High Procalcitonin in a Patient with Drug Hypersensitivity Syndrome

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Abstract

We present a patient who developed carbamazepine (CBZ)-induced Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome associated with high serum procalcitonin (PCT). The presentation (high fever, hepatosplenomegaly, leukocytosis), high PCT and CRP initially suggested sepsis, and he was treated with antibiotics, while CBZ was continued. The rash and hepatitis worsened. After withdrawal of CBZ, corticosteroid therapy was administered and the patient recovered with normalization of PCT. This case demonstrates that PCT may be increased in patients with DRESS. This is the first report of CBZ-induced DRESS associated with high PCT, and the second case of increased PCT in DRESS.

Key words: procalcitonin, drug hypersensitivity syndrome, DRESS, carbamazepine

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Introduction

Drug rash, eosinophilia, and systemic symptoms (DRESS) syndrome is one of the most severe drug hypersensitivity reactions, most frequently caused by anticonvulsants, dapsone, salazosulfapyridine, allopurinol and minocycline (1). Anticonvulsant-induced DRESS, is a rare (1 in 1,000 to 10,000 exposures), but potentially fatal (10%) systemic reaction, which occurs 1-8 weeks after exposure to aromatic anticonvulsants: carbamazepine (CBZ), oxcarbamazepine, phenytoin and phenobarbital (2). Signs and symptoms of DRESS typically include high fever, morbilliform rash, facial edema, lymphadenopathy, hepatosplenomegaly, hepatitis and hematological abnormalities (1).

Although some data suggest CBZ-induced T cell activation (3), it is more widely accepted that arene oxides, cytotoxic metabolites of CBZ, have a pivotal role in the pathogenesis of DRESS (4, 5). Moreover, it has been recently shown that systemic manifestations of DRESS are provoked by sequential reactivation of several human herpesviruses (HHV), HHV-6, HHV-7, Epstein-Barr virus and cytomegalovirus (1, 6, 7).

PCT, the precursor of hormone calcitonin, under normal conditions is produced in the C cells of the thyroid, but microbial infections induce release of PCT from all cell types throughout the body (8). PCT is superior to C-reactive protein (CR-P), tumor necrosis factor (TNF)-α and interleukin (IL)-6 in the early diagnosis of sepsis (8, 9). Mild to moderate increases of the PCT level may occur in viral infections and various chronic inflammatory diseases (arthritis, vasculitis) (8, 10). Here, we present a case of an adolescent who developed CBZ-induced severe DRESS associated with high serum procalcitonin (PCT) levels, initially misdiagnosed as sepsis.

Case Report

A young man, aged 18, was admitted to our hospital with fever lasting for 10 days, nausea, diarrhea and abdominal pain. He had a two-day history of maculopapular rash with edema of the face. Before the hospitalization, the patient treated himself with amoxicillin 500 mg tid. In his past history, grand mal epilepsy was diagnosed in 1994 and he was treated with phenobarbital. In 1999, phenobarbital was replaced with valproate. Because of inadequate disease con-
Disseminated maculo-papular rash.

trol, CBZ was added to his therapy 3 weeks before the onset of high fever. The patient had no history of previous adverse drug reactions. He had no relatives who experienced DRESS.

On admission, the patient was febrile (39.5°C), with maculopapular rash (Fig. 1), generalized lymphadenopathy (nodes 2 cm), hepatomegaly (18 cm), and splenomegaly (17 cm). Lung X-rays showed infiltration in the right cardiophrenic angle. Laboratory analyses showed leukocytosis (17.9 × 10^9/L), with 12% of atypical lymphocytes, and eosinophilia (9% (1,611 × 10^9/L). Erythrocyte sedimentation rate (ESR) and fibrinogen were normal. Procalcitonin was highly elevated (2.64 ng/mL, normal <0.1 ng/mL), as well as C-RP (59 mg/L, normal <5 mg/L). Other analyses were as follows: AST 108 (normal <37 U/L), ALT 444 (normal <41 U/L), bilirubin 41.3 (normal <20.5 μmol/L), direct bilirubin 19.9 (normal <7 μmol/L), alkaline phosphatase 197 (normal 40-120 U/L), gamma-GT 318 (normal <55 U/L), LDH 1,136 (normal 220-460 U/L).

Other routine analyses were normal. The ANA, rheumatoid factor and standard virologic and parasitologic tests were negative. Serum IgG 6.4 (normal 7-16 g/L) and IgA 0.58 (normal 0.7-4 g/L) were slightly low. Urine and blood cultures were repeatedly sterile.

At presentation, our patient had 4 criteria for sepsis: one general (fever >38.3°C) and 3 criteria that belong to inflammatory variables: leukocytosis (WBC >12,000 × 10^9/L), C-RP >2 SD and PCT >2 SD above the normal values (11). He had two criteria for systemic inflammatory response syndrome (SIRS) (fever >38°C and leukocytosis >12,000 × 10^9/L (11). Based on the presumptive diagnosis of sepsis, the patient was treated with broad-spectrum antibiotics (clindamycin and ceftriaxone) and paracetamol. CBZ therapy was continued. Five days later, the patient developed high grade fever (40-41°C), severe hepatitis with further elevation of AST to 5,252, ALT to 3,749 U/L, LDH to 6,628 U/L and total bilirubin 83 mmol/L, with prolonged prothrombin time (INR 1.9) and low haptoglobin level (<0.13 g/L). PCT level was increased to 3.84 ng/mL and C-RP to 72 mg/L. The patient experienced frequent seizures during fever spikes and occasionally had altered mental status. At that time 2 additional arbitrary criteria for sepsis were met: coagulation abnormality (INR >1.5) and hyperbilirubinemia >70 mmol/L (11). Due to suspected hepatotoxicity, CBZ was replaced with phenobarbital.

Finally, the diagnosis of DRESS was confirmed 1 week after the admission, by the presence of five of the six diagnostic criteria (1): 1) maculopapular rash developing >3 weeks after starting therapy with CBZ, 2) lymphadenopathy, 3) fever (>38°C), 4) leukocytosis >10 × 10^9/L (atypical lymphocytosis, eosinophilia), 5) hepatitis (ALT >100 U/mL). The sixth criterion, HHV-6 reactivation, was not tested.

Phenobarbital and valproate were immediately discontinued. Treatment with parenteral therapy with methylprednisolone (120 mg/day) and topical therapy with bland emollients and mild topical steroids was introduced. Three days later, PCT dropped to 0.8 ng/mL. The epilepsy was treated with topiramate (25 mg, bid) and diazepam intravenously during seizures. One week later, valproate was reintroduced (500 mg, bid). After 7 days, methylprednisolone was switched to oral prednisone (1 mg/kg), the dose was gradually tapered, and after 4 weeks switched to alternate day therapy. After a further transient elevation of AST to 5,700 U/L, ALT to 3,800 U/L and LDH to 6,700 U/L, hepatic enzymes gradually normalized. The patient completely recovered two months after CBZ discontinuation, with normalization of clinical symptoms and laboratory results, except for slightly elevated ALT 82 and AST 50. After 6 months, we performed the patch test with CBZ 10% w/w in white petrolatum, according to the standard protocol (12), and the test was positive.

**Discussion**

The diagnosis of DRESS may be difficult, since many of the clinical features can be nonspecific and the syndrome can mimic infectious, neoplastic or autoimmune diseases. Variability in clinical and laboratory presentation and concomitant use of other drugs often delay the diagnosis, leading to significant morbidity. Family history was negative in our patient, but familial cases of anticonvulsant-induced DRESS have been reported (5).

Typical morbilliform rash may progress to erythroderma, and, on rare occasions, may lead to toxic epidermal necrolysis (1). Hepatitis is generally mild and anicteric; if severe, it can proceed to liver failure, the most common cause of death in patients with DRESS (2). Other organ involvement (pneumonitis, nephritis, myocarditis, thyroiditis, diabetes mellitus and colitis) is seen in 50-60% of cases (1, 2). Hematological abnormalities include eosinophilia, atypical lymphocytosis (predominantly of activated CD8+ T cells) and tender lymphadenopathy (1, 6). We also observed a decrease of IgG and IgA, reflecting immunosuppressive potential of CBZ (6). In our patient, discontinuation of immunosuppressive CBZ allowed a reconstitution of strong T cell response, with a protracted rash and further elevation of AST, ALT
and LDH, similar to immune reconstitution syndrome (1, 6, 7).

CBZ is primarily metabolized via cytochrome P450 (CYP 3A3/4) to reactive epoxides - arene oxides responsible for direct cytotoxicity (2). Arene oxides are detoxified mainly by epoxide hydrolase and by conjugation with glutathione (4). Valproate inhibits epoxide hydrolase, while paracetamol, by depleting hepatic glutathione, increases CBZ toxicity (2, 4). Taken together, the additional use of valproate and paracetamol could have contributed to the severe clinical presentation in our patient.

In addition to direct cytotoxicity, arene oxides, after interaction with proteins, lipids and nucleic acids, are involved in the formation of protein-drug complexes that are potential targets for immune-mediated injury (1, 3). In addition to classic MHC-dependent T cell activation, drug-specific T cells in DRESS are stimulated directly, as with superantigen. Such activation induces production of high amounts of cytokines (13). Various proinflammatory cytokines (TNF-α, IL-5, IL-6, IL-2, IFN-γ), which are markedly increased in DRESS, induce synthesis of PCT (8). High levels of PCT may be important in the differential diagnosis between infectious and non-infectious origin of SIRS, acute respiratory distress syndrome, pancreatitis, and acute graft rejections (8, 9). In healthy subjects, PCT levels are <0.1 ng/mL, and concentrations >0.5 ng/mL are considered consistent with bacterial infection (8, 10). It has been proposed that PCT level >1.2 ng/mL is an indication for antibiotic treatment without a positive blood culture (10). In systemic bacterial, parasitic and fungal infections, PCT levels rise 10-100 fold and sometimes even more (9, 10). Significant viral infection (cytomegalovirus, Epstein-Barr and Enterovirus) may be also associated with mildly or moderately elevated PCT levels, up to 1.1 ng/mL (10). However, early elevation (after 1-2 days) has been documented in non-infectious causes of SIRS such as heat stroke, burns and severe trauma (9). Here, even though the last meta-analysis showed that PCT could not reliably differentiate sepsis from other, non-infectious causes of SIRS (14), most investigators have found that daily consecutive measurement is very important for sepsis detection (15). Later, a secondary PCT increase strongly suggests systemic bacterial infection in progression (8, 9, 15).

Although eosinophilia is not associated with systemic bacterial infections, the present patient “looked septic” and PCT concentrations (initially 2.64 ng/mL, with secondary increase to 3.84 ng/mL) were suggestive of sepsis (concentrations in sepsis 2-10 ng/mL) (8, 15, 16). Negative blood cultures may have resulted from previous antibiotic treatment. On the other hand, drugs can induce reactions with clinical and laboratory signs overlapping, in part, with systemic bacterial infection (1, 11). To date, significant elevation of PCT has been described in only one patient with DRESS induced by oxcarbamazepine (17).

We showed that biomarkers such as PCT must be only a part of integrated clinical assessment of critically ill patients. PCT-guided diagnosis of sepsis without a careful history of drug intake has important limitations, especially in patients with DRESS syndrome.

Although the relationship between toxic, viral and immune mechanisms in DRESS remains unresolved, the present case demonstrates that DRESS should be included in the differential diagnosis of patients with fever, leukocytosis, hepatosplenomegaly, rash and high PCT and CRP. To the best of our knowledge, this is the first report of CBZ-induced DRESS associated with significant PCT elevation.

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References


