Thrombocytopenia in a patient on peritonela dialysis

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SUMMARY

Adverse reactions to drugs occur in up to 6% of hospitalized patients and are an important cause of increment in morbimortality. The widely-prescribed antibiotics beta-lactams and sulfamides are the most frequently associated to adverse reactions and hypersensitivity. Vancomycin is a glycopeptidic antibiotic used to treat infections caused by Staph. coagulasa positive (S. aureus) and Staph. coagulasa negative. Nowadays its extensive use is a consequence of bacterial resistance to classical antibiotics such as beta-lactams. In Nephrology Units, vancomycin is the antibiotic of first choice to treat staphylococcal infections related to central venous catheters for hemodialysis, as well as for the treatment of peritonitis in patients undergoing peritoneal dialysis. Toxicity due to vancomycin includes the «red man syndrome», ototoxicity and hematological toxicity. The most common sign of haematological toxicity is mild neutropenia; less frecuent are leukocytosis, eosinophilia, agranulocytosis and thrombocytopenia.

Key words: *Rhabdomyolysis. Thrombocytopenia. Peritoneal dialysis. Vancomycin. Rituximab.*

RESUMEN

Las reacciones adversas a fármacos ocurren hasta en un 6% de los pacientes hospitalizados y son una causa importante de morbi-mortalidad. Los antibióticos, clásicamente los beta-lactámicos y las sulfamidas son los más frecuentemente asociados a reacciones adversas y de hipersensibilidad. La vancomicina es un antibiótico glucopéptido cuyo uso está dirigido a infecciones por *Staphylococcus aureus* resistente a meticilina (SARM) y St. coagulasa negativo. En las Unidades de Nefrología, la vancomicina es, en muchos protocolos, el antibiótico de primera elección para el tratamiento de infecciones estafilocócicas en relación con catéteres centrales de hemodiálisis y el tratamiento de las peritonitis en pacientes en diálisis peritoneal. La toxicidad secundaria a vancomicina incluye «síndrome del hombre rojo», ototoxicidad y toxicidad hematológica. Dentro de esta última, la más frecuente es la neutropenia leve; menos frecuentes son la leucocitosis, eosinofilia, agranulocitosis y la trombopenia. Presentamos un paciente con ERC 5 en programa de diálisis peritoneal continua ambulatoria (DPCA), que presentó una trombopenia secundaria a la administración intraperitoneal de vancomicina. La ausencia de mejoría en la cifra de plaquetas con tratamientos clásicos obligó a la utilización del anticuerpo monoclonal anti-CD20, el rituximab, con recuperación rápida tras cuatro dosis de la cifra de plaquetas.

Palabras clave: Trombocitopenia. Diálisis peritoneal. Vancomicina. Rituximab.

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Adverse drug reactions occur in up to 6% of hospitalized patients and cause significant increases in morbidity and mortality. Beta-lactam and sulfonamide antibiotics are the drugs most commonly associated to hypersensitivity and adverse reactions.

Vancomycin is a glycopeptide antibiotic used mainly to treat infections caused by methycillin-resistant *Staphylococcus aureus*. (MRSA) and coagulase-negative staphylococci. Vancomycin is widely used today because of bacterial resistance to conventional antibiotics (beta-lactams). In nephrology units, vancomycin is often the first choice antibiotic to treat staphylococcal infections in central hemodialysis catheters and peritonitis in patients on peritoneal dialysis. Vancomycin toxicity includes the «red man syndrome», ototoxicity, and hematological toxicity. Within hematological toxicity, mild neutropenia is most common; leukocytosis, eosinophilia, agranulocytosis, and thrombocytopenia occur less commonly.

CASE REPORT

A 47-year-old male patient with no known drug allergies and stage 5 chronic kidney disease (CKD) secondary to diabetic nephropathy who had been on a program of continuous ambulatory peritoneal dialysis (CAPD) since 6/2/2006.

