SPONTANEOUS BLEEDING AND PLEURAL EFFUSION IN PATIENTS WITH MULTIPLE MYELOMA: CASE REPORT

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ABSTRACT

Multiple myeloma (MM) is one of types of malignant hematological neoplasm. MM involves the bone marrow primarily but it has a potent tendency to involve extraosseous organs and to present with various manifestation such as central nervous system, lungs and gastrointestinal system. In the present study, we reported a 57-year-old woman who initially demonstrated spontaneous bleeding manifestation and pleura effusion for the first time and was finally diagnosed with MM. Multiple myeloma (MM) patients presenting with extraosseous manifestation pose a great diagnostic challenge. In this study some examinations, including radiology, analysis of globulin in the blood and cytology of pleural fluid supported this diagnosis while bone marrow aspiration and colonoscopy results was unclear. Therefore, emergency management of bleeding and early diagnosis of the disease are very important in this case to prevent fatal outcome.

Keywords: Multiple Myeloma, Spontaneous Bleeding, Pleura Effusion, Radiology, Emergency Management

I. INTRODUCTION

Multiple myeloma (MM) is one of the types of hematological malignancies with the second highest prevalence and the mortality rate about 2% of all malignancies. A characteristic of MM is the clonal proliferation of plasma cells in the bone marrow and is associated with overproduction of immunoglobulins.[1] In MM, there is a malignancy of plasma cell clonal stem cells which mainly involve the bone marrow but has the potential to involve other organs directly and indirectly or as a complication.[2] Furthermore, the clinical manifestations that are characteristic of MM are found with the signs and symptoms of CRAB which stands for hypercalcemia, renal involvement, anemia and bone lesions.[3] However, in some case reports patients with MM show clinical manifestations of extraosseous which are most common or almost two-thirds of cases are found in the liver, lien and spleen glands. Meanwhile, other organs such as the central nervous system, pleura, lungs, skin and GI tract have also been reported.[1,4] In this study, we report a female patient with manifestations of intracranial and GI (GI) bleeding and pleural effusion which on subsequent examination was confirmed as a clinical manifestation of MM. Moreover, the manifestations of bleeding and pleural effusion in MM patients are very rarely found in our centers, so the problem in these patients is emergency management that can be fatal due to bleeding and pleural effusion and diagnosis enforcement to determine definitive therapy in this case.

II. CASE REPORT

A 57-year-old woman admitted to emergency room with decreased of consciousness and hematochezia since 1 day ago. Initially the patient slept more and eventually was difficult to wake up. Two days earlier the patient had complained of bleeding every time she defecated but not much, no diarrhea, no abdominal pain and 1 day before she was admitted to the hospital, more and more blood came out without feces. Previously, the patient did not complain of headache, seizures, severe vomiting or falls. No fever, shortness of breath and cough. Three days earlier the patient only complained of weakness and occasional palpitations and decreased appetite. The last urination was not known because the patient was wearing a diaper, due to a lot of blood coming out of the anal.

The patient had a history of hypertension and arrhythmias for the last 2 years. Check with a cardiologist every 2-3 months and receive clopidogrel 75mg and bisoprolol 2.5 mg prescription but do not take it regularly. The patient latest control was a week ago, and she was given additional drug, warfarin 5 mg once daily. The patient has been taking medication regularly since then. Apart from heart medication, the patient do not take other drugs. Then, in 3 months ago the patient had uric acid checked due to the pain in his toes and the patient was said to have a high uric acid level of about 8 mg/dL, but did not take medication. There was no history of trauma and complaints of blood or bleeding in other places before and the patient was able to carry out daily activities at home independently. History of drastic weight loss, diabetes mellitus, kidney disease, stroke or malignancy was denied. The patient has gone through menopause 6 years ago. Suspected family history of the same illness.

