Case Report

DOI: 10.6966/EDMJ.202203_9(1).0004

Waldenström's Macroglobulinemia Presenting as Refractory Recurrent Epistaxis with Bilateral Sudden Vision Loss: A Case Report

Hun-Ju Yu[1,†], Liang-Chun Chiu[2,6,†], Yu-Chieh Su[3,6], Chao-Ping Wang[4,7], Tzer-Zen Hwang[5,7], Pang-Yu Lai[3], Chih-Chun Wang[5,6,8,]*

Waldenström's macroglobulinemia is an uncommon lymphoplasmacytic lymphoma with excessive production of immunoglobulin M monoclonal protein. Common symptoms and signs include general weakness, fatigue, anemia, hepatosplenomegaly, lymphadenopathy, or hyperviscosity syndrome (bleeding, vision loss or neurological disturbance). Both epistaxis and acute visual change are common complaints in clinical practice and require meticulous evaluation to confirm the etiology. If blood dyscrasia is the cause, systemic workup is necessary to achieve definite diagnosis and best management. Once Waldenström's macroglobulinemia is impressed, even asymptomatic in the initial stage, it is necessary to start monitoring the lymphoplasmacytic lymphoma cells in the hematopoietic organ and the monoclonal IgM in peripheral blood. With precise evaluation of the genetic status, accurate diagnosis, suitable treatment for symptomatic patients, better outcome or prognosis can be achieved. We herein report a 61-year-old male with Waldenström's macroglobulinemia presenting initially as refractory recurrent epistaxis followed by sudden visual loss due to simultaneous bilateral central venous stasis retinopathy.

Key words: Waldenström's macroglobulinemia, epistaxis, vision loss

Introduction

Waldenström's macroglobulinemia, first described in 1944 by Jan Gösta Waldenström, is a B cell lymphoproliferative malignant disorder characterized by lymphoplasmacytic lymphoma cells infiltrated in bone marrow and IgM monoclonal gammopathy in peripheral blood.[1] The incidence is 0.57 per 100,000 person-years with male preponderance.[2] It is more common in Caucasians, and the incidence is 0.032 per 100,000 person-years in Taiwan.[3] The patient may be asymptomatic but may also present with fatigue, hepatomegaly, splenomegaly, lymphadenopathy, or hyperviscosity syndrome.[2]

Epistaxis, one of the common otolaryn-

From the [1]Department of Ophthalmology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine; [2]Department of Obstetrics and Gynecology, E-Da Dachang Hospital; [3]Division of Hematology-Oncology, Department of Internal Medicine, [4]Division of Cardiology and [5]Department of Otolaryngology, E-Da Hospital; [6]School of Medicine, [7]School of Medicine for International Students and [8]School of Chinese Medicine for Post-Baccalaureate, I-Shou University, Kaohsiung, Taiwan.
(† signifies equal contribution compared to the first author)
Received: September 6, 2020 Accepted: January 20, 2021
* Address reprint request and correspondence to: Chih-Chun Wang, Department of Otolaryngology, E-Da Hospital, No.1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 82445, Taiwan
Tel: +886-7-615-0011 ext. 2973, Fax: +886-7-615-0913, Email: ccw5969@yahoo.com.tw

gology emergencies, can be caused by many possibilities such as idiopathic, trauma, anticoagulation drug, blood dyscrasia, neoplasm, or hypertension.[4] Therefore, it always requires cautious evaluation in order to make correct diagnosis and arrange suitable management. Epistaxis can originate from anterior nasal cavity, such as Kiesselbach's plexus bleeding at nasal septum, which is easily accessible and often requires only conservatively simple local treatment or merely nasal packing. In contrast, posterior nose bleeding which is relatively hard to be accessed may require even surgical intervention such as endoscopic cauterization or vessel ligation.

