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Autoimmune Hemolytic Anemia, Amoebic Dysentery, And Intracranial Hemorrhage as Rare Manifestations of Smoldering Multiple Myeloma: A Case Report

Anemia hemolítica autoinmune, disentería amebiana y hemorragia intracraneal como manifestaciones raras de mieloma múltiple latente: Reporte de un caso

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SUMMARY

Background: *Smoldering multiple myeloma (SMM) is in asymptomatic stages before overt multiple myeloma (MM) but it also has an increased risk of thrombosis, infection, autoimmune, and hemorrhage. SMM is usually recognized coincidentally during the workup of a variety of symptoms.*
Case Presentation: *A 37-year-old male patient presented to the hospital with bloody diarrhea for two weeks. He was diagnosed with SMM with autoimmune hemolytic anemia (AIHA) and amoebic dysentery and treated for approximately 18 days then discharged to continue as an outpatient but he never attended. Seven months later he returned to the hospital with seizures. Computed tomography (CT-scan) was conducted, conforming had an intracranial hemorrhage and progressed to hydrocephalus.*
Conclusion: *This case report shows that nowadays SMM needs to be aware even in the absence of progression to overt MM. Exploring medical history, physical examination, laboratory, and imaging examination need to be paid attention to carefully to diagnose SMM considering that it is often found coincidentally among various manifestations.*

Keywords: *SMM, AIHA, amoebic dysentery, intracranial hemorrhage.*

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RESUMEN

Antecedentes: *El mieloma múltiple latente (SMM) es una etapa asintomática antes del mieloma múltiple (MM) manifiesto, pero también tiene un mayor riesgo de trombosis, infección, autoinmunidad y hemorragia. SMM generalmente se reconoce coincidentemente durante el estudio de varios síntomas.*

Presentación del caso*: un paciente masculino de 37 años se presentó en el hospital con diarrea sanguinolenta durante dos semanas. Fue diagnosticado con SMM con anemia hemolítica autoinmune (AIHA) y disentería amebiana y fue tratado durante aproximadamente 18 días, luego fue dado de alta para continuar como paciente externo, pero nunca asistió. Siete meses después volvió al hospital con convulsiones. Se realizó una tomografía computarizada (CT-scan), conforme tuvo hemorragia intracraneal y progresó a hidrocefalia.*

Conclusión: *Este caso muestra que hoy en día SMM debe ser consciente incluso en ausencia de progresión a MM manifiesto. Se debe prestar atención a la exploración de la historia clínica, el examen físico, el laboratorio y el examen de imágenes para diagnosticar la SMM, ya que a menudo se encuentra coincidentemente entre varias manifestaciones.*

Palabras clave: *SMM, AIHA, disentería amebiana, hemorragia intracraneal.*

INTRODUCTION

Smoldering Multiple Myeloma (SMM) is a precursor asymptomatic state of Multiple Myeloma (MM). There is no organ or tissue damage found in SMM, unlike MM who may develop signs and symptoms. Patients with SMM may experience a slow disease course (1). Because of incidence SMM data is unknown, The Iceland Screens, Treats or Prevents Multiple Myeloma (iStopMM) study screened a large (N>75 000) population-based, and it showed the prevalence of SMM is 0.5 % in persons 40 years or older (2). Smoldering multiple myeloma is an entity between monoclonal gammopathy of undetermined significance (MGUS) and MM. Unfortunately, there are no specific pathologies or molecular abnormalities that can be used to differentiate between SMMs who have a high risk of developing MM (3).

This case is unique because a young adult male suffered from SMM who initially came because of bloody diarrhea and autoimmune hemolytic anemia which later developed into intracranial hemorrhage and then progressed to hydrocephalus. Although SMM is a precursor to MM, it caused several risks including autoimmune, infection, and hemorrhage.

CASE PRESENTATION

A 37-year-old male patient came to the Emergency room at Dr. Seotomo Teaching Hospital. He was referred patient from a rural hospital presenting bloody diarrhea for two weeks. The frequency of diarrhea was more than 3 times per day to 10 times per day, with a great amount volume of liquid stool, and no mucus. He admitted that his appetite had decreased. He also had nausea and abdominal pain. He also lost weight, from 63 kg to 58 kg. He had a history of mild hemorrhoids which rarely bled. He had a history of difficulty finding a suitable blood donor from the previous hospital because he suffered from anemia. He denied any fever or family medical history of the same disease.

