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Renal failure in a patient with multiple myeloma as thrombotic microangiopathy after gastrointestinal infection

Ostra niewydolność nerek u chorego leczonego z powodu szpiczaka plazmocytowego IgG kappa w przebiegu sepsy z cechami mikroangiopatii zakrzepowej

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S u m m a r y

Multiple myeloma despite new drugs is recognized as an incurable disease. Lymphoid neoplasms are characterized by deep secondary immunodeficiency.

In patients with a diagnosis of multiple myeloma, immunodeficiency mainly affects the humoral immune response. Therefore, infections are the biggest threat to these patients and treatment, as always, is more costly than prevention. Renal failure is common for patient with multiple myeloma with progression diseases and may cause diagnostic difficulties due to other causes. At the end of the fourth cycle of treatment Revlimid with Dexamethasone, the patient failed to follow his diet for one meal and developed intense diarrhea, which quickly lead to dehydration and electrolyte imbalance, resulting in atrial fibrillation and poor performance status. The patient was admitted to the emergency clinic with symptoms of hypovolemic shock. He was qualified for haemodiafiltration with plasma exchange in the Intensive Care Unit due to anuria and neurological symptoms.

Key words: multiple myeloma, thrombotic thrombocytopenic purpura

S t r e s z c z e n i e

Szpiczak plazmocytowy mimo nowych leków, jest chorobą nieuleczalną o wieloletnim przebiegu. Nowotwory układu chłonnego charakteryzują się głębokimi wtórnymi niedoborami odporności. U chorych z rozpoznaniem szpiczaka plazmocytowego upośledzenie odporności głównie dotyczy odpowiedzi humoralnej. Dlatego chorzy ci są narażeni na ciężkie, zagrażające życiu infekcje, których dodatkowo leczenie jest znacznie droższe niż możliwa profilaktyka. W obrazie szpiczaka często dochodzi do niewydolności nerek, która najczęściej wynika z progresji choroby i może sprawiać trudności diagnostyczne spowodowana innymi przyczynami. W przypadku naszego chorego po, czwartym cyklu leczenia Revlimidem z Dexamethasonem, po infekcji jelitowej, doszło do rozwoju biegunki, która szybko doprowadziła do odwodnienia i migotania przedsionków w wyniku zaburzeń elektrolitowych.. Chory w stanie ciężkim został przyjęty do kliniki z objawami wstrząsu hipowolemicznego. W kolejnych dniach wymagał hemodiafiltracji z wymianą osocza w Oddziale Intensywnej Opieki Medycznej z powodu anurii i objawów neurologicznych. Pacjenci z rozpoznaniem szpiczaka IgG w trakcie leczenia z niskim poziomem IgG wymagają substytucji dożylnych immunoglobulin.

Słowa kluczowe: szpiczak plazmocytowy, wtórne niedobory odporności, mikroangiopatia zakrzepowa

INTRODUCTION

Lymphoid neoplasms are characterized by deep secondary immunodeficiency.

The problem is exacerbated by the medical treatment that interferes with the immune system, impairing both the cellular and humoral response. In patients with a diagnosis of multiple myeloma, immunodeficiency mainly affects the humoral immune response and this is due to the reduced secretion of normal polyclonal immunoglobulins and their increased breakdown.

Therefore, infections are the biggest threat to these patients and treatment, as always, is more costly than prevention. Thrombotic microangiopathy is a life threatening condition if left untreated and inevitably leads to death.

Clinically, this disease can occur in two forms: the first is haemolytic-uraemic syndrome (HUS), which is more common in children and the predominant symptom is renal failure; and the second is thrombotic thrombocytopenic purpura (TTP), where the predominant symptoms are neurological. This form occurs only in adults. Although once considered variants of a single syndrome, recent evidence suggests differing pathogenic mechanisms of TTP and HUS. The causes of these diseases are diverse and include infections, especially with strains of Vero cytotoxin-producing *Escherichia coli*, *Shigella dysenteriae*, but also cancers and cytotoxic drugs. The clinical presentation is characterized by a microangiopathic haemolytic anemia with renal failure without background immunity, thrombocytopenia, and more or less severe neurological symptoms (1-5).

CASE PRESENTATION

A 68 year-old man was referred to the Department of Lymphoid Malignancies in October 2008 with a 2 month history of intermittent severe pain of the lumbar spine, weight loss and fatigue and was diagnosed as multiple myeloma IgG kappa in stage III B according to Durie-Salmon.

On examination, he was pale with a tumour detected in the left subclavian area at the height of the 3rd rib with a diameter of 1.5 cm, hard, fixed to the base, a bit tender as well as palpation tenderness of the spine in the lumbar-sacral area. The blood test results showed normochromic anaemia: Hb – 7.3 g/dl, Ht – 21.5%, RBC – 2.32 T/L, with raised WBC – 13.54 G/L (Neu – 7.37 G/L, Lym – 3.68 G/L, Mon – 2.17 G/L, Eo – 0.25 G/L, Baso – 0.07 G/L) and platelet count in normal ranges: PLT – 224 G/L.

