

Case report

Multiple Myeloma, Renal Involvement and Sepsis - Case Report

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Abstract

Multiple myeloma represents a malignant proliferation of plasma cells derived from a single clone. Systemic chemotherapy is applied for the treatment and control of the progression of the myeloma. Combination of thalidomide and dexamethasone is effective for patients with refractory and/or relapsed multiple myeloma. Thalidomide is a drug with anti-angiogenic, anti-inflammatory, and immunomodulatory effects.

We present a patient with multiple myeloma, treated with thalidomide and dexamethasone, with chronic renal failure on maintenance hemodialysis (MHD) programme. The patient was hospitalized because of high temperature and fever, pancytopenia, DIC, high levels of serum aminotransferases and C - reactive protein.

There was a suspicion for severe sepsis although the blood cultures were sterile in four attempts. The blood marrow aspiration confirmed that the myeloma is in remission. The terrible abdominal pain was the reason for repeated ultrasonographic examination of the abdominal organs, resulting in an enlarged gall-bladder filled with thick mud and a large gall-stone included in the infundibulum. Because of the serious health condition of the patient, an invasive surgical approach on the gall-bladder was impossible to be performed. The patient died after 45 days of hospitalisation, in a clinical picture of a septic shock.

The case was presented in order to report our dilemma for the cause of sepsis in a patient with multiple myeloma on MHD programme with a fatal outcome. Combination of thalidomide and dexamethasone has adverse effects such as susceptibility to bacterial infections, pancytopenia, and acute cholecystitis and can be the causes for development of the sepsis. Whether the acute cholecystitis and cholangitis were fatal complications of severe sepsis or the cholelithiasis with a consequent obstruction and inflammation and can be responsible for the development of the septic condition.

Keywords: multiple myeloma, thalidomide, maintenance hemodialysis programme, sepsis

Introduction

Multiple myeloma represents a malignant proliferation of plasma cells derived from single clone. The cause of myeloma is unknown. The incidence is 40 new cases per million inhabitants per year. Myeloma accounts for 13% of all haematological cancers in whites and 33% in blacks. It is more common in people at the age of 60, and a middle diagnostic age is 68. The tumor, its products, and the host response to it, result in a number of organ dysfunctions and symptoms of bone pain or fracture, renal failure, susceptibility to infection, anemia, hypercalcemia, and occasionally clotting abnormalities, neurologic symptoms and vascular manifestations of hyperviscosity. Renal failure occurs in nearly 25% of myeloma patients as a result of light chain toxic effects on tubules, glomerular deposits of amyloid, hypercalcemia and recurrent infections. The classic triad of myeloma is: marrow plasmacytosis (> 10%), lytic bone lesions, and a serum and/or urine component of paraproteins. A systemic chemotherapy is applied for the treatment and control of the progression of the myeloma. Combination of thalidomide and dexamethasone is effective for patients with refractory and/or relapsed multiple myeloma [1,2].

Case report

A 48-old male patient born in Skopje, with a multiple myeloma, chronic renal failure on maintenance hemodialysis, was hospitalized at the Department of Nephrology because of febrile syndrome and pancytopenia. Multiple myeloma in the patient was diagnosed (May, 2000) at the Department of Nephrology, where he was hospitalized for the first time because of end stage renal disease. Subsequently he was transferred to the Department of hematology for treatment with chemotherapy. The patient started with regular hemodialysis at the Department of Nephrology (July, 2000), having received arterio-venous fistula. No complications occurred during the intra- and inter-dialysis periods. The patient had clinical remission associated with his main disease, but after three years a relapse followed with a diffuse bone pain. The patient consulted a hematologist from the

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Clinical Centre "Rebro" in Zagreb, Croatia, on his own. Bone marrow aspiration was performed in Zagreb, with findings of 40% marrow plasmacytosis (at certain places to 60% with repressing the other hematopoietic stem cells). Therefore therapy with thalidomide and dexamethasone was started and regular ambulatory controls at the Department of hematology, Clinical Centre, Skopje were performed.

The somatic status of the patient at the hospitalisation at the Department of Nephrology (July, 2004) was characterised by a high fever (40 C°), facies lunata, pale coloured skin and mucous membranes, tachycardia (100/min) and hypotensia (100/60 mmHg) due to febrile syndrome and pancytopenia. The first laboratory tests showed pancytopenia, high levels of serum aminotransferases and a high value of C-reactive protein (CRP). There was a suspicion of severe sepsis. Four samples of blood culture from a peripheral vein of the patient were

taken during four subsequent attacks of fever with high body temperature. All blood cultures were negative. During the whole hospitalisation the patient was highly febrile and therefore he received a parenteral antibiotic therapy with third-generation of cephalosporins combined with antimycotic drugs and metronidasole.