Vision loss can be due to trauma, acute angle closure glaucoma, vitreous hemorrhage, retinal artery or vein occlusion, retinal detachment, optic neuritis, ischemic optic neuropathy or cerebral vascular accident. Simultaneous bilateral central retinal vein occlusion was rare and highly suggestive of hyperviscosity syndrome.[5] We herein report a 61-year-old male with Waldenström's macroglobulinemia presenting initially as refractory recurrent epistaxis followed by sudden visual loss due to simultaneous bilateral central venous stasis retinopathy

Case Report

A 61-year-old male with diabetes mellitus presented to our emergency department with severe spontaneous epistaxis that could not be managed by simple local treatment by primary care physician. Although active bleeding from bilateral nostrils and bloody sputum were noted, he did not feel dizziness or dyspnea. Sinonasal endoscopic examination showed blood oozing around posterior ends of the inferior and middle turbinate in each nasal cavity (Fig. 1). Blood tests showed normal white blood cell count; however, hemoglobin level was 8.6 g/dL and the platelet count was 139,000/μl. The prothrombin time and activated partial thromboplastin time were normal. Renal and liver functions were also normal. Blood transfusion with packed red blood cells and empirical tranexamic acid were given. After nasal packing stabilizing the epistaxis, the patient was then admitted for further care and then the patient discharge after primary local treatment with stable condition. However, the symptoms persisted and several episodes of mild epistaxis still occurred. One week later, he visited our emergency department again due to sudden onset of severe headache and deterioration of vision in both eyes. Brain magnetic resonance imaging revealed no structural abnormality. The visual acuity decreased to 20/100 OD and 20/200 OS. The intraocular pressure of both eyes was normal. Fundus image revealed multiple retinal hemorrhages, retinal vein sausaging, and optic disc edema of both eyes (Fig. 2). The optical coherence tomography showed macular exudative detachment margined by retinoschisis suspiciously due to the proteinaceous osmotic leakage from the retina and even from the choriocapillris into the subretinal space.

During admission, laboratory tests revealed persistent anemia (hemoglobin level, 8.7 g/dL) and thrombocytopenia (platelet

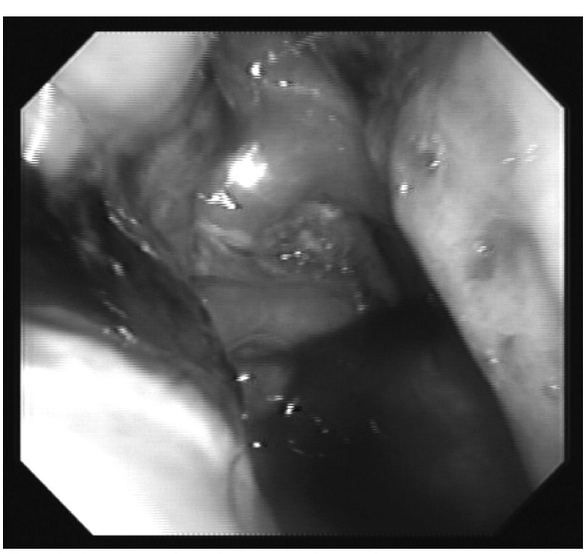

Fig. 1 Sinonasal endoscopy showed no gross tumor but diffuse oozing blood from posterior ends of inferior and middle turbinate.

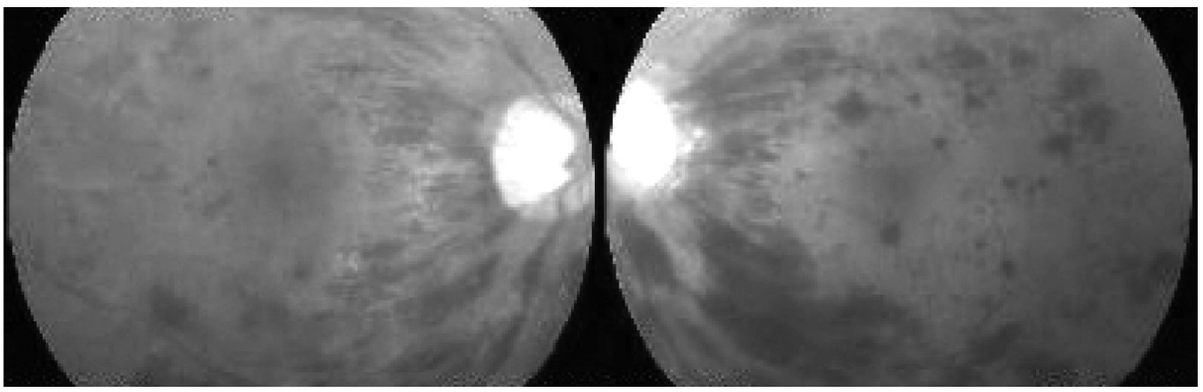

Fig. 2 Fundus photography showed bilateral scattered retinal hemorrhages and sausage-like retinal venous engorgement (dilated and tortuous vein).

count, 58,000/μl). Peripheral blood smear revealed Rouleaux formation and many lymphoplasmacytoid cells were found (Fig. 3). We consulted hematologist and bone marrow study revealed hypercellular bone marrow (cellularity of 95%) with diffuse infiltration of lymphoplasmacytoid cells and immunohistochemistry stain were positive for CD3, CD20, and CD138, but negative for CD19, CD10, CD5, kappa and lambda light chain (Fig. 4). The results suggested of lymphoplasmacytoid malignancy. High level immunoglobulin M (11729.1 mg/dL) as well as low level immunoglobulin G (220.10 mg/dL) and immunoglobulin A (19.8 mg/dL) were found. In addition, high serum viscosity (6.7 centipoise) was also noted. High resolution serum protein electrophoresis revealed the presence of a monoclonal gammopathy ('M'spike) in gamma globulin

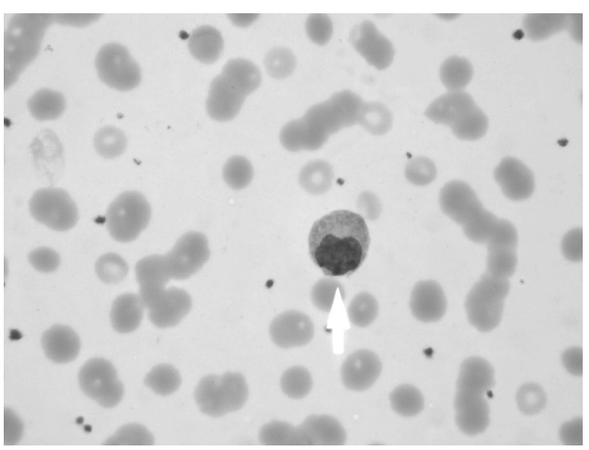

Fig. 3 Peripheral smear of blood showed Rouleaux formation and lymphoplasmacytic cell (arrow) (1000x).

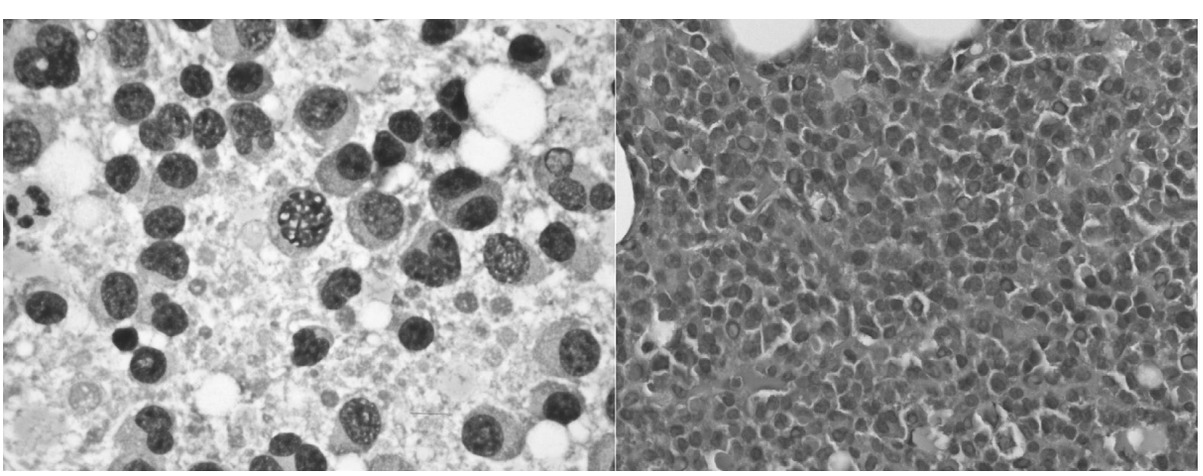

Fig. 4 Bone marrow smear showed largely of lymphoplasmacytic cells that have the nuclear spoke-wheel pattern of a plasma cell but the low cytoplasmic volume that is more characteristic of a small lymphocyte. Bone marrow biopsy revealed a hypercellular bone marrow with diffuse infiltration of little small lymphocytes admixed with predominantly variable numbers of plasma cells and plasmacytoid lymphocytes.

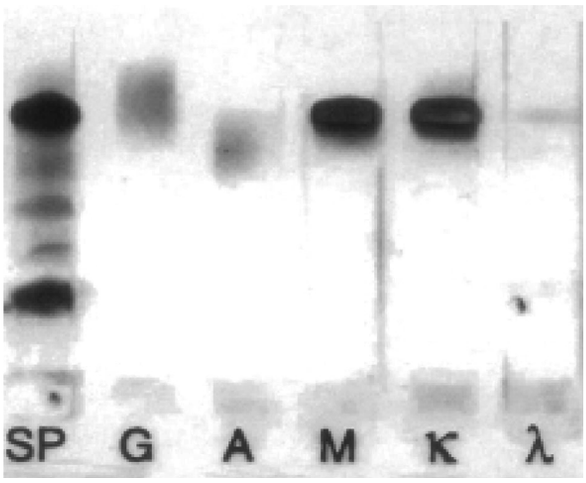

Fig. 5 Immunofixation electrophoresis (IFE) showed the presence of a monoclonal IgM gammopathy ('M' spike) in the serum.

region (Fig. 5). Hepatosplenomegaly with intra-abdominal lymphadenopathy were also noted by CT scan. Waldenström macroglobulinemiawith hyperviscosity syndrome was finally confirmed.

After emergent plasmapheresis for 5 days, his serum viscosity level decreased to 1.52 centipoise and epistaxis dramatically subsided. However, his visual acuity did not improve. He then received chemotherapy, including COP regimen (cyclophosphamide, vincristine, and prednisolone) for two cycles, and following DCEP regimen (dexamethasone, cyclophosphamide, etoposide, and cisplatin). The immunoglobulin M level decreased from 11729.1 mg/dL to 1544.80 mg/dL. After these treatments, the epistaxis resolved gradually. Loss of vision resolved after 2 more courses of chemotherapy. This was followed up with six more courses of inpatient chemotherapy. Patient then received regular follow up at out-patient-department.

Discussion

The pathophysiology of Waldenström's macroglobulinemia is the lymphoplasmacytoid lymphoma cells infiltration of the hematopoietic organ or lymphatic system and the volume effect of excessive monoclonal IgM in peripheral blood.[6] Common symptoms include nonspecific constitutional symptoms (such as fever, night sweats, fatigue, or weight loss), hyperviscosity syndrome (such as bleeding, vision loss or neurological disturbance), or various neurological symptoms (such as paresthesia).[7] Characteristic signs include anemia, eye fundic changes, lymphadenopathy, hepatomegaly, splenomegaly, or cryoglobulinemia.[7] Initially, the disease would be asymptomatic, and at this stage, it should be IgM monoclonal gammopathy of undetermined significance (IgM level < 3 g/dL and bone marrow infiltration < 10%) or smoldering Waldenström macroglobulinemia (M spike > 3 g/dL and bone marrow infiltration > 10%).[2,6,8] Progressively, IgM immunologic effect related disorders (such as cold agglutinin hemolytic, type II cryoglobulin, peripheral neuropathy, amyloidosis) would appeared.[2,6,8] Finally, bone marrow, liver, spleen, and lymph nodal infiltration with lymphoplasmacytoid lymphoma would cause anemia, hyperviscosity, hepatosplenomegaly, and lymphadenopathy.[2,6,8]

Hyperviscosity syndrome was present in about 30% patients with Waldenström macroglobulinemia.[9] The association was first described in 1944 by Jan Gösta Waldenström and would typically occurs when the plasma viscosity > 4 centipoise.[1] It was related to exceeding levels of IgM pentamers causing erythrocyte aggregation. The resistance of blood flow would increase due to elevated osmotic pressure which was caused by increased intravascular concentration of the large monoclonal IgM binding water.[10] Due to shear force disrupting venous channels, the patient would present with spontaneous bleeding from nasal cavity, gingival mucosa, or retina.[2] Because of the interaction with coagulation factors and platelets, the clotting function would be impaired and the bleeding time wound be prolonged. This insufficient microcirculation would lead to further visual disturbance or other neurological disturbance.[2] Clinically,

presence of the triad of mucosal bleeding, visual disturbances, and neurological deficits would suggest hyperviscosity syndrome.[11]

Waldenstrom macroglobulinaemia is an indolent cancer. The median survival is approximately 6 years, and the disease-specific survival is more then 10 years (median: 11 years).[12] For those patients with asymptomatic IgM monoclonal gammopathy of undetermined significance or smoldering Waldenström macroglobulinemia, observation and monitoring are required.[2,8] Progressively, while it is symptomatic due to IgM protein immunologic effect, starting treatment with rituximab is justified.[2,8] Finally, while bone marrow, liver, spleen, and lymph nodal extensive infiltration with lymphoplasmacytoid lymphoma, multi-agent chemotherapy including rituximab (monoclonal anti-CD20 antibody) would be better than rituximab monotherapy.[2,8] Cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (R-CHOP) treatment would achieve 90% response rate.[13] As for hyperviscosity syndrome, the initial treatment of choice for is plasmapheresis and following systemic chemotherapy to reduce tumor mass is necessary. Tranexamic acid, an antifibrinolytic drug, which is commonly used in various bleeding conditions to promote hemostasis, is clearly not suitable for hyperviscosity syndrome due to active intravascular clotting. Red blood cell transfusion is not suggested to be prior to plasmapheresis because it would aggravate viscosity level.[14] For patients with relapsed disease, autologous stem cell transplantation may be the salvage treatment option and the overall survival rate was about 50% at 5 years.[15] Older patients (age > 65 years) or elevated β2-microglobulin level (> 3 mg/L) was associated with poor prognosis.[2]

The patient did not receive further genetic study due to insufficient pathological specimen and lack of facilities. However, genetic status plays an important role in diagnosis, clinical presentation, treatment response and outcome. According to whole-genome sequencing study, about 90% of patients would have MYD88 L265P somatic mutation.[16] This phenomenon helps in differentiating Waldenström's macroglobulinemia from other B-cell malignancies. In addition, MYD88 L265P somatic mutation is associated with better survival while CXCR4 nonsense mutation is associated with the clinically severe symptoms including hyperviscosity syndrome. Furthermore, ibrutinib, an inhibitor of Bruton's tyrosine kinase, would give better response on the patients with MYD88 L265P somatic mutation and wild-type CXCR4.[17]

Conclusion

Either epistaxis or vision loss is a common complaint seen in primary care or emergent department setting. Although the ordinary etiology is usually confined to the ENT or ophthalmological systems, systemic hematological disorders could also be the underlying causes if the patient suffered recurrent epistaxis. Complete blood count and biochemical survey should be considered if we encountered a patient with intractable epistaxis.

References

1. Waldenström J: Incipient myelomatosis or "essential" hyperglobulinemia with fibrinognenopenia—a new syndrome? Acta Med Scand 1944;117:216-247. doi: 10.1111/j.0954-6820.1944.tb03955.x.
2. Gertz MA: Waldenström macroglobulinemia: 2019 update on diagnosis, risk stratification, and management. Am J Hematol 2019;94:266-76. doi: 10.1002/ajh.25292.
3. Iwanaga M, Chiang CJ, Soda M, et al: Incidence of lymphoplasmacytic lymphoma/Waldenström's macroglobulinaemia in Japan and Taiwan population-based cancer registries, 1996-2003. Int J Cancer 2014;134:174-80. doi: 10.1002/ijc.28343.
4. Kotecha B, Fowler S, Harkness P, et al: Management of epistaxis: a national survey. Ann R Coll Surg Engl 1996;78:444-446.
5. Aderman CM, Schwartz DM: Acute Bilateral Vision Loss. JAMA Ophthalmol 2016;134:235-6. doi: 10.1001/jamaophthalmol.2015.3572.

6. Owen RG, Treon SP, Al-Katib A, et al: Clinicopathological definition of Waldenström's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström's Macroglobulinemia. Semin Oncol 2003;30:110-5 doi: 10.1053/sonc.2003.50082.
7. García-Sanz R, Montoto S, Torrequebrada A, et al: Waldenström macroglobulinaemia: presenting features and outcome in a series with 217 cases. Br J Haematol 2001;115:575-82. doi: 10.1046/j.1365-2141.2001.03144.x.
8. Gertz MA: Waldenström macroglobulinemia treatment algorithm 2018. Blood Cancer J 2018;8:40. doi: 10.1038/s41408-018-0076-5. Erratum in: Blood Cancer J 2019;9:53.
9. Mehta J, Singhal S: Hyperviscosity syndrome in plasma cell dyscrasias. Semin Thromb Hemost 2003;29:467-71. doi: 10.1055/s-2003-44554.
10. Dimopoulos MA, Kyle RA, Anagnostopoulos A, et al: Diagnosis and management of Waldenström's macroglobulinemia. J Clin Oncol 2005;23:1564-77. doi: 10.1200/JCO.2005.03.144.
11. Fahey JL, Barth WF, Solomon A: Serum hyperviscosity syndrome. JAMA 1965;192:464-67. doi: 10.1001/jama.1965.03080190030008.
12. Ghobrial IM, Fonseca R, Gertz MA, et al: Prognostic model for disease-specific and overall mortality in newly diagnosed symptomatic patients with Waldenstrom macroglobulinaemia. Br J Haematol 2006;133:158-64. doi: 10.1111/j.1365-2141.2006.06003.x.
13. Buske C, Hoster E, Dreyling M, et al: The addition of rituximab to front-line therapy with CHOP (R-CHOP) results in a higher response rate and longer time to treatment failure in patients with lymphoplasmacytic lymphoma: results of a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG). Leukemia 2009;23:153-61 doi: 10.1038/leu.2008.261.
14. Treon SP: How I treat Waldenström macroglobulinemia. Blood 2015;126:721-32. doi: 10.1182/blood-2015-01-553974.
15. Cornell RF, Bachanova V, D'Souza A, et al: Allogeneic transplantation for relapsed Waldenström macroglobulinemia and lymphoplasmacytic lymphoma. Biol Blood Marrow Transplant 2017;23:60-6. doi: 10.1016/j.bbmt.2016.10.010.
16. Hunter ZR, Xu L, Yang G, et al: The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood 2014;123:1637-46. doi: 10.1182/blood-2013-09-525808.
17. Treon SP, Tripsas CK, Meid K, et al: Ibrutinib in previously treated Waldenström's macroglobulinemia. N Engl J Med 2015;372:1430-40. doi: 10.1056/NEJMoa1501548.