Letter to the Editors

Ceftobiprole associated agranulocytosis after drug rash with eosinophilia and systemic symptoms induced by vancomycin and rifampicin

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Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe drug hypersensitivity reaction [1]. Sulfonamides, antiepileptics, allopurinol, minocycline, diltiazem, vancomycin and β -lactam antibiotics are the most common elicitors. Symptoms include fever, skin rash, facial oedema, organ involvement such as hepatitis or interstitial nephritis, pneumonitis and myocarditis. Lymphadenopathy and splenomegaly may occur. DRESS syndrome is characterized by the presence of eosinophilia and atypical lymphocytes in blood. The syndrome occurs within 1–12 weeks after initiating drug treatment [2]. Mortality is around 10%, most often due to liver failure. Drug-specific circulating T-cells seem to play a central role in its pathogenesis [3].

Ceftobiprole is a fifth-generation broad-spectrum cephalosporin with activity against many Gram-positive and Gram-negative bacteria. It is the first cephalosporin with activity against methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci. It is approved in Switzerland, Canada and the European Union under the trade name of Zeftera® for the treatment of complicated skin and skin-structure infections, including diabetic foot infection without osteomyelitis [4]. Most common side-effects are dysgeusia, nausea and headache. Hypersensitivity with rash and pruritus has been described in rare cases [5]. The manufacturer recommends caution with treatment longer than 14 days due to limited experience with the drug [6].

Agranulocytosis following treatment with cephalosporins is a rare but recognized side-effect [7]. It typically occurs after prolonged treatment. Here we present a first report on ceftobiprole-associated agranulocytosis.

A 65-year-old woman underwent elective cardiac surgery to replace the mitral valve due to midgrade mitral valve insufficiency that had caused several episodes of left-sided heart failure over the past 6 years. The medical history showed recurrent cerebrovascular ischaemia 13

and 7 years before admission and chronic renal insufficiency. Anticoagulation was done for 6 years with acetylsalicylic acid and was later changed to phenprocoumon. The patient was being treated with metoprolol 100 mg once daily and perindopril 10 mg once daily. A summary of clinical events, antibiotic treatment and laboratory results is given in Figure 1A. Mitral valve replacement was combined with bypass surgery due to right coronary artery stenosis. Following surgery, the patient exhibited a complete atrioventricular block, requiring pacemaker implantation. Twelve days after surgery, the patient developed fever. Laboratory tests showed a C-reactive protein of 222 mg L⁻¹ and a leukocytosis (14.3 g L⁻¹). Two of four blood cultures and probes from the sternal wound and pus grew coagulase-negative staphylococci (resistant to penicillin, oxacillin and ciprofloxacin, sensitive to gentamicin, clindamycin, tetracycline, vancomycin, sulfamethoxazole/trimethoprim and rifampicin). Sternal osteomyelitis was diagnosed and endocarditis was suspected, first not documented, but later confirmed by echocardiography. Repeated blood cultures were negative. Treatment was initially begun with vancomycin 1 g i.v. twice daily, rifampicin 600 mg P.O. once daily and gentamicin 1 mg kg⁻¹ i.v. three times daily. Gentamicin and vancomycin were briefly replaced with sulfamethoxazole/trimethoprim 800 mg/160 mg P.O. three times daily 16 days after diagnosis, but soon discontinued, and vancomycin and gentamicin were administered again, because of vegetations on the mitral valve.

Eleven days after modification of antibiotic therapy, the patient was feverish with an exanthema of the trunk, arms and legs. She was icteric. Laboratory tests showed a C-reactive protein of 104 mg L⁻¹, an eosinophilia of 0.61 g L⁻¹, atypical lymphocytes 0.5%, a bilirubinaemia of 50 μ mol L⁻¹, elevation in transaminases (alanine aminotransferase 218 U L⁻¹ and aspartate aminotransferase 758 U L⁻¹), alkaline phosphatase was 450 U L⁻¹, γ -glutamyltranspeptidase 980 U L⁻¹ and lactate

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Figure 1

(A) Treatment history and laboratory data. The duration of antibiotic treatment is shown by the black bars and the duration of prednisolone treatment by the grey bar. Arrows denote the following: a, mitral valve replacement; b, sternal osteomyelitis; c, endocarditis; d, DRESS; and e, agranulocytosis. The number of leukocytes, eosinophil and neutrophil granulocytes are given as the percentage of leukocytes. Abbreviations: ALAT, alanine aminotransferase (U l⁻¹); ASAT, aspartate aminotransferase (U l⁻¹); Bili, Bilirubin (U l⁻¹); and CRP, C-reactive protein (mg l⁻¹). (B) Proliferation after drug stimulation of peripheral blood mononuclear cells isolated from the patient. The lymphocyte transformation test (LTT) was performed as described before [8]. Stimulation indices (SIs) were calculated from triplicate cultures as counts per minutes in culture medium with antigen divided by counts per minutes in culture medium without antigen. As a positive control, cells of the patient were stimulated with tetanus toxoid. An SI_{LTT} >2 is considered as positive [8].

dehydrogenase 1110 U l^{-1} . A DRESS syndrome was suspected, and treatment was discontinued for 2 days. Prednisolone 100 mg once daily was given. Treatment was restarted with daptomycin 6 mg kg^{-1} i.v. once daily. After 7 days of daptomycin treatment, the number of eosinophils (2.81 g l^{-1}) increased. Antibiotic treatment was discontinued for 9 days, and eosinophil counts, bilirubin and transaminases normalized. Treatment with ceftobiprole 500 mg i.v. three times daily was started, and prednisolone was gradually reduced to 5 mg once daily. Perindopril was reinstalled 5 days after start of ceftobiprole treatment, and acetylsalicylic acid 100 mg once daily and metoprolol were given again 11 days after start of ceftobiprole treatment.