Three successive chest X-rays were performed having identical findings of normal lung transparency with right platelet atelectasis and raised right diaphragma due to the enlarged liver. The nephrologist, who performed the first ultrasonography of the abdominal organs, noticed a slight increase of the liver and the spleen with homogenic structure with no focal defects, normal gall bladder and channels, and small kidneys without obstruction and calculosis. The control laboratory tests confirmed the presence of the anemia (Figure 1), leucopenia (Figure 1), increased levels of liver enzymes and bilirubin (Table 1) and increased values of CRP.

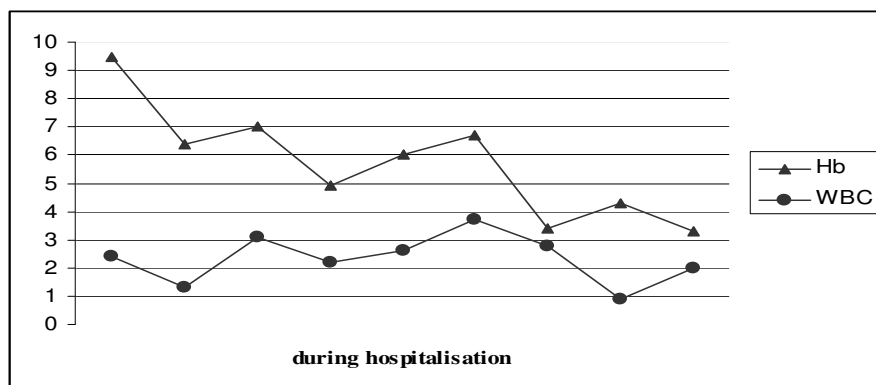


Fig. 1. Serum levels of the patient's hemoglobine (Hb, g/dl) and white blood cells count (WBC, 10⁹/l) during hospitalisation

Table 1. Median values (X ± SD) of the patient's liver enzymes and bilirubin during hospitalisation

Liver enzymes (U/L)		
Billirubin (µmol/L)	X ± SD	ref. value
ALP	186 ± 136.5	11 - 85
AST	222.2 ± 158.2	4 - 34
ALT	73.2 ± 45.8	3 - 45
LDH	1199 ± 383.2	120 - 240
GGT	701.5 ± 2.12	4 - 28
Total bilirubin	154 ± 10.1	6.8 - 20.5
Unconjugated billirubin	54 ± 10.0	1.5 - 6.8
Conjugated billirubin	100 ± 10.1	5.1 - 13.6

The anemia was treated with erythropoetin in a dosage of 12 000 IU weekly and a transfusion of packed red blood cells. The leucopenia was treated with 5 doses of granulocyte colonostimulating factor (G-CSF), which gave only a transitory effect. The clinicopathologic results showed impaired hemostasis followed by thrombocytopenia and disseminated intravascular coagulation (DIC), and appearance of diffuse blood suffuses across the patient's body. Heparin with low molecular weigh and transfusions with platelets and fresh frozen plasma were administrated after consulting a transfusiologist. The bone marrow aspiration showed normal to rich cell bone marrow, plasma cells till 4%, diagnosis of mye-

loma remission, and outcome in favour of a septic condition. An infectologist and pneumophysiologists suggested a change of antibiotic therapy with quinolones for parenteral application. The condition of the patient got worse with the appearance of melena as a result of acute erosions of the gaster mucose and the presence of stress duodenal ulcer, diagnosed by a gastroduodenoscopy. The patient's serum was sent to the Institute "Pasteur" in Paris, France, and the results were negative for antibodies of *Candida albicans* and all immunological and virological investigations. The strong abdominal pain in the patient was the reason to repeat the ultrasonographic examination of the abdominal organs, this time performed by a gastroenterohepathologist who noticed enlarged and edematous gall-blader filled with thick mud and a large stone inclaved in the infudibulum. In favour of this findings were the increased values of liver enzymes and the bilirubin (Table 1). The patient's critical condition prevented any attempt to perform invasive surgical intervention in order to solve the obstruction of the gall. The patient died after 45 days of hospitalisation with clinic septic shock. The patient's family did not consent to autopsy.

