中華民國血液病學會
The Hematology Society of Taiwan

Waldenström's Macroglobulinemia e-Casebook

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目錄

Prologue

Waldenström's macroglobulinemia (WM), a slow-growing type of non-Hodgkin lymphoma, is an uncommon blood cell cancer that originates from malignant B-cells. WM mostly forms in the bone marrow and can slow normal blood cell growth, which can lead to anemia and a weakened immune system. The disease occurs because of an abnormality in B lymphocytes in the bone marrow, causing them to produce too much immunoglobulin M protein that thickens the blood. Moreover, more than 90% of WM patients have a myeloid differentiation primary response 88 (*MYD88*) mutation.

At present, most of the diagnostic methods for WM in Taiwan involve the aspiration or sectioning of bone marrow for immunohistochemistry, and the use of flow cytometry for immunophenotyping. Hematologists in Taiwan currently face the challenge of limited accessibility to the *MYD88*^{L265P} test because it is not available for routine clinical use. However, we discuss the methods of detection of *MYD88* mutations in WM using the allele-specific-polymerase chain reaction method in the following chapter.

Although WM shares similarities with multiple myeloma and indolent lymphoma, it is a form of lymphoplasmacytic lymphoma, a low-grade (or indolent) type of lymphoma. Not every patient with WM needs to be treated; some patients benefit from a "watchful waiting" approach. While WM is incurable and will return despite treatment, many people are able to lead active lives and may experience years of symptom-free remission after treatment.

The current therapeutic approach in WM is being driven by insights into the disease biology and the genomic landscape. Specifically, Bruton's tyrosine kinase (BTK) is now known to play a key role in signaling pathways for survival of the WM clone, and inhibiting this enzyme has changed the treatment landscape of the disease.

Hence, a WM Casebook has been created by the Hematology Society of Taiwan Lymphoma working group to provide an easily accessible, quick reference tool for junior hematologists to learn about WM. The Casebook contains insightful case-based discussions that enhance and summarize the key aspects of this disease. The cases demonstrate the unique presentations, histories, and clinical courses of WM, with expert insights regarding the management of this disease in real-life settings. Each case includes key points and a summary to update clinicians about various

issues concerning the management of different aspects of WM. In addition to outlining current knowledge, each case also identifies opportunities for future research in the field.

We hope that this book, and the many outstanding, informative cases penned by experts in the field, will serve as a platform for learning and contribute to the growing interest in this rare disease.

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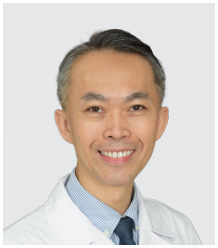

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Global Trends in the Diagnosis and Management of Waldenström's Macroglobulinemia and Current Clinical Landscape in Taiwan

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The current diagnostic criteria for asymptomatic Waldenström's macroglobulinemia (WM) include an immunoglobulin M (IgM) concentration of above 30 g/L and infiltration of the bone marrow by lymphoplasmacytic cells. Moreover, more than 90% of the patients have myeloid differentiation primary response 88 (*MYD88*) mutation. The common indications for treatment include IgM concentration of above 60 g/L or symptomatic hyperviscosity, low levels of hemoglobin (Hb), neutrophil, or platelet, and symptomatic organ enlargement[1].

At present, most of the diagnostic methods for WM in Taiwan involve the aspiration or sectioning of bone marrow for immunohistochemistry (IHC) and the use of flow cytometry for immunophenotyping. Hematologists in Taiwan currently face the challenge of limited accessibility to the *MYD88* L265P test, which is not available for routine clinical use. This test can only be conducted in specific laboratory settings overseen by a few professors, making it impractical for widespread clinical application. The same limitation also applies to the test for C-X-C chemokine receptor type 4 (*CXCR4*) mutation. Only a few institutes in Taiwan perform the cryocrit and antibody tests recommended by the National Comprehensive Cancer Network (NCCN), and not all clinicians implement the assessment of risk scores for asymptomatic WM in their evaluation. For instance, the most common indications for which WM therapy is initiated by the physicians of National Taiwan University Hospital include hyperviscosity, neuropathy, and cytopenia.

The most commonly used first-line chemotherapies for WM are dexamethasone + rituximab + cyclophosphamide (DRC) and bendamustine + rituximab (BR). Patients treated with DRC had a median progression-free survival (PFS) period of 35 months[2], whereas those treated with BR had a median PFS period of 69.5 months and did not require maintenance therapy after the completion of BR regimen[3].

Bruton’ s tyrosine kinase (BTK) inhibitors play a role in the treatment of WM. Ibrutinib, a first-generation BTK inhibitor, was used as a monotherapy in phase II clinical trials of patients with relapsed/refractory (r/r) WM who had been treated with more than one line of therapy. The results demonstrated that ibrutinib significantly reduced serum IgM level and increased Hb level[4,5], and the five-year PFS and overall survival (OS) rates of the patients were 54% and 87%, respectively. However, the survival of the patients depended on their genetics. Patients with only *MYD88* mutation had the highest survival rate, whereas those with both *MYD88* and *CXCR4* mutations had a moderate survival rate, and those without *MYD88* and *CXCR4* mutations had the lowest survival rate (Figure 1)[5].

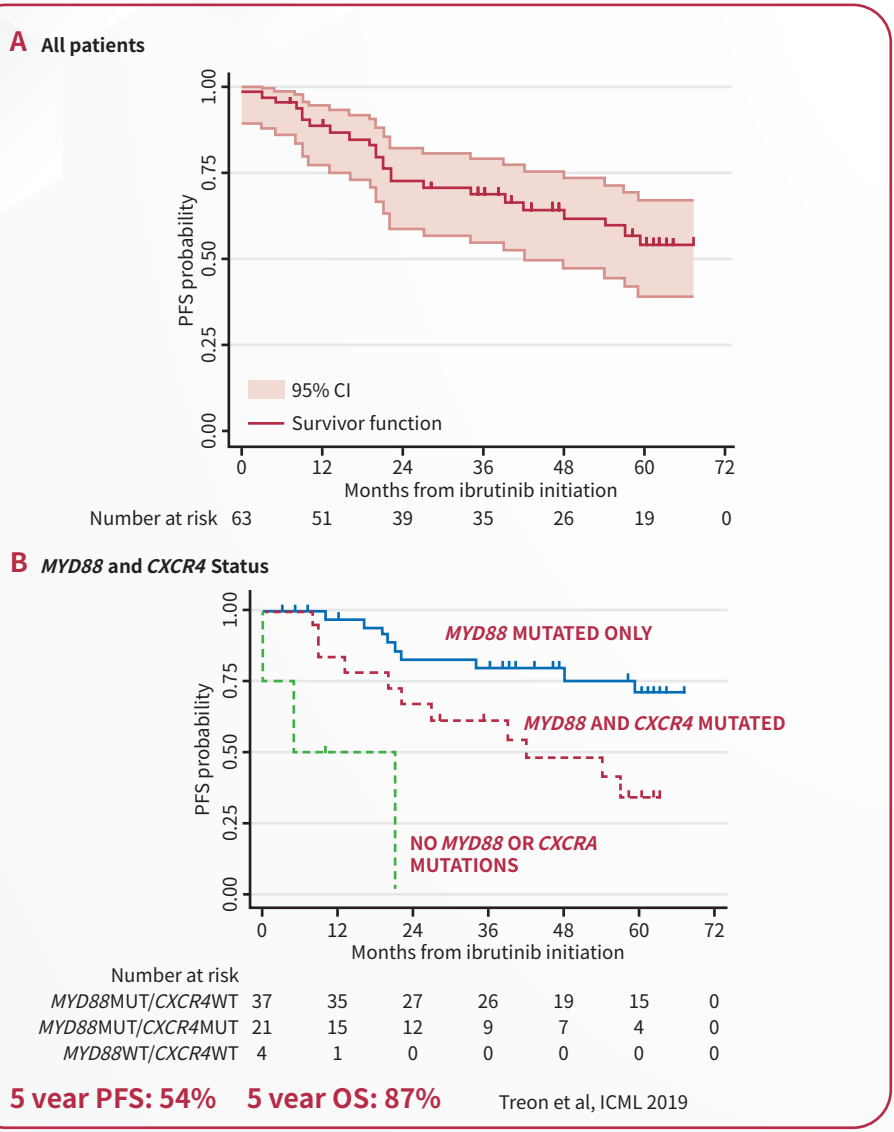


Figure 1. PFS/OS results of the phase II clinical trials examining ibrutinib as a monotherapy in the treatment of WM

In the pursuit of better results, another BTK inhibitor, zanubrutinib (BGB-3111), was developed. Zanubrutinib exhibits a similar inhibitory potency against BTK as ibrutinib but is more selective compared to other types of receptors or kinases (Table 1). As a result, this treatment approach is less likely to impact non-target cells and minimize the occurrence of side effects. The human body exhibits relatively inefficient absorption of ibrutinib, even with a full dose of 560 mg, which fails to achieve high drug plasma concentrations. In contrast, a dose of 80 mg of zanubrutinib can achieve a similar plasma concentration as that of ibrutinib, and a dose of 320 mg of zanubrutinib can achieve a plasma concentration 10 times the maximum concentration of ibrutinib (Figure 2)[7,8].

Equipotent against BTK compared to ibrutinib Higher selectivity vs EGFR, ITK, JAK3, HER2 and TEC				
Targets	Assays	Ibrutinib IC_{50}(nM)	BGB-3111 IC_{50} (nM)	Ratio (BGB-3111:Ibrutinib)
BTK	BTK-pY223 Cellular Assay	3.5	1.8	0.5
	Rec-1 Proliferation	0.34	0.36	1.1
	BTK Occupation Cellular Assay	2.3	2.2	1.0
	BTK Biochemical Assay	0.20	0.22	1.1
EGFR	p-EGFR HTRF Cellular Assay	101	606	6.0
	A431 Proliferation	323	3,210	9.9
ITK	IT Occupancy Cellular Assay	189	3,265	17
	p-PLC_{y1} Cellular Assay	77	3.433	45
	IL-2 Production Cellular Assay	260	2.536	9.8
	ITK Biochemical Assay	0.9	30	33
JAK3	JAK3 Biochemical Assay	3.9	200	51
HERZ	HER2 Biochemical Assay	9.4	661	70
TEC	TEC Biochemical Assay	0.8	1.9	2,4

Table 1. Comparison of inhibitory potency against the targets between ibrutinib and zanubrutinib (BGB-3111)

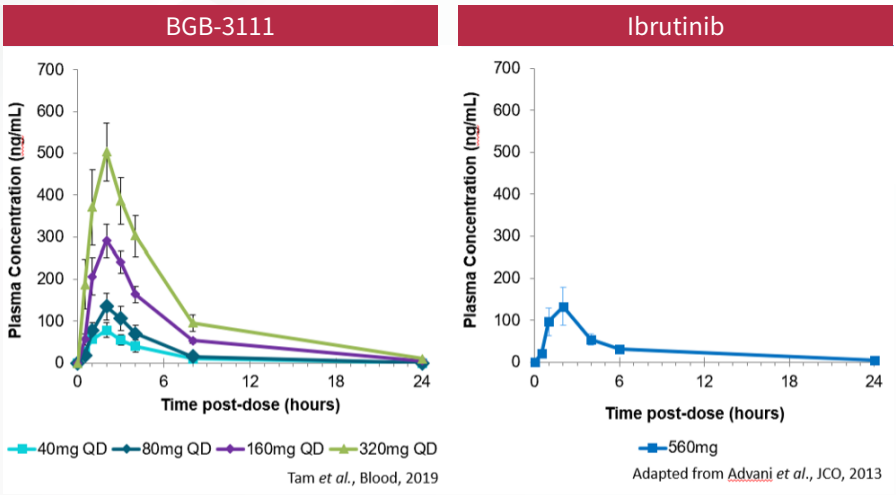
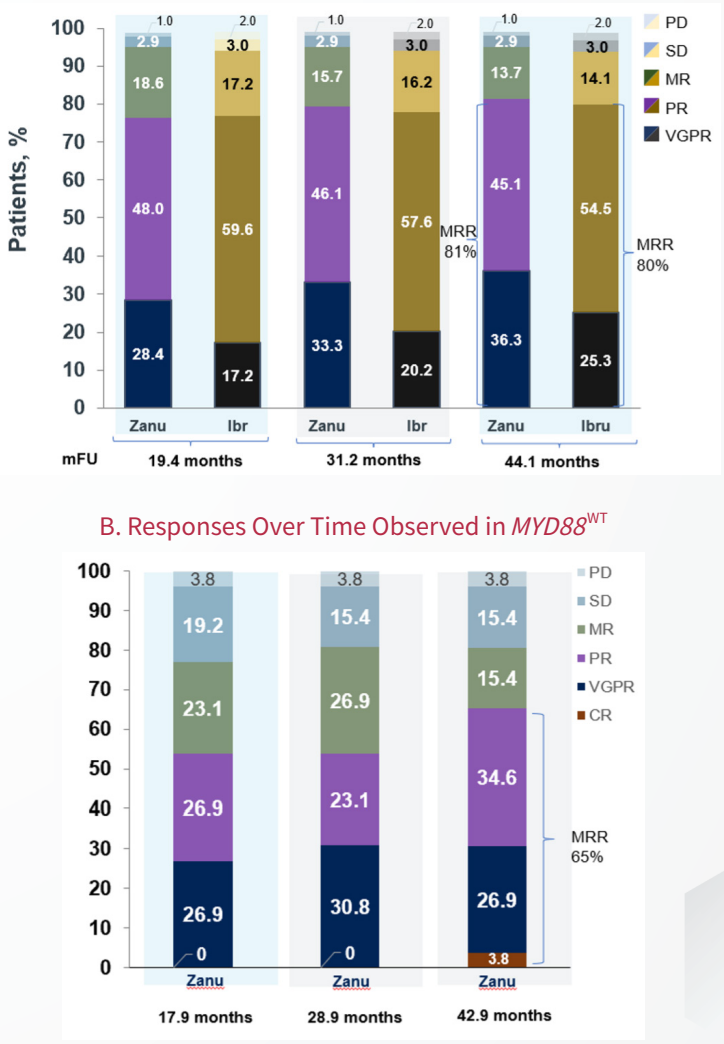


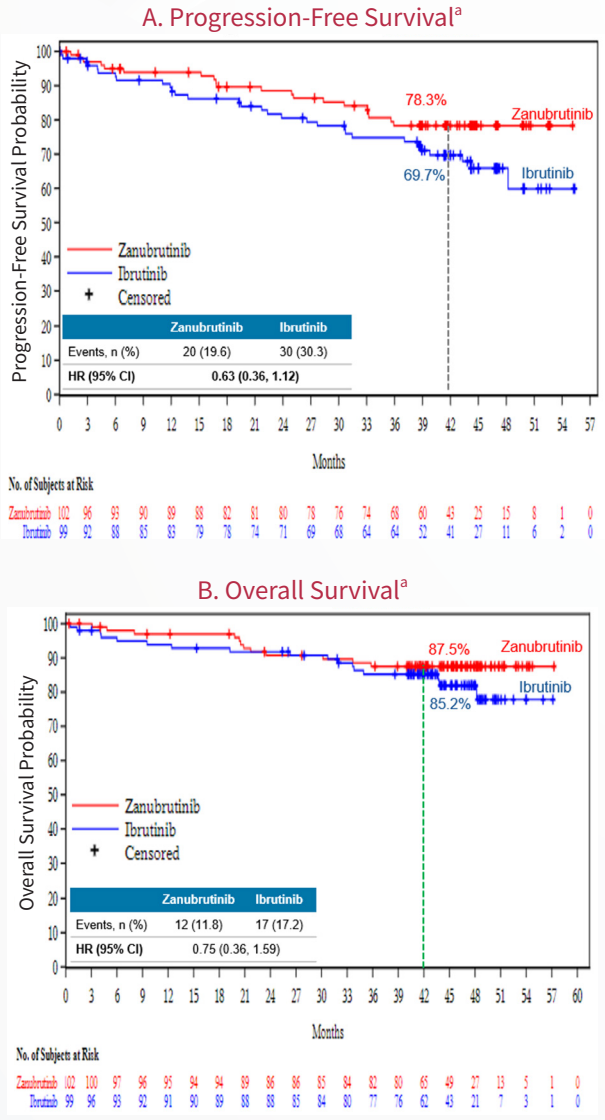
Figure 2. Comparison of plasma concentrations between ibrutinib and zanubrutinib (BGB-3111)

ASPEN study was conducted to directly compare the therapeutic effects of zanubrutinib and ibrutinib on WM. The patients with mutated *MYD88* were first differentiated from the patients with wild-type *MYD88*, divided into two groups with a ratio of 1:1, and treated with the two aforementioned experimental drugs, respectively. All the patients with wild-type *MYD88* were treated with zanubrutinib for ethical reasons[9]. Up to early 2022, the preliminary results showed that a higher proportion of the patients with mutated *MYD88* achieved a very good partial response (VGPR) in zanubrutinib group than in ibrutinib group. A significant proportion of patients with wild-type *MYD88* who did not respond to ibrutinib developed a response to zanubrutinib (Figure 3)[10], and zanubrutinib group appeared to have better performance in terms of PFS and OS outcomes. However, the results were not statistically significant due to the limited duration of observation (Figure 4)[10].



Data cutoff: October 31. 2021
CR. complete response: Ibr, ibrutinib; mFU, median follow-up; MR, major response: MRR, major response rate: PD, progressive disease: PR, partial response: SD, stable disease: VGPR, very good partial response ; Zanu, zanubrutinib.

Figure 3. Preliminary treatment response results of ASPEN study



Data cutoff: October 31 2021
[a]Bv investigator assessment.
CI. confidence interval: HR, hazard ratio: ITT, intent to treat; OS, overall survival; PFS, progression-free survival.

Figure 4. Preliminary survival results of ASPEN study

In the ASPEN study, the incidence rates of atrial fibrillation/flutter (Af/AF), diarrhea, and bