed drug eruption
Fixed drug eruption (FDE) is the development of a limited number of usually solitary well circumscribed dusky red burning or painful macules, eventually evolving into an oedematous plaque with or without blistering. The incidence is 0.6 per million person-years, mostly caused by anticonvulsants and antimicrobials. FDE appears within 30 minutes to 24 hours after exposure to the causative drug and resolves within 10 days. Re-exposure to the drug gives hyperpigmented lesions at the same anatomic location, with systemic involvement.[17-19] It is thought that both skin and mucous membranes are involved as a prominent histological feature is lichenoid tissue reaction with apoptotic keratinocytes in different layers of the epidermis and vacuolar changes. Also, sub-epidermal and intra-epidermal blistering may occur. A more severe and rare variant of FDE is generalised bullous fixed drug eruption, which presents with macules or plaques with overlying bullae and is associated with high mortality.[20]

Haemophagocytic lymphohistiocytosis
Beside SCARs, there are some diseases with a fulminant course and cutaneous manifestations such as haemophagocytic lymphohistiocytosis, which has an incidence of 1.8 per 100,000 live births and is a severe inflammatory syndrome caused by activation of the mononuclear phagocytic system, with insufficient downregulation of active macrophages and lymphocytes, resulting in an uncontrolled hyperinflammatory response.[21] Our patient fulfilled some of the criteria for haemophagocytic lymphohistiocytosis, such as purpura, fever (>39.6 °C), anaemia (5.2 mmol/l), thrombocytopenia (128/nl), hypertriglyceridaemia (4.3 mmol/l) and high values of ferritin (10,457 μg/l) and sIL-2R (>7500 U/ml).[22] However, in the absence of neurological symptoms, no involvement of the liver and a rapid recovery with a moderate dose of steroids, we thought this diagnosis was most unlikely.

Treatment
The treatment of the patient is described in the case presentation.

Outcome and follow-up

When the patient initially presented to the ED, azathioprine and co-trimoxazole were stopped and the patient was treated with metronidazole and erythromycin. The erythromycin was switched to cefotaxime on the first day of admission. On the third day of admission to hospital, the azathioprine was restarted, later that day the patient developed a rash and cefotaxime was switched to ceftriaxone. Eight hours later the skin eruptions deteriorated, the azathioprine was discontinued and ceftriaxone was switched to meropenem. On the fourth day of admission, the patient showed signs of airway obstruction, he was intubated and received noradrenaline and RRT on the ICU due to hypotension and acute kidney injury. From the fourth day until the seventh day of admission, the skin eruptions did not change. At the beginning of the eighth day of admission the skin eruptions and the oedema of the neck started to improve and completely resolved on the tenth day. The RRT and mechanical ventilation with minimal support was stopped on the eleventh day of admission and the patient was discharged to the ward. Six days later the patient was discharged home on mycophenolate mofetil 1000 mg twice daily and prednisone 20 mg daily, the latter could be further tapered and stopped over several weeks. Three months after discharge the patient underwent an allergologic diagnostic work up (see above). The patient refused further skin testing with intradermal tests. Provocation tests were not done. At the moment he is doing well.

Discussion

Azathioprine inhibits RNA and DNA synthesis. It is metabolised into two products, mercaptopurine (6-MP) and an imidazole derivate. The 6-MP is metabolised through various pathways to the active component of the drug, 6-thioguanine (6-TGN). Thiopurine methyltransferase (TMPT) also breaks down the 6-MP, but converts it into 6-methylmercaptopurine (6-MMP) and eventually into 6-methylmercaptopurine ribonucleotides (6-MMPR). When levels of 6-MMP and 6-MMPR become too high, the patient experiences azathioprine toxicity causing hepatotoxicity. When the levels of 6-TGN are too high, patients experience myelotoxicity and nausea. The hypersensitivity reaction to azathioprine, however, is dose-independent and can occur regardless of thiopurine levels and TPMT functionality. The trigger and pathogenesis of this hypersensitivity reaction is still largely unknown as some studies suggest the imidazole compound is the culprit, while others found a hypersensitivity reaction after rechallenging with 6-MP. Either 6-MP or imidazole trigger a systemic hypersensitivity reaction type IV (T-cell mediated). Rechallenge to these antigens leads to cytokine storm resulting in circulatory collapse.[3,23,24]

The serum levels of the azathioprine metabolites 6-TGN and 6-MMP are, unfortunately, unknown.