Discussion

In most patients with multiple myeloma, the clinical follow-up of the disease is with chronic course for 2 to 5 years, before developing an acute terminal phase, usually marked by development of pancytopenia with acellular bone marrow that is refractory to treatment. About 46% of patients die in chronic phase of the disease from progressive myeloma and renal failure, sepsis or both [1]. The therapy in patients with multiple myeloma is presented with systemic chemotherapy to control the progression of myeloma and symptomatic supportive therapy to prevent serious morbidity from the complications of the disease. In patients with refractory and/or relapsed multiple myeloma, thalidomide is also effective. It is a drug with anti-angiogenic, anti-inflammatory, and immunomodulatory effects. Combination of thalidomide and dexamethasone shows a strong therapeutic answer, but also adverse effects. A group of internists from Taiwan, reported that in 50 patients with multiple myeloma, treated with thalidomide and dexamethasone, the following adverse effects occur: leucopenia, vascular thrombosis, acute cholecystitis, and idiopathic interstitial lung disease [3]. Wofler A *et al.* reported two myeloma patients with fatal sepsis after combined thalidomide/dexamethasone treatment. The patients were hospitalised because of fever, productive cough, and increasing dyspnea. The laboratory tests revealed pancytopenia, increasing creatinine levels, hyperkalemia, and signs of DIC. Thalidomide and dexamethasone cause inhibition of production of tumour necrotic factor – alpha (TNF- α) from the activated monocytes. TNF- α is an important mediator of local inflammation and is vital in keeping infections localized, which explains the susceptibility as well vulnerability to overwhelming bacterial infections in patients treated with combination of thalidomide and dexamethasone. There is strong recommendation for close monitoring of infections in patients treated with these drugs, although the contribution of thalidomide to the fatal infection is not proven [4]. Severe sepsis is a septic condition with one or more signs of organ dysfunction: hypotension, hyperventilation, DIC, stress ulceration, oliguria, cholestatic jaundice...A majority of patients with clinical signs of severe sepsis or septic shock have had a negative blood cultures [6]. Rintala E (1994) reported that in 554 febrile episodes in 126 patients with hematological malignancy, the blood cultures were positive in only 19% of the febrile episodes [5]. The described clinical symptoms of organ dysfunction (hypotension, DIC, stress ulceration, cholestatic jaundice) in severe sepsis were showed in the reported case. Despite the clinical signs of severe sepsis, the four subsequent blood cultures were negative. The first ultrasonography of the abdominal organs of the patient did not show obstruction of the gall bladder beyond the elevation in serum aminotransferases and bilirubin. The terrible abdominal pain of the patient in septic condition was reason to repeat the ultrasono-

graphy of the abdomen, which showed a large stone included in the infundibulum of the edematous gall bladder. The acute cholecystitis and cholangitis result from inflammation which usually requires at least partial obstruction of the flow of the bile, and there is characteristic presentation of biliary colic, jaundice and fever. The acute suppurative cholangitis leads to symptoms of systemic toxicity: mental confusion, bacteremia and septic shock. Response to antibiotics is relatively poor and the mortality rate approaches 100% unless prompt endoscopic or surgical relief of the obstruction and drainage of infected bile are carried out [7].

Conclusions

We presented this case in order to report our dilemma for the cause of sepsis in the patient with multiple myeloma on regular hemodialysis having fatal outcome. Causes for development of sepsis can be adverse effects of the combined therapy of thalidomide and dexamethasone, such as susceptibility to bacterial infections, pancytopenia, and acute cholecystitis. The other reasons for development of the septic condition can be acute cholecystitis and cholangitis as a fatal complication of severe sepsis, or the cholelithiasis with a consequent obstruction and inflammation. The dilemma persists: would the patient have died if the differential diagnostic problems were enlightened timely and the obstruction of the gall bladder was solved when the patient was not in critical condition. We can conclude that all mentioned factors resulted in fatal outcome regardless of the long and intensive treatment of the patient.

References

1. Longo DL. Plasma cell disorders. Harrison's principles of internal medicine. 15th ed. New York, NY: *The McGraw Hill Companies* 2001; 727-733.
2. Sajhuja V, Jha V, Varma S *et al.* Renal involvement in multiple myeloma: a 100 year study. *Ren Fail* 2000; 22(4): 465-477.
3. Huang SY, Tang JL, Yao M *et al.* Reduction of leukocyte count is associated with thalidomide response in treatment of multiple myeloma. *Ann Hematol* 2003; 82(9): 558-564.
4. Wofler A, Bauer F, Zollner G *et al.* Fatal sepsis after thalidomide/dexamethasone treatment in two patients with multiple myeloma. *Haematologica* 2003; 88 (04): 256-278.
5. Rintala E. Incidence and clinical significance of positive blood cultures in febrile episodes of patients with hematological malignancies. *Scand J Infect Dis* 1994; 26(1): 77-84.
6. Munford RS. Sepsis and septic shock. Harrison's principles of internal medicine. 15th ed. New York, NY: *The McGraw Hill Companies* 2001; 799-804.
7. Greenberger NJ and Paumgartner G. Diseases of the gallbladder and bile ducts. 15th ed. New York, NY: *The McGraw Hill Companies* 2001; 1776-1778.