After 18 days of ceftobiprole treatment, the patient became progressively tired, and the laboratory showed a neutropenia of 0.08 g l^{-1} . The following day, neutrophils were down to zero and atypical lymphocytes were detected (1.5%). Ceftobiprole and acetylsalicylic acid were stopped as being the most likely cause, and prednisolone was given at 60 mg once daily. Since the patient had neutropenic fever that day without focus, empirical treatment with meropenem 1 g i.v. three times daily was begun. Neutrophil leukocytes recovered 9 days after discontinuation of ceftobiprole and acetylsalicylic acid to normal levels without the use of haematopoietic growth factors, and meropenem was stopped. The patient was discharged with a neutrophil count of 4.42 g l^{-1} . Acetylsalicylic acid was reinstalled and was tolerated well, as neutropenia did not recur in an 8 week follow-up. The incident was reported to the Swiss Pharmacovigilance Center.

Allergy testing revealed a positive skin test for amoxicillin, but negative results for vancomycin, rifampicin, daptomycin and a weak positive result for gentamicin. *In vitro* lymphocyte transformation testing, performed as described before [8], showed clear positive responses to amoxicillin, vancomycin, rifampicin and ceftobiprole but negative results for daptomycin and gentamicin (Figure 1B).

Drug-induced agranulocytosis is an idiosyncratic adverse reaction to drugs which may be life threatening [9]. It results in a severe reduction of granulocytes in the peripheral blood with an absolute neutrophil count of under 0.5 g l^{-1} , often under 0.1 g l^{-1} . Many drug categories have been reported to be involved in drug-induced agranulocytosis, such as antithyroids, antiplatelets, antipsychotics and anti-inflammatory agents. β -Lactams, including cephalosporins, sulfasalazine and sulfamethoxazole/trimethoprim and vancomycin are reported to be the most common causes of anti-infective drug-induced agranulocytosis. The median duration of β -lactam exposure before onset of acute agranulocytosis is reported in a range of 19–25 days [10]. The median time between onset of β -lactam-associated agranulocytosis and normalization of neutrophil count has been reported to be in the range of 4–12 days. Regarding our patient, ceftobiprole or acetylsalicylic acid were considered as causes of agranulocytosis

and stopped, while the time interval between onset of agranulocytosis and perindopril and metoprolol treatment was rather short, and such side-effects are not described.

As acetylsalicylic acid rarely causes agranulocytosis and was tolerated well by the patient for years before mitral valve replacement and was tolerated again after normalization of neutrophil counts, we excluded acetylsalicylic acid as the offender and considered ceftobiprole as the most likely cause of agranulocytosis. The duration of ceftobiprole exposure (18 days) before agranulocytosis occurred and the time of recovery (8 days) are in the range of occurrence of β -lactam-associated agranulocytosis.

The pathogenesis of drug-induced agranulocytosis appears complex, as nonimmune and immune mechanisms might take place [9]. Reactive oxygen species may oxidize drugs, leading to altered drug metabolites, causing immune reactions against the neutrophil or the neutrophil precursors [11]. Host genetics or epigenetics (the interaction of drugs with gene expression) may play a role in development [12]. Drug–drug [13] and disease–drug interactions [14] have been reported.

Immunological mechanisms may play an important role in β -lactam antibiotic-associated agranulocytosis. The involvement of antibodies has been documented for penicillins and cephalosporins [15], but a T-cell-mediated pathomechanism is also possible. β -Lactam antibiotic-associated agranulocytosis is often preceded by a rash and fever, appears to be dose dependent and rarely lasts more than 10 days [7, 16, 17]. The fact that our patient showed a positive result to ceftobiprole in lymphocyte transformation testing supports the hypothesis of a T-cell-mediated pathomechanism.

Our patient had a DRESS syndrome preceding agranulocytosis. This syndrome is thought to be due to drug-specific T-cells [18] with cytotoxic potential. DRESS syndrome is often followed by reactivation of herpes viruses in the second or third week after the start of symptoms. Moreover, DRESS may be followed by antibody deficiency and autoimmune phenomena [19], and also by an intolerance or even allergy to another drug [20]. Such a flare-up reaction [21] seemed to have occurred with daptomycin treatment, where an increased eosinophilia was observed. It is also quite possible that the DRESS and its associated immune alterations were important for the drug-induced haematological disease. Indeed, the reappearance of activated lymphocytes during agranulocytosis underlines the presence of a massive immune activation during this phase of the disease, and is a further argument that the side-effect is more immune mediated than toxic.

In summary, the present case report shows that prolonged ceftobiprole treatment can be associated with agranulocytosis. To our knowledge, this is the first report on ceftobiprole-associated agranulocytosis, and T-cells appear to be involved in the pathogenesis. Thus, we recommend careful monitoring of neutrophil counts in a prolonged treatment course with ceftobiprole.

Competing Interests

There are no competing interests to declare.

Supported by SCAHT (Swiss Center of Applied Human Toxicology).

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RECEIVED

7 May 2010

ACCEPTED

17 October 2010

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