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From the physical examination, the general condition was sufficient with GCS 224-235. Blood pressure 135/80 mmHg, pulse 110-120/minute, irregular, lifting strength. Breathing 24-26x/minute, axillary temperature 36.8°C, SpO2 99% with O2 support 6 liters per minute, the pain scale is difficult to evaluate. Examination of the head and neck revealed pale conjunctiva and dyspnea, no icterus sclera and no cyanosis. There was no increase in jugular venous pressure or enlarged lymph nodes and thyroid. In the right temporal area, a hematoma with a size of ± 4x5 cm was found. Thorax examination: asymmetrical breath movements, lagging right, no intercostal or supraclavicular retractions were found. On cardiac examination, theictus cordis border widened to the intercostal V midaxillary line, irregular single S1 and S2 heart sounds, no murmur, gallop rhythm or pericardial friction. Pulmonary examination revealed decreased vesicular breath sounds in the right hemithorax, no rhonchi or wheezing in both lungs. Abdominal examination: Flat, increased intestinal noise. Hepar and lien within normal limits. Examination of the extremities: warm, dry, pale, capillary refill time less than 2 seconds and hematomas were found in the right and left cubital and wrist regions. As a result of examination of the rectal toucher (RT), the anal sphincter tone was normal, the mucosa was smooth, there was fresh blood flowing and some clotting, no mass and feces.

Supporting examination, laboratory results dated May 28, 2021: ESR 60 mm/h, Hb 7.6 g / dL, RBC 2.4 x 10⁶ / µL, HCT 22.4%, MCV 93.0 fl, MCHC 31.3 pg, MCH 33.6 g/dL, WBC 8180/µL, Neut 59.8%, lym 24.2%, Baso 1.1%, Eos 0.5%, Mono 13.9%, PLT 249,000/µL and blood smear conclusion was normocromic normosistem anemia, anisopolikilositosis, leukocytes with immature granulocytes. Blood random glucose 136 mg/dL, Sgot 26 U/L, SGPT 13 U/L, BUN 54 mg/dL, SK 2.7 mg/dL, Albumin 2.6 g/dL, PPT 30.6 seconds (control 11.1 seconds), APTT 31.3 (control 25.9 seconds), Na 145, K 4.1, Cl 106, Ca 13.5, HbsAg and HIV rapid test showed non-reactive result. Blood gas analysis was normal. ECG: Atrial fibrillation 115-125x/minute. Chest x-ray showed right pleural effusion, cardiomegali. Abdominal ultrasound showed right nephroliasis (+/- 0.66x 0.86 cm in upper pole calyx). CT scan of head without contrast was administrated for this patient (Figure 1) Analysis of pleural fluids showed pH 7.4, WBC 0.38 x10³, RBC 0.001x 10⁶, MN 0.034x10⁹ (87.2%) and PMN 0.049x10⁹ (12.8%). Glucose 104, Protein 5.5, LDH 686.

Based on those initial data the patient was diagnosed with a suspected Multiple Myeloma (MM) with a concomitant diagnosis of Cardiomegaly, moderate AF with a history of anticoagulants (warfarin and clopidogrel) and a diagnosis of complications such as right pleural effusion, encephalopathy due to metabolic and intracranial bleeding, hematochezia, acute renal failure, hypercalcemia, anemia, hypoalbuninemia and right nephroliasis. So the patient was given initial therapy: nephisrol 100cc every 6 hours per sonde. For hypercalcemia we administrated intravenous rehydration fluid with NaCl 0.9%, intravenous diuretic with furosemide and intravenous dexamethasone. For spontaneous bleeding we administrated intravenous Vit.K and intravenous tranexamic acid and blood transfusion with packed red cell and fresh frozen plasma. Hence, we continued bisoprolol 2.5mg once daily for her arrhythmia. Since there was no respiration distress, we delayed pleural fluid evacuation. Neurosurgery peer consultation said that there was no indication for surgery. Patients will be examined for BMA, INR, Bene Jones protein and Eshbach protein in urine, uric acid, phosphate, serum protein electrophoresis, and ADA test and cytology of pleural fluid and echocardiography in the next planning.

During hospitalization, the patient’s condition improved day by day. On the 5th day of treatment, the patient showed good orientation and there was no rectal bleeding. On examination, vital signs showed GCS 356-456, BP: 130/80, HR 130-140x/minute, RR 22x/minute, SpO2 99%. Haemoglobin level, creatinin serum, calcium serum, uric acid and PPT/APTT returned to normal level. Total of 1000 ml pleura fluid that evacuated within 4 days showed red fluid and sent to anatomic pathology department. ADA test of pleura effusion was 18.8 U/L. The electrophoresis serum examination showed decreased albumin, α-2 globulin and β globulin with increased γ-globulin monoclonal which suggests a monoclonal gammopathy. Bene jones protein from urine was negative. After the patient condition was
completely stable, we performed echocardiography, bone marrow puncture and colonoscopy. The echocardiography showed moderate mitral valve regurgitation (carpentier type IIIb mechanism, ERO 0.3 cm², MR RV 49 ml). Since the bone marrow analysis (BMA) result did not meet the criteria of MM and the colonoscopy result was not representative too so we decided to wait the cytology of pleural fluid result. Consequently, the patient was discharged on the 15th day of treatment and returned three days later with mild GI bleeding to our hematology-oncology clinic. Therefore, a week later the result of pleura fluid cytology revealed plasmacytoma and immunohistochemistry examination showed CD 138 (+) and CD 20 (-). Based on the overall clinical data and supporting examination, it was concluded that the patient's diagnosis was Multiple myeloma (MM) the patient with Multiple myeloma (MM) with manifestations of spontaneous intracranial and GI bleeding and pleural effusion and had comorbid heart disease, moderate mitral regurgitation and hypertension. However, the patient refused to have chemotherapy and we suggested the patient to visit our hematology-oncology clinic regularly.

Fig2. A) Chest x-ray on admission; B) Chest x-ray after 2nd pleural fluid evacuation; C) Chest x-ray after last pleura fluid evacuation

III. DISCUSSION

Multiple myeloma (MM) is a plasma cell malignancy in which the most common clinical manifestations are 'CRAB' which stands for hyperCalcemia (serum calcium >10mg/dL), Renal insufficiency (serum creatinine 1.73 mmol/L), Anemia (Hb value <10 g/dL) and Bone lesions (osteolytic lesions, severe osteopenia, or pathologic fractures). In this case, a patient without a previous history of MM was brought to the emergency room Dr. Soetomo Hospital Surabaya with decreased consciousness and bleeding from the GI tract. At the time of the first inspection, we suspected the decreased consciousness could be due to a hemorrhagic/thrombotic stroke and GI bleeding was the result of heart disease and the use of anticoagulants in this case is warfarin. However, after obtaining more complete data from laboratory and radiological examinations, we found hypercalcemia, increased serum creatinine, anemia and bone lytic in the calvaria so that it met the 'CRAB' criteria in the patient so that the patient's diagnosis was strongly suspected of leading to MM. Intracranial and GI bleeding manifestations may be associated with MM in patients who are at risk of bleeding from warfarin therapy. Meanwhile, pleural effusion can be caused by MM directly or as a complication of MM.

Based on the criteria for the diagnosis of MM by Salmon-Durie, in addition to the clinical manifestation of 'CRAB', there are additional investigations that must be carried out such as bone marrow aspiration (BMA) or a biopsy which shows the plasma cell composition of at least 10% and the examination of monoclonal protein in the serum with protein electrophoresis examination and shows increased levels of monoclonal globulin. In this case, we found ‘CRAB’ and the protein electrophoresis and cytology of pleural fluid met criteria of MM. However the patient came with bleeding manifestations and pleura effusion that are rare in patient with MM in our center.