The laboratory tests showed symptoms of renal failure: urea – 104.3 mg/dl, creatinine – 2.1 mg/dl, and high levels of total protein: TP – 122.7 g/L at a reduced level of albumin to 21 g/L and a grossly raised ESR (130 mm/hr). The serum calcium level was raised – 3 mmol/L as well as lactate dehydrogenase up (LDH) 434 IU/L. This was correlated with multiple osteolytic bone lesions detected on a standard bone X-ray and fractures of vertebral bodies (Th12 – L1). Moreover, a high level of Monoclonal (M) protein in the serum, ≥ 3 g/dL (IgG 7.28 g/dL, kappa light chains – 2.53 g/dL). High levels of M protein and light chains crowded out the normal functioning of immunoglobulins (IgA – 0.023 g/dL, IgM – 0.018 g/dL, lambda light chains – 0.009 g/dL).

The patient had a high level of beta-2 microglobulin (ß2-M) 6.12 mg/mL which was an additional adverse prognostic factor. Both bone marrow aspiration and biopsy determined infiltration by plasma cells respectively by 60% and 56%.

The patient was treated with the chemotherapy regime CTD (Cyclophosphamide, Thalidomide and Dexamethasone) and radiotherapy for bone lesions. After the sixth cycle of chemotherapy, he achieved complete remission (CR).

Then, the patient continued to take Thalidomide as maintenance monotherapy 100 mg p.o. daily until neurological side effects like peripheral neuropathy and tremors occurred.

The dosage of Thalidomide was sequential reduced until withdrawn.

The patient remained in observation for a period of 5 months, after which there was a relapse with the appearance of monoclonal protein in serum and new osteolytic lesions of bone. Due to the diagnosis of severe neuropathy, the patient was disqualified from treatment with Bortezomib. Instead, he was qualified for treatment with Revlimid, a reduced dose of Dexamethasone due to his diabetes and radiotherapy of the bone lesions. Even after the first cycle of therapy, the patient achieved a very good response with a significant reduction in serum monoclonal protein and relief of the pain previously reported. After the second cycle of therapy, he achieved complete remission of monoclonal protein.

At the end of the fourth cycle of treatment, the patient failed to follow his diet for one meal and developed intense diarrhea, which quickly lead to dehydration and electrolyte imbalance, resulting in atrial fibrillation and poor performance status. The patient was admitted to the emergency clinic with symptoms of hypovolemic shock.

On admission, the blood tests showed severe anemia, with features of hemolysis with negative Coombs' reaction and the presence of schistocytes in a blood smear as well as decreased platelets blood counts of 50 g/L and rising renal failure parameters.

Furthermore, a deep shortage of immunoglobulins was detected, with a decrease of IgG to 200 mg/dL. Despite comprehensive care including intensive antiinfective empiric treatment with broad spectrum antibiotics such as imipenem, linezolidum, metronidazole, acyclovir, immunoglobulin suplementation, red blood cells transfusion, monitoring vital signs, fluid balance, supervision of central venous pressure (CVP), equalization of electrolytes and forced diuresis, the patient's poor performance status did not improve.

On the 3rd day of hospitalization, the patient's condition was getting worse and he was qualified for haemodiafiltration with plasma exchange in the Intensive Care Unit due to anuria and neurological symptoms of confusion and incoordination.

Diarrhea did not respond to the applied treatment and it led to profound hypoalbuminemia 10.1 g/L, the total protein was 28.4 g/L with massive ascites and edema of lower limbs.

The blood culture was positive with *Streptococcus viridans*. Culture of *Clostridium difficile* in stool was detected, and *Aspergillus fumigatus* and *Candida albicans* cultures were present at sputum. As antifungal treatment enabled caspofungin intravenous.

On the 4th day of hospitalization, the patient was intubated. Paracentesis was performed to exclude progression of myeloma. The test fluid from the peritoneal

cavity showed only a number of inflammatory cells, without infiltration of plasma.

Hemodiafiltration was continued for another 5 days and resulted in an improvement of the performance status and recovery of renal function. After 7 weeks of intensive treatment, the patient was discharged home. Treatment with revlimid was withdrawn. Currently, the patient is in good performance status and remains in observation, in the second complete remission of over 12 months.

DISCUSSION

Therefore, if we are proposing patients diagnosed with multiple myeloma new drugs that significantly prolong disease-free period, we also have to pay a lot of attention to supportive care including anti-infective treatment according to experience and the results of clinical trials of intravenous immunoglobulin substitution (6-8).

From our own observations, we know that, in patients treated for multiple myeloma (especially IgG type) with either Thalidomide or Revlimide, we can expect a significant reduction in the level of normal gammaglobulin. According to the literature, patients with multiple myeloma are in a high risk group of developing life-threatening infections. Despite this recommendation, the use of prophylactic intravenous IgG preparations apply only to patients who have experienced severe infectious complications. IgG levels of at least 500 mg/dl should be deemed sufficient, which not only improves the humoral immune response but also cellular immunity, protecting the patient from a severe course of infection (6-8).

Patients with a diagnosis of cancer of the lymphatic system are a group of patients at particular risk of fatal infectious complications.

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