A 44-Year-Old Man with Waldenstrom Macroglobulinemia and Bilateral Maxillary Sinusitis

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ABSTRAK

Waldenstrom macroglobulinemia adalah penyakit kelainan limpoproliferatif yang bersifat kronik dan indolen dengan karakteristik adanya IgM makroglobulin yang tinggi, peningkatan viskositas serum, dan infiltrasi limfoplasmasitik pada sumsum tulang. Manifestasi klinis terjadi karena adanya IgM paraprotein dan infiltrasi sel limfoplasmasitik maligna pada sumsum tulang dan jaringan yang lain. Telah dilaporkan laki-laki dengan Waldenstrom macroglobulinemia dan sinusitis maksillaris bilateral, diberikan terapi simptomatik dan antibiotik untuk sinusitis, transfusi FFP dan PRC untuk memperbaiki kondisi umumnya, dan kemoterapi regimen CHOP sebagai terapi definitifnya.

Kata kunci: *Waldenstrom macroglobulinemia, monoclonal gammopathy, CHOP.*

ABSTRACT

Waldenstrom macroglobulinemia is a chronic, indolent, lymphoproliferative disorder, which is characterized by the presence of a high macroglobulin (IgM) level, elevated serum viscosity, and the presence of a lymphoplasmacytic infiltrate in the bone marrow. Clinical manifestations may be found due to the presence of IgM paraprotein and malignant lymphoplasmacytic cell infiltration of the bone marrow and other tissues. We reported a case of male patient with Waldenstrom macroglobulinemia and bilateral maxillary sinusitis. He had received symptomatic and antibiotic treatment for his sinusitis, FFP and PRC transfusion to improve his general condition and chemotherapy with CHOP regimen as definitive treatment.

Keywords: *Waldenstrom macroglobulinemia, monoclonal gammopathy, CHOP.*

INTRODUCTION

Waldenstrom macroglobulinemia (WM), one of the malignant monoclonal gammopathies, is a chronic, indolent, lymphoproliferative disorder.[1] WM is currently classified by the Revised European American Lymphoma (REAL) and World Health Organization (WHO) systems as a lymphoplasmacytic lymphoma.[2]

Waldenstrom macroglobulinemia is a relatively rare condition with 1500 cases diagnosed per year in US accounting for approximately 2% of hematologic malignancies. In UK, the annual incidence of this disease is 10.3 per million. It is common in elderly individuals, i.e. among 7th – 8th decade of life with median about 65 years and a slight male predominance.[3-5]

CASE ILLUSTRATION

A 44-year-old male patient came to hospital with general weakness since 1 month ago, which had been worsened since 2 weeks ago. He also complained of tension-type headache, especially in the front head and in his left cheek, there was smelly odor from his nose with purulent-greenish discharge from his left nose and his throat. He also suffered from sorethroat and nasal blockage. Previously, he complained about intermittent nasal discharge and sneezing, especially when he was exposed to cold weather. He had toothache of his left upper third molar since 1 year ago with intermittent pain, but since 1 month ago, he started to feel pain again and the pain did not subside. He experienced weight loss since 3 months ago without any change of eating habit. In the past 1 week, he started to feel tingling sensation on his right forefoot. The patient had already visited ENT specialist and dentist. He was told that he has maxillary sinusitis and pulp gangrene. He received pain killer as well as antibiotics, but because his hemoglobin level was low, he was referred to an internist and subsequently was advised to be referred to Saiful Anwar General Hospital due to a suspicion of aplastic anemia. He is a married man with 2 children, and works as a farmer.

Physical examination revealed blood pressure of 120/80mmHg, pulse rate of 82 beats/minute, respiratory rate of 18x/minute, axillary temperature of 36.7^{0}C, anemic conjunctiva, left maxillary tenderness, bilateral edema of medial conchae with bilateral purulent discharge from the medial meatus, hyperemic pharynx with multiple granulae, pulp gangrene on the left upper M3, traube space dullness; while others findings were within normal limit.

Laboratory tests showed a hemoglobin level of 6.80 g/dl, leukocyte count of 3,700/µL, hematocrit of 21.50%, platelet count of 110,000/µL, (diff count 0/0.3/0/47.8/40.5/10). Blood smear examination showed anisocytosis normochromic anemia indicating reduced leukocytes and platelets. The blood smear also showed giant platelets. His serum albumin level was 3.16 g/dL with globulin level of 8.21 g/dL, total protein of 11.49 g/dL and positive result of FOBT with prolonged hemostatic function result. His serum electrolyte, renal function test, liver function test, LDH, bilirubin and urinalysis were within normal range. Waters' view sinus X-ray showed that there was acute on chronic maxillary sinusitis on his left sinus, chronic maxillary sinusitis on his right sinus and rhinitis. Abdominal USG revealed splenomegaly. Protein electrophoresis was carried out 3 days later with a result indicating a monoclonal gammopathy and his bone marrow puncture showed infiltration with 80% cells consist of lymphocytes, plasmacytoid, and plasma cells. We concluded that the diagnosis of the patient was suspected Waldenstrom macroglobulinemia and immunofixation is needed to confirm the diagnosis.

Bone marrow immunohistochemistry revealed negative result for CD20; while the immunofixation showed positive result for monoclonal IgM Lambda and serum immunohistochemistry showed no positive dominant markers. Unfortunately, the amount of samples obtained from bone marrow aspiration was too little for immunohistochemistry assay and therefore, the result only showed for the CD 20.

Patient was diagnosed with Waldenstrom macroglobulinemia, hypoalbuminemia, acute on chronic maxillary sinusitis on left sinus, chronic maxillary sinusitis on right sinus and rhinitis. He received high calories high protein meal 2100 kCal/day, 20 drops/minute of IVFD of normal saline (0.9% NaCl solution), PRC transfusion 2 packs/day until his Hb >10 g/dL, 400 mg intravenous ciprofloxacin twice daily, 625 mg amoxycillin-clavulanic acid three times daily, 50 mg natrium diclofenac twice daily, pseudoephedrine Hcl 60 mg/tripolidine HCl 2.5 g twice daily, 2 tablets of Vit B6/B12 three times daily and 1000 µg folic acid daily.

On day 3, the patient was hospitalized. He had dark tarry stool, his FOBT result was positive and he had prolonged hemostatic function. He received FFP transfusion of 4 packs/day afterward. He also received Short Wave Diathermi 6x to relieve his maxillary pain. During therapy, his condition was improved with Hb level of more than 10 g/dL; his weakness, headache and nasal discharge subsided gradually.

He was scheduled for chemotherapy with 6 series of CHOP regimen (Cyclophosphamide, Doxorubicin, Vincristin, Prednison) with 21 days cycles and showed good response to the treatment.

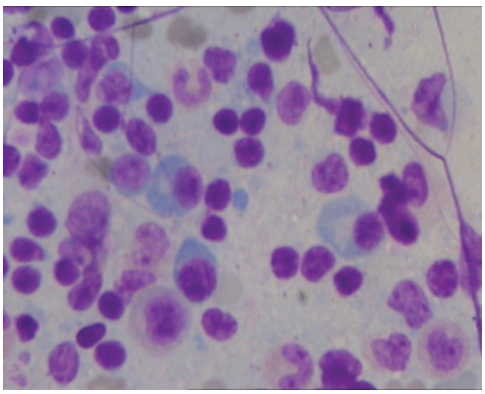

Figure 1. Bone marrow aspiration showing infiltration of lymphocyte, plasmacytoid and plasma cells

DISCUSSION

Waldenstrom macroglobulinemia is a malignant disease of B cells that appear to be a hybrid of lymphocytes and plasma cells. These cells characteristically secrete an IgM paraprotein and many clinical manifestations of the disease are related to this macroglobulin.[5]

Clinical manifestations of this disorder result from 2 important factors. The first factor is the secretion of the IgM paraprotein that may lead to hyperviscosity and vascular complications because of physical, chemical, and immunologic properties of the paraprotein. Monoclonal IgM causes hyperviscosity syndrome, cryoglobulinemia types 1 and 2, coagulation abnormalities, sensorimotor peripheral neuropathy, cold agglutinin disease and anemia, primary amiloidosis, and tissue deposition of amorphous IgM in the skin, GI tract, kidneys, and other organs. The second factor is neoplastic lymphoplasmacytic cells that infiltrate the bone marrow, spleen, and lymph nodes. Less commonly, these cells can infiltrate the liver, lungs, GI tract, kidneys, skin, eyes, and CNS. Infiltration of these organs causes numerous clinical symptoms and signs. Occasionally, IgM paraprotein has Rheumatoid Factor activity, antimyelin activity that can contribute to peripheral neuropathy, and immunologically related lupus anticoagulant activity.[2]

The differences between WM and Multiple myeloma (MM) are WM does not cause bone lesions or hypercalcemia, the size of the IgM paraprotein results in little renal excretion, and only ~20% of patients excrete light chains. Therefore, renal disease is not common.The light chain isotype is kappa in 80% of the cases. Patients present with insidious weakness, fatigue, anorexia, weight loss and recurrent infections, bleeding diasthesis, visual disturbances, and neurologic symptoms such as peripheral neuropathy, dizziness, headache, and transient paresis.[6]

Physical examination reveals adenopathy and hepatosplenomegaly; while ophthalmoscopic examination may reveal vascular segmentation and dilatation of the retinal veins, which is a characteristic sign of hyperviscosity.

Periorbital mass resulting from infiltration into retro-orbital structures and the lacrimal gland have been described, thus it may cause proptosis and occular nerve palsies. Purpura and other hemorrhagic manifestations could be found due to interference of macroglobulin with hemostatic factors as well as platelet function. Patients may have a normocytic, normochromic anemia with rouleaux formation and positive Coombs test. Anemia is caused by plasma hemodilution, decreased life span of erythrocyte, blood loss due to bleeding, and bone marrow failure. Malignant lymphocytes are usually present in the peripheral blood. About 10% of macroglobulins are cryoglobulins. These are pure M components and are not the mixed cryoglobulins seen in rheumatoid arthritis and other autoimmune diseases. Mixed cryoglobulins are composed of IgM or IgA complexed with IgG, for which they are specific. In both cases, Raynaud's phenomenon and serious vascular symptoms precipitated by the cold may occur.[6]

Some of signs and symptoms, but not all, can be found in this patient. General symptoms such as weakness, weight loss, fatigue, and recurrent infections could be caused by anemia, leukopenia and netropenia, or by malignancy itself. Tingling sensation on his right forefoot

could be caused by peripheral neuropathy due to IgM secretion, but it still need to be confirmed by further examination such as ENMG, since his neurological examinations revealed normal results. Melena was suspected due to prolonged results on hemostatic function tests, which were associated with alteration of macroglobulin. Splenomegaly found in this patient is consistent with WM characteristics. Other positive findings were related to sinusitis. Our patient was found accidentally with primary complaints related to sinusitis, as mentioned in literature, that the disease is indolent and sometimes the complaints are found accidentally during medical check up or due to complications.[2,3,6]

According to literatures, no definite etiology has existed for Waldenstrom macroglobulinemia. Environmental (works with pesticides, paint, metal, woods, textile, asbestos, and gasoline industries, radiation), race (Afro-America), gender (male), age (old age), familial, genetic, and viral factors have been reported as some of precipitating factors. IgM Monoclonal Gammopathies of Undetermined Significance (MGUS) are considered the precursors of Waldenstrom macroglobulinemia. Hepatitis C, Hepatitis G, and Human Herpes virus 8 have been implicated, but no strong data has supported a causative link between these viruses and Waldenstrom macroglobulinemia. Our patient is male and at middle age, which has no family history of malignancies and the only possible risk factor was the environmental factor, i.e. pesticides exposure since he works as a farmer.[7,8]

Waldenstrom macroglobulinemia can be identified by the abovementioned signs and symptoms as well as results of several additional examinations such as complete blood count, blood smear, hemostatic function, ESR, IgM monoclonal serum, lymph node histology (if any), and bone marrow examination. Diagnosis Waldenstrom macroglobulinemia is characteritized by (1) serum IgM monoclonal level was more than 15 g/dL; (2) biopsy of bone marrow showed pleomorphic infiltrations by small lymphocytes, plasma cells, plasmacytoid cells, mast cells, and hystiocytes. Trephine biopsy may showed nodular form, which indicates better prognosis compared to diffuse infiltration; (3) increased erythrocyte sedimentation rate; lymphocytosis with some of them were plasmacytoid; and (4) lymph node histology revealed covered sinus architecture with disappeared folicular pattern combined with similar cellular infiltration found in bone marrow.[9]

Splenic Marginal Zone Lymphoma (SMZL) and other lymphoproliferative disordes can be distinguished from WM based on their clinical signs and symptoms, immunophenotypic and molecular cytogenetic.[10,11] Our patient showed vague signs and symptoms and therefore, at first, we suspected that the diagnosis was aplastic anemia. His complete blood count (CBC) revealed pancytopenia with lymphocytosis, which might be related to bone marrow failure due to cell infiltration, inversed ratio of albumin and globulin indicating the predominance of globulin protein, which was related to increasing amount of gammaglobulin in circulation. These findings suggested that the pancytopenia could also be caused by gammopathies, including multiple myeloma, waldenstrom macroglobulinemia, POEM syndrome, heavy-chain disease, amiloidosis, or even- benign monoclonal gammopathy.

Results of protein electrophoresis supported the possibility of gammopathies since it demonstrated monoclonal gammopathy and the results of bone marrow biopsy exactly showed the same histology described for Waldenstrom macroglobulinemia. Furthermore, the diagnosis is highly suspected because the results showed that the IgM monoclonal was IgM monoclonal lambda. However, immunophenotyping/ immunohistochemistry and molecular cytogenetic examination had not been performed in our patient due to lack of BMA samples. The examination was only performed for CD20, which showed negative results; while the immunohistochemistry of serum showed no positive dominant markers. However, the clinical symptoms were quite obvious and we could distinguish between MM and WM since there was no bone or renal involvement in our patient. Moreover, there was also different morphology of cells in bone marrow. Thus, our patient has met the diagnostic criteria for Waldenstrom

macroglobulinemia.[11]

Hyperviscosity syndrome should be suspected only in patients who have a serum viscosity greater than 4. Plasma exchange is an accepted treatment approach for hyperviscosity, but it should be considered as a temporary measure until systemic chemotherapy can be initiated, which can successfully downsize the tumor mass and IgM level. Patients with WM and associated hyperviscosity may need emergency treatment, i.e. paraprotein reduction using plasmapheresis. About 2 to 3 plasma exchanges are required to reduce the IgM levels by 30%-60%. This measure is absolutely necessary, particularly before starting a rituximab-containing regimen because rituximab has been known to cause a flare reaction in patients with WM-associated hyperviscosity.[12,13]

Our patients received supportive treatment to correct anemia, bleeding and sinusitis infection. Plasmapharesis could not be performed due to lack of facilities although the hyperviscosity syndrome was suspected. The patient had headache, which is debatable, but he had prolonged test results on hemostatic function, which is mainly caused by interference related to WM. Moreover, densitometry to confirm the diagnosis also could not be performed due to lack of facilities. Autologous stem cell transplantation is still not available in this hospital. Many factors must be considered when deciding the best treatment approach for the patient, including age, comorbidities, cytopenias, hyperviscosity, neuropathy, and organ dysfunction.

For initial management of asymptomatic or smoldering disease, observation without treatment is recommended. Asymptomatic or smoldering disease is defined as a disorder with hemoglobin level of over 11 g/dL, a platelet count of more than 100 X 109/L and an absence of neuropathy, hyperviscosity or WM-associated hemolytic anemia or constitutional symptoms.[13]

In initial treatment of non-bulky symptomatic disease, single-agent rituximab therapy should be considered. Nonbulky symptomatic disease is characterized by WM-associated neuropathy, anemia or cytopenias, low-volume nodal disease and asymptomatic splenomegaly. Bulky symptomatic disease is characterized by bulky adenopathy, symptomatic splenomegaly, cytopenias, hyperviscosity, neuropathy, or constitutional symptoms, which is considered to be a match for our patient (splenomegaly, cytopenia, hyperviscosity, and neuropathy).[13]

The combination of CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) and rituximab (CHOP-R) has been tested in patients with WM. The response rate in the CHOP-R was 94% compared to 69% in the CHOP.[14]

The role of maintenance therapy in patients with WM/LPL remains controversial, as there are no prospective trials demonstrating any benefit. However, many centers extrapolate the indolent lymphoma data and would consider rituximab maintenance in patients who show response to a rituximab-containing induction regimen. Many of the regimens listed above, which are not used as initial therapy, can be considered as a salvage approach. In addition, many centers recommend retreatment with the initial regimen if there is a durable remission (lasting >2 years) and the treatment was well tolerated. Other salvage approaches include alemtuzumab, bortezomib/rituximab, everolimus, ofatumumab, autologous and allogeneic transplantation.[13]

When considering initial and salvage therapies for patients who may eventually be considered for autologous transplant, exposure to stem cell damaging agents such as alkylating agents and purine analogs should be avoided. Because many of the standard regimens do contain alkylating agents and purine analogs, many centers recommend either collecting stems cells early to be sequestered for a later transplant or not waiting later than the second or third chemosensitive salvage before considering autologous transplantation.[13]

While some allogenic transplantation has demonstrated very durable remissions, transplant-related mortality remains very high. Approaches that use reduced intensity conditioning regimens appear promising, with durable remissions and reduced transplant-related mortality. Allogenic transplantation has demonstrated durable remissions with much lower transplant-related mortality but it should be considered only in younger patients with highly

refractory disease or as part of a clinical trial.[13]

The use of radioimmunotherapy such as iodine 131I-tositumomab radioimmunotherapy in WM has been limited since the high level of bone marrow involvement limits their use. However, case reports have shown that these therapies may be effective in patients with WM who have <25% bone marrow involvement.[14] The development of novel agents (proteosome inhibitor, immunomodulatory agents, monoclonal antibodies and blocking protein, signalling pathways inhibitor) and stem-cell sparing agents has been prioritized in the treatment of WM.[14]

According to this recommendation, CHOP-R is quite a good choice with overall survival rate of 94%. Nevertheless,our patient has health insurance coverage for rituximab treatment, but the coverage can be given only if his CD20 is positive. The negative result of CD20 has prevented our patient to have rituximab treatment. We considered to give 6 series of CHOP regimens with 21 cycles as the treatment that could be fully covered by his insurance with good overall survival rate.

Factors associated with poor prognosis in patients with WM include advanced age, high β2-microglobulin, cytopenias, low albumin, and organomegaly. Age, hemoglobin concentration, serum albumin level, and β2-microglobulin are identified as the predominant outcome predictors. An International Prognostic Scoring System (WM-IPSS) has been presented as a staging system for survival for symptomatic patients who are in need of therapy. The parameters used to stratify the risk were in our patient were age over 65 years, β2-microglobulin level of greater than 3 mg/L, monoclonal protein level of greater than 70 g/L, hemoglobin of less than 11.5 g/dL, and platelet count of less than 100 × 109/L.

Low risk is defined as the presence of fewer than 1 adverse characteristic, except age; while high risk is defined as the presence of more than 2 adverse characteristics; therefore, patients with 2 adverse characteristics or older than 65 years have intermediate risk. Other prognostic markers, which have been considered in current studies are the serum free light chain and serum soluble CD27. Our patient had Hb of less than 11.5 g/dL, but other factors such as β2 microglobulin level and quantitative IgM level were not measured yet due to lack of facilities, thus we could not justify his prognosis.[14]

CONCLUSION

We reported a 44-year-old male with Waldenstrom Macroglobulinemia and bilateral maxillary sinusitis with improved general condition. He has received therapy for sinusitis and chemotherapy with CHOP regimen afterward.

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