A straight Tenckhoff peritoneal catheter was implanted on 16/01/06. Signs consistent with exit site infection (ESI) occurred after implantation. Teicoplanin 400 mg IM, followed by three successive 200 mg doses, was therefore administered according to our unit procedures. Peritoneal dialysis with a three exchange scheme (two 1.36% Physioneal and one Extraneal exchanges) was started on February 6. On the following day, the patient noticed a turbid effluent in the night exchange and returned to the unit, where vancomycin 2 g IP was administered. On that same evening, the patient experienced

dry cough and low grade fever. Two days later, peritoneal fluid leak occurred around the catheter due to persistent cough, and peritoneal line was therefore temporarily closed.

The patient attended the emergency room on 11/02/2006 for persistent cough and fluid leak around the catheter, with fever up to 39 ºC.

On physical examination, the patient was eupneic, tachycardiac, conscious, oriented, and cooperative, with BP values of 150/70 mmHg and Sat 02 91%-92% (FI02 21%) Abdominal palpation revealed no tenderness or hepatosplenomegaly. A small amount of clear peritoneal fluid came out after Valsalva maneuvers. No inflammatory signs were seen in the peritoneal catheter exit site. Cardiopulmonary auscultation was normal. No nuchal rigidity and negative meningeal signs. A non-palpable, non-pruritic petechial purpura was seen in both lower limbs up to the knees, the upper chest, and the face. Microbiological samples of peritoneal fluid and urine and blood cultures were taken. Chest X-rays and abdominal ultrasound with no pathological findings. Laboratory test findings included platelet count 23,000/µL (confirmed three times), WBC count 6,900/µL with 12.6% eosinophils, Hb 11 g/dL, Hct 31.5%, LDH 683 mU/mL, normal liver enzymes, haptoglobin, and total bilirubin, QI 80%, and mildly increased D dimer. Antipyretic and empiric antibiotic therapy with amoxicillin-clavulanate and levofloxacin was started.

In view of persistence of the condition despite antibiotic treatment and negative imaging and microbiological tests, diagnosis of thrombocytopenia secondary to vancomycin versus teicoplanin was considered. Treatment was started with methylprednisolone 1 mg/kg. Patient fever and other symptoms disappeared. A platelet count of 9,000 was found two days after the start of steroid treatment. While the patient had a good residual kidney function, function impairment occurred. A central line for hemodialysis was inserted and platelet transfusion was started, after which the patient experienced chills, a temperature increase, and dyspnea. A transfusional reaction was suspected, and samples were therefore sent for direct and indirect Coombs' tests, that were both negative. Tests for IgG and IgM antiplatelet antibodies were positive. A platelet count of 4,000 was found on the following day. Corticosteroid dose (1 mg/kg/day) was maintained, and non-specific IV immunoglobulin was additionally administered at 1 g/kg/day for 2 days. A clear clinical improvement occurred, but platelet count continued to be under 30,000. Bone marrow aspiration showed megakaryocytic elements in different maturation stages.

Thirty days after start of the condition, and since thrombocytopenia persisted, treatment was started with rituximab at a dose of 375 mg/m^2 IV. A weekly dose was administered for four weeks.

On discharge, platelet count was 17,000, and patient had successfully resumed CAPD. Three additional rituximab doses were administered, and platelet count gradually improved to normal levels.

Table I shows changes in laboratory test results with treatment.

DISCUSSION

Thrombocytopenia is an uncommon complication after vancomycin administration. Eight cases have been reported in the literature, of which only one occurred after intraperitoneal administration in a patient on CAPD.

Thrombocytopenia has been mainly reported to result from hypersensitivity or an immune mechanism. In both cases, thrombocytopenia resolves in a few days after drug discontinuation. However, when mediated by an immune event, administration of corticosteroids or even intravenous immunoglobulins may be required. The presence of vancomycin-dependent IgG antibodies directed against GP IIb/IIIa in the platelet surface has been reported. Thrombocytopenia is refractory to platelet transfusion and even worsens upon transfusion, and IV administration of corticosteroids and immunoglobulins is required. A third mechanism involved in vancomycin-induced thrombocytopenia is a direct toxic effect of the drug on bone marrow, particularly in septic patients administered the antibiotic for a long time.