The patient had abnormal physical examination findings, such as tachycardia 115 x/min, anemic conjunctiva, and increased bowel sounds. The abnormal laboratory finding was hemoglobin (Hb) 8.1 g/dL, platelets 134.000/μL, leucocytes 40.860/μL with lymphocytes 16.7 %, monocytes 34.1 %, eosinophils 0.6 %, basophils 0.1 %, neutrophils 48.5 %. Albumin serum was decreased to 1.7 g/dL. The liver enzyme, urea, and creatinine serum were normal. Increased levels of C-reactive Protein (CRP) and LDH 12.4 ng/dL and 334 U/L, respectively, normal total bilirubin 0.18 and calcium 7.2 mg/dL were not increased. Stool examination showed macroscopically: blood (+), soft consistency, mucus (+), brown color; microscopically: amoeba (-), bacteria (3+), erythrocytes > 100, fungi (2+), cysts (-), leukocytes > 100, fat (2+), parasites (-), worm eggs (-), food waste (3+). He had positive direct and indirect Coomb tests. Peripheral blood smear: erythrocytes: normochromic anemia anisopoikilocytosis, leukocytosis with plasmablasts 9 % and plasma cells 27 %,

thrombocytopenia suggested suspicious of a plasma cell leukemia and normal Chest x-ray (CXR).

From the data above, at first, we diagnosed the patient with autoimmune hemolytic anemia (AIHA) caused by plasmacytoma colon with differential diagnoses of multiple myeloma, inflammatory bowel disease (IBD), and/or infectious diarrhea. We also planned additional tests such as protein electrophoresis, Beta 2 microglobulin, bone marrow aspiration, bone survey (Figure 1), fecal calprotectin, abdominal CT scan with contrast, and colonoscopy. He was treated with an intravenous (IV) drip of ceftriaxone 1 gram every 12 h, IV bolus of methylprednisolone 125 mg every 8 h, IV bolus of omeprazole 40 mg IV every 12 h, albumin transfusion, packed red cell (PRC) transfusion, and fentanyl patch for reducing pain.

On the second day of treatment, he still complained of bloody diarrhea, stomach cramps, and nausea. The results of the protein electrophoresis examination showed a decrease in albumin, alpha 2, and beta globulin fractions with an increase in alpha 1 and monoclonal gamma globulin (suspecting a monoclonal gammopathy) with the amount of M-protein 5 g/dL (Figure 1).

On the fifth day of treatment, He still complained same symptoms but less severe. His laboratory evaluation results showed improvement, Hb 10.7 g/dL, leukocytes 9430/µL, platelets 180 000/mm^3, albumin 2.6 g/dL. Fecal calprotectin and beta 2 -Microglobulin were performed, it reached >2000 (<50 μg/g) and 2.57 mg/L (0.81-2.19), respectively. Both tumor markers were normal, CEA < 0.5 mg/mL (<= 5) and Ca 19-9 4.8 U/mL (< 37). HIV infection is also excluded, confirmed by a negative HIV test. Bone marrow aspiration results reflected 8.28 % plasma cells. The results of the bone survey did not show any lytic lesions (Figure 2). CT scan of the abdomen with contrast: asymmetrical wall thickening with a maximum thickness of ± 1.5 cm in the rectosigmoid, ± 5.5 cm long with a distance of ± 5.2 cm from the anus, and spondylosis of lumbar. On colonoscopy examination, it was found that there was an edematous mucosa accompanied by whitish patches, the mucosa was fragile and bleeds easily, there was no intraluminal mass, no ulcer was seen, and suspicious pseudomembranous colitis. On the 8th day of treatment, an anatomical pathological examination of the rectosigmoid from colonoscopy found mucosal of the partially ulcerative colon, lamina propria with scattered inflammatory cells of lymphocytes, histiocytes, plasma cells, and neutrophil cells. Necrotic tissue was found on the mucosa and among them there was trophozoite entamoeba histolytica. There were no signs of malignancy. An IV bolus of Methylprednisolone was reduced to 62.5 mg per 8 h, IV antibiotic was replaced with an IV drip of ciprofloxacin 400 mg every 12 h and an IV drip of metronidazole 500 mg every 8 h.

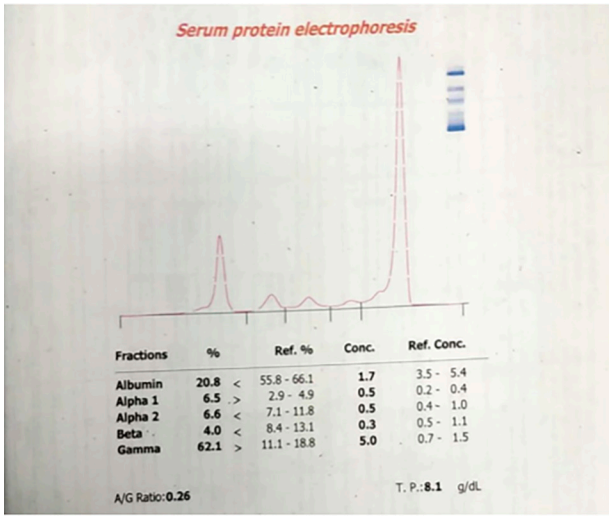

Figure 1. Serum Electrophoresis Protein.

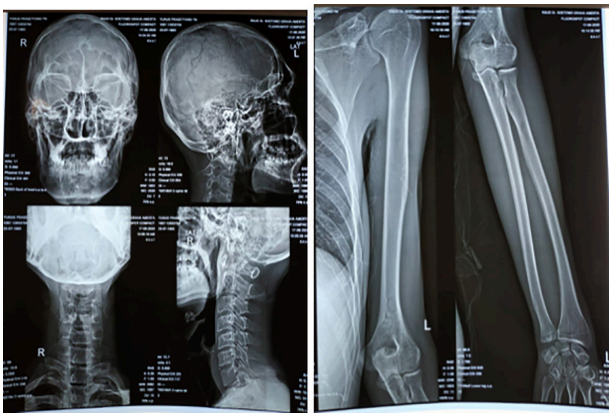

Figure 2. No evidence of bone lytic lesions on the bone survey.

He had unremarkable complaints on the 18th day of treatment then he was discharged from the hospital. Light chain examination was performed that showed kappa free light chain 9.96 (3.30-19.40 mg/L), lambda free light chain 57.99 (5.71-26.30 mg/L), kappa/lambda ratio 0.17 (0.26-1.65 mg/L), increased lambda light chain with decreased kappa/lambda ratio, suggested of monoclonal lambda gammopathy. Immunofixation test showed IgG Lambda monoclonal gammopathy (Figure 3).

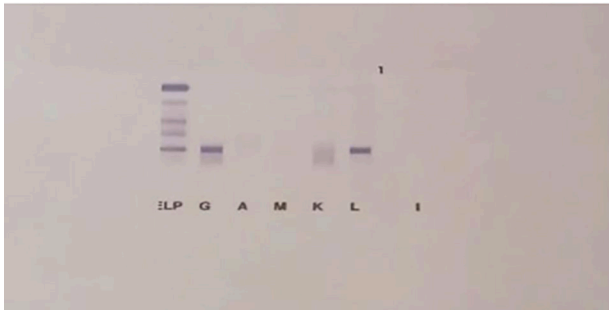

Figure 3. Serum Immunofixation.

In the end, he was diagnosed with smoldering multiple myeloma, AIHA, and amoebic dysentery. He was educated in routine control at the outpatient clinic, but he never attended. Then he came to the emergency room 7 months later with seizures. The general examination was decreased consciousness with GCS 346, blood pressure 100/60, pulse 105 x/min, temperature 37° C, respiratory rate 20 x/min. Complete blood count showed Hb 9.9 g/dL, leucocytes 13 380, and platelets 122 000. A CT scan of the head showed multiple lesions with perifocal edema accompanied by intra-tumoral and peritumoral hemorrhage in the subcortex of the left parietal lobe, left frontal lobe, right left temporal lobe, right cerebral tonsil, which could be multiple metastases with intra-tumoral hemorrhage and peritumoral hemorrhage with multiple simultaneous intracerebral hemorrhage (SIH) (Figure 4).