The clinical range of 6-TGN is 230 to 260 (pmol/8 x 10^8 red blood cells (RBC)), elevated levels over 450 (pmol/8 x 10^8 RBC) can cause bone marrow toxicity. If the levels of 6-MMPR exceeds 5700 (pmol/8 x 10^8 RBC) it can cause hepatotoxicity.[24] In our patient TPMT genotyping was performed for the most prevalent single nucleotide polymorphism (238G>C, 460G>A and 719A>G) associated with loss of catalytic activity and this test was negative. AHS, however, is a dose-independent hypersensitivity reaction, in which any levels of metabolites can trigger the hypersensitivity reaction.[23]

Of the patients who are treated with azathioprine, 28% develop adverse reactions. Most of these adverse reactions are due to toxicity of azathioprine. AHS is rare and scarcely reported in medical literature with an incidence likely less than 1%.[3] Azathioprine-induced Sweet's syndrome (AISS) can appear within four weeks after initiation of azathioprine to up to years after exposure to the drug. It must contain all five criteria proposed by Walker et al. consisting of: abrupt onset of painful, erythematous plaques or nodules, histopathological evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis, a fever higher than 38 °C, a temporal relationship between drug ingestion and clinical presentation or temporally related recurrence after oral challenge and temporally related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids.[25] Both AHS and AISS are neutrophil-driven reactions and differentiating between them is difficult due to similar skin manifestations and the same culprit drug. There are, however, differences in presentation. In AHS, 58% of patients have additional systemic symptoms such as arthralgia, abdominal pain and nausea. A rechallenge with azathioprine can lead to more severe systemic symptoms of AHS with shock, multiorgan failure and sometimes even death. Hypotension is reported in one third of patients with AHS and usually responds well to intravenous fluid therapy and in some cases, vasopressors.[6,26] In AISS all patients always present with skin manifestations, in AHS these are not always present and, therefore, it is mistaken for sepsis or exacerbation of underlying disease in up to 65% of patients. One of the criteria of AISS is resolutions of lesions with systemic corticosteroids, while in AHS 39% of patients use corticosteroids while developing the disease.[3,4,27]

Oral provocation tests or challenge tests are considered the gold standard diagnostic procedure for determination of the culprit drug. However, these are considered dangerous in patients with SCARs. Due to the possible hypersensitivity reaction that can result in severe shock syndrome, multiple organ dysfunction syndrome or even death in AHS, oral rechallenge is contraindicated. Despite low sensitivity, patch tests can be performed, being a simple and safe way to confirm the diagnosis if positive. Skin patch tests are considered safe, as systemic reactions are infrequent and not life-threatening. The sensitivity of skin patch testing varies between the SCARs and between culprit drugs. Guidelines support the use of intradermal testing in negative patch testing in patients with SCAR, outside SJS/TEN in which it is contraindicated.[3,28,29]

Diagnosis of adverse drug reactions is made by the typical clinical dermatological picture confirmed by dermato-histopathology,

possibly specific and unspecific laboratory findings and allergological work-up. A structured evaluation of these patients is important with information about known allergies, concomitant diagnoses, symptoms, timing of reaction, description of the skin eruption and the development over time, current medications and those stopped over the last months. Furthermore, microbiological, laboratory, histopathological and imaging results should be obtained.

By weighting the symptoms, diagnostic results and the clinical course of our patient, AHS seems to be the most likely diagnosis. At presentation to the ED there was no skin eruption, but the patient did show signs of shock. As one third of the patients with AHS have systemic symptoms without cutaneous manifestations, confusion with sepsis is a known pitfall.[27] Second, the fact that our patient was admitted to the ICU twice, first after the introduction and second after the rechallenge with azathioprine, makes azathioprine a highly suspect culprit drug. Finally the clinical course after the start of azathioprine, the rechallenge and final discontinuation is in accordance with the literature about AHS. The cutaneous findings, histology results and the time frame between the start of the culprit drug and development of cutaneous lesions in our patient meant that drug-induced Sweet's syndrome was considered a possible diagnosis.The presence of painless skin lesions while being treated with systemic corticosteroids is rather untypical for Sweet's syndrome. However, this finding does not exclude this diagnosis. A severe drug reaction to one of the antibiotics cannot be ruled out as an explanation for the second ICU admission.

If our patient needs antibiotic treatment in the future, we advise to avoid the most suspected antibiotic drugs as cefotaxime, erythromycin and metronidazole. Corticosteroids and a histamine antagonist can be administered to reduce the risk of a severe hypersensitivity reaction, but efficacy of such premedication is doubtful and never guarantees safe drug administration. Remission-preserving treatment for his granulomatosis with polyangiitis should be given by methotrexate or rituximab but not with azathioprine.

Learning points / take home messages

Diagnosis of severe adverse drug reactions is made by a structured evaluation, the typical clinical dermatological picture confirmed by dermato-histopathology, laboratory findings and allergological work-up. AHS is a rare syndrome with systemic symptoms as fever, nausea, vomiting, diarrhoea, arthralgias, myalgias, liver and/or renal involvement and even shock.

Early recognition of this syndrome and the discontinuation of azathioprine seems vitally important to prevent morbidity or even mortality.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

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