Temporal relationship between vancomycin administration and thrombocytopenia, as well as worsening of the latter after platelet transfusion and presence of IgG antiplatelet antibodies, suggest that vancomycin was responsible for the condition in this patients. Differential diagnosis should include (a)

Rituximab dose: 375 mg/m^2 body surface area

Rituximab	1st	2nd	3rd	4th
Platelets	17,000	23,000	78,000	183,000

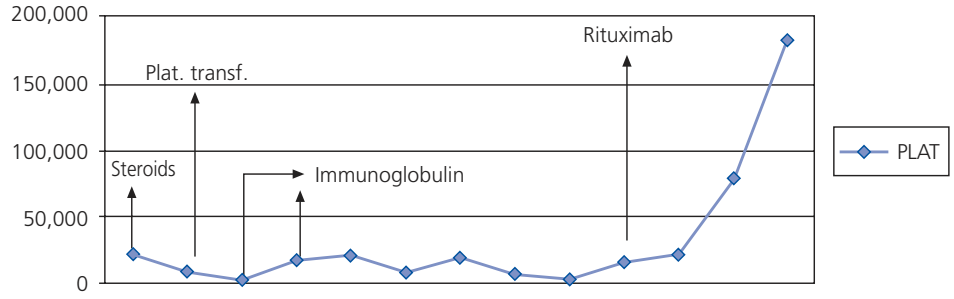

Figure 1. Treatment and course.

thrombocytopenia of an infectious origin, because of the presence of fever, cough, and dyspnea. However, WBC count and differential were normal, except for eosinophilia. No infection site was found neither in microbiological nor imaging tests. Direct inspection and culture of peritoneal fluid were repeatedly negative. The patient did not respond to broad-spectrum antibiotic therapy, and clearly improved when IV corticosteroids were started. (b) Thrombotic thrombocytopenic purpura: no neurological impairment or laboratory findings suggesting hemolytic anemia occurred at any time. No schistocytes or broken erythrocytes were seen in the peripheral blood smear. (c) Drug-induced thrombocytopenia: IP vancomycin and teicoplanin were among the drugs received by the patient in recent days. Teicoplanin, a drug of the same class as vancomycin used some days before could also had been responsible for the condition, because of cross-reactivity between both drugs. However, making this final diagnosis is highly complex, and clinical signs occurred closer in time to vancomycin than to teicoplanin. It would be advisable not to use in the future in this patient neither of the two antibiotics. Opiates were not administered, but analgesic and anti-inflammatory drugs (acetaminophen and ASA) were taken by the patient. The usual patient medication included antihypertensives such as alpha-blockers, ACEIs, and ARBs, allopurinol, atorvastatin, sodium bicarbonate, and pentoxyphylline, none of which has been related to the occurrence of thrombocytopenia. Immediate symptom improvement following the start of corticosteroid treatment suggested that the condition was induced by a drug, and eosinophilia supported this assumption. Complement activation and consumption sometimes occur, but not in our case. In the specific case of vancomycin, IgG antiplatelet antibodies frequently appear.

Corticosteroid treatment improves thrombocytopenia when this is mediated by an immune mechanism, but use of second-line drugs such as intravenous immunoglobulin and anti-CD20 (rituximab) is sometimes required. Rituximab is not included in therapeutic protocols for drug-induced thrombocytopenia, but is recommended as second or third-line drug for treating idiopathic thrombocytopenic purpura refractory to corticosteroid treatment and thrombocytopenia secondary to leukemia or lymphoma. The action mechanism of rituximab in this case has not been fully elucidated. It is thought that its anti-CD20 action partly blocks the humoral immune mechanism mediated by B lymphocytes involved in production of antiplatelet antibodies. The recommended dose is 375 mg/m^2 body surface area as four boluses (a weekly dose for four weeks). This case would somehow «pioneer» use of rituximab for the treatment of drug-induced thrombocytopenia.

In conclusion, it should be stated that thrombocytopenia is a potential complication in patients treated with vancomycin. In the specific case of patients on peritoneal dialysis, vancomycin is the first-choice antibiotic for treating peritonitis in many protocols in our setting. If thrombocytopenia, fever, and skin rash occur and do not improve on antibiotic therapy, and microbiological and imaging tests rule out the existence of infection, a drug-induced condition should be suspected.

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