Spontaneous bleeding manifestations in MM cases can be caused by several causes including impaired platelet function and coagulation factors which are estimated to be the cause of 1/3 of bleeding cases in MM. Dysproteinemias in MM can cause coagulopathy in MM due to several mechanisms including the influence of paraproteins on normal coagulation factors, increased clearance of coagulation factors by the reticuloendothelial system (RES), paraprotein anticoagulant activity, platelet dysfunction, excessive fibrinolysis and blood hyperviscosity. In this case, it is strongly suspected that the risk of bleeding is the prolongation of homeostatic function (PPT and APTT) but it can also be caused by warfarin. Spontaneous Subdural hemorrhage (SDH) can occur without a history of head trauma. Spontaneous SDH cases are very rare, but increase the mortality rate by around 60-76.5%. Based on the results of discussions with neurosurgeon colleagues, in this case there is no indication for evacuation of SDH bleeding because the bleeding area is not more than 1 cm and there is no midline shift, so we give an anti-fibrinolytic agent, namely tranexamic acid is often used in cases of chronic SDH.
GI bleeding in MM can be caused by a common cause of bleeding in MM patients or by indirect plasmacytomas, amyloid infiltration in the intestinal wall, thereby increasing capillary fragility and the recurrent GI bleeding is specific in MM.\(^1\) Case report by Lin et al., reported a patient who had been diagnosed with MM and had refractory hematochezia revealed gastric mucosal edema and duodenal ulcers by gastroscopy and colonoscopy and after 6 months of chemotherapy the patient never complained of GI bleeding.\(^1\) In this case, unfortunately the colonoscopy result was not representative. The management of bleeding in this case without involving surgical procedures, supportive therapy such as adequate fluid, blood volume replacement, injection of Vit. K and anti-fibrinolytic is quite effective in dealing with the manifestation of patient bleeding during hospitalization but that cannot guarantee the occurrence of re-bleeding in patients.

Pleural effusion (PE) is not rare in patients with MM, with an estimated frequency of up to 11%. The study by Byun et al., showed that 13.9% of patients with MM showed clinical manifestations of PE during illness.\(^9\) The etiology of PE in MM is multifactorial (myelomatous and non-myelomatous) and PE due to myelomatous is very rare. In the literature it is stated that 80% of PE due to myelomatous factors are caused by malignancy by IgA and have a tendency to invade extraosseous structures. On the other hand, PE due to non-myelomatous factors is the most common and is usually caused by heart failure secondary to blood hyperviscosity or amyloidosis, renal failure due to paraprotein infiltration in the renal tubular and effusion due to pneumonia.\(^9,2\)

In this case, PE was caused by myelomatous factors which was supported by the results of cytological examination and cell block with hematoxylin and eosin (HE) staining and immunohistochemistry (IHC) examination of pleural fluid which showed plasmacytoma with CD 138 (+), CD 20 (-) (Figure 3). Pleural effusion in MM needs to be distinguished from lymphoma and TB infection. In this case, lymphoma can be excluded by obtaining a negative CD20 result with IHC examination.\(^10,2\) Meanwhile, pleural TB infection can be ruled out with normal results of the ADA test.\(^11\)

The mechanism of myelomatous PE is the high number of immunoglobulins due to malignant plasma cells in or around the pleura causing colloid osmotic pressure of the pleural fluid that exceeds its absorption capacity.\(^12\) The characteristic of PE due to myelomatous factors is frequent relapse, and is associated with a poor prognosis for MM with a reported median survival of 2.8 to 4 months without aggressive therapy. Moreover, the current management of PE due to myelomatous factors is to use a combination of systemic therapy and local therapy. Systemic therapy with chemotherapy which sometimes also uses radiotherapy in cases of local invasion or local therapy using injection of bortezomib, Adriamycin and intrapleural interferon.\(^13\) In this case, the evacuation of pleural fluid every two days was still effective in reducing the patient's respiratory symptoms even though the evaluation results of the post-evacuation chest x-ray were not good enough.

In this case the patient had comorbid heart disease which was a special consideration for systemic chemotherapy therapy. At our center, chemotherapy options for MM covered by government health insurance are very limited. The usual regimen given is the VAD regimen (Vincristin, Adriamycin and oral dexamethasone) which are the initial chemotherapy regimen in MM and according to the report on the Adriamycin regimen (doxorubicin) have side effects of cardiotoxicity.\(^13\) Unfortunately, in the end the patient refused chemotherapy, so we continued supportive therapy to maintain the patient's optimal condition and after 2 weeks of treatment, the patient was allowed to go home and was able to control the hematopoiesis poly at Dr. Soteomo Hospital Surabaya.

**IV. CONCLUSION**

It has been reported a 57-years old woman who experienced spontaneous subdural hemorrhage and GI bleeding and pleura effusion for the first time and later those caused by Multiple myeloma. Spontaneous intracranial and GI bleeding and Pleura effusion in patient with MM is very rare in our center. Emergency management of bleeding and early diagnosis of the disease are very important in this case to prevent fatal outcome.

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