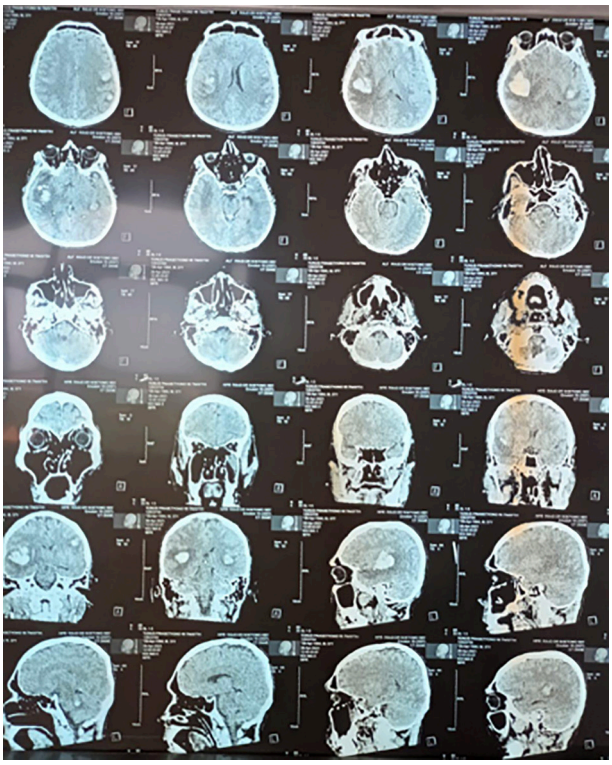

Figure 4. Head CT-scan.

Then after the general condition improved, the patient underwent bortezomib chemotherapy for 3 cycles. Six months later, he came to the ER again with complaints of profuse vomiting, headache, and decreased consciousness, CT scan of the head without contrast found active communicating hydrocephalus and brain edema. The patient's course of the disease was briefly explained in Figure 5.

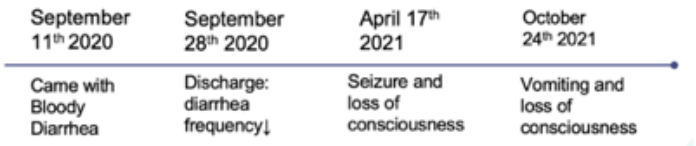

Figure 5. Patient's disease course.

DISCUSSION

The duration of diarrhea can provide information on the etiology of diarrhea. Based on the duration of diarrhea, is divided into three (1), acute diarrhea: 14 days, (2) persistent diarrhea > 14 days, and (3) chronic diarrhea > 30 days. Acute diarrhea is usually caused by viral and bacterial infections. If the duration of diarrhea is prolonged, you should start thinking about causes other than infection. A non-infectious etiology should be considered when no pathogen is found, and diarrhea becomes chronic. If there is profuse diarrhea that results in hypovolemia, diarrhea with blood, fever, > 6x/day, and severe abdominal pain, in the elderly > 70 years, in immunocompromised patients, an additional examination is necessary to find the etiology of diarrhea (4).

The role of endoscopic examination in acute diarrhea is to (1) differentiate inflammatory bowel disease (IBD) and infectious diarrhea because IBD can initially appear as acute diarrhea, (2) the presence of a pseudomembrane in toxic patients to diagnose *C. difficile* while waiting toxin stool test but it should be noted that colonoscopy can cause perforation in patients with impaired intestinal integrity, (3) immunocompromised patients are at risk for opportunistic infections such as cytomegalovirus (CMV) (4). We also had a running of Fecal Calprotectin which is a biomarker to assess intestinal inflammation (5). Direct Coomb's Test is used to detect autoantibodies on the surface of red blood cells characterized by the presence of C3 and/or IgG that bound to red blood cells while indirect Coomb's test can detect about 80 % of antibodies in serum. Transfusion is not an absolute contraindication in AIHA patients, but corticosteroids should be given before the transfusion (6).

A study conducted by Kristinsson et al. showed a new perspective that MGUS significantly increases the risk of infection. A high concentration of M protein at diagnosis shows an association with a high risk of infection (7). Some studies also show inflammatory/infectious states such as pneumonia, sepsis, meningitis, and osteoarthritis increase the development of MGUS and some cases progress to MM (8). This indicates that a severe inflammatory process can trigger the development of MGUS and myeloma. Infection is known to cause clonal proliferation by triggering certain genetic translocations (9).

Smoldering multiple myeloma criteria based on the International Myeloma Working Group (IMWG) must meet two of these criteria (1). Serum monoclonal protein 3 g/dL or urinary monoclonal protein ≥ 500 mg/24 h and or bone marrow plasma cells 10 %-60 % and (2) No incidence showing myeloma/amyloidosis (10).

MGUS is characterized by the presence of monoclonal gammopathy < 3 g/dL, bone marrow aspiration with plasma cells < 10 %, and the absence of CRAB criteria as in MM. According to IMWG, MGUS is subdivided into Non-IgM MGUS, IgM MGUS, and light chain MGUS. The diagnostic criteria for light chain MGUS were abnormal free light chain (FLC) ratio (<0.26 or >1.65), increased light chain (increased FLC in patients with FLC ratio > 1.65 and increased FLC in patients with FLC ratio < 0.26), no heavy chains were found on immunofixation examination, no organ damage, plasma cells on bone marrow aspiration < 10 %, and urine monoclonal protein < 500 mg/24 h based on the IMWG, the diagnostic criteria for MM are plasma cells in the bone marrow 10 % or proven by bone biopsy or extramedullary plasmacytoma and one or more of the following events: (1) Calcium > 0.25 mmol/L (1 mg/dL) higher than normal or > 2.75 mmol/L (> 11 mg/dL), (2) Renal insufficiency (creatinine > 2 mg/dL or 177 mmol/L) or creatinine clearance < 40 mg/dL, (3) Anemia (Hb < 10 g/dL or Hb>2g/dL below normal limits), (4) One or more osteolytic lesions on bone radiography, CT, or FDG PET/CT, (5) Bone marrow plasma cells 60 %, (6) FLC involved : uninvolved ratio > 100, (7) > 1 focal lesion on MRI 5 mm (10).

MM/MGUS is often accompanied by autoimmune diseases, including AIHA. Inflammation that occurs in autoimmune diseases can trigger the occurrence of MGUS and MM. In addition, genetic influences also influence the development of both autoimmune diseases and MM/MGUS (11). MGUS is known to initiate MM with an estimated 1 % risk that it will develop into MM (12). Although some MGUS did not develop into real MM. There is evidence that immune dysregulation or continued immune

stimulation may play a role in the development of MM/MGUS (13). A population-based study and a case series demonstrated that several immune-mediated conditions are associated with a risk of developing MGUS (14).

Several cases have been reported that AIHA and Evan syndrome was found in MM patients. The possible mechanism that can occur is M-protein type IgG that causes hemolysis, but this is not yet known for sure. It is not known whether the acquired autoimmune manifestations are events caused by MM or just coincidence. There was a study that showed that the M-Protein known at that time was a type of IgG kappa that attacks red blood cells. MM is known to be a B-cell malignancy accompanied by an immune disorder that causes clones to develop and produce antibodies against erythrocyte surface antigens (15).

Management of SMM can be treated earlier before MM occurs by doing risk stratification. There are 3 risk stratifications, low, medium, and high risk. Risk stratification aims to determine how often patients with SMM are monitored and when to start therapy, and earlier intervention to prevent progression to active MM and to achieve complete remission. High-risk SMM is an indication for therapy (1). High-risk criteria according to the Mayo clinic are 20/2/20, the percentage of plasma cells in the bone marrow > 20 %, M-protein > 2 g/dL, and FLC ratio > 20 (16).

There are no reports that discuss SMM patients in young patients, and how the prognosis and management are, but there is a study that discusses where patients diagnosed with MM at a young age are important for optimal treatment to improve good outcomes and minimize treatment-related toxicity (17).

No one has described a case of SMM with the central nervous system affected. However, there is a case report from Kumar et al., describing a 52-year-old woman presenting with headache and loss of consciousness. After further examination, a primary cerebral plasmacytoma with a bleeding tumor without progressing to MM was found because there were no lytic lesions in the bone and only 1 % plasma cells were found on bone marrow aspiration. However, in this case, an excision of the tumor was carried out, histopathological and immunohistochemical examinations were performed and it showed a plasmacytoma (18).

Another case reported by Onodera et al. was an intracranial plasmacytoma secondary to MM with cerebral hemorrhage without the involvement of bone lesions. In this case, coagulability disorders are caused by MM itself and the side effects of chemotherapy and radiotherapy that also cause massive hematomas (19). MGUS, SMM, and MM may have complications in the form of thrombosis or bleeding. The bleeding may be related to the presence of monoclonal protein immunoglobulins. Characteristics of specific paraprotein affinity with coagulation factors or platelet surfaces have been associated with bleeding in some cases of severe bleeding with monoclonal gammopathy (20).

ICH in this case can cause by platelet dysfunction or coagulation disorders, although the patient data cannot be proven due to the limitations of the examination in our hospital.

CONCLUSION

SMM needs to be aware even in the absence of progression to overt MM. Exploring medical history, physical examination, laboratory, and imaging examination need to be paid attention to carefully to diagnose SMM considering that it is often found coincidentally among various manifestations. Further research is required to study early treatment in high-risk SMM to prevent progression to active MM.

Conflicting interest

The authors declare that there are no conflicts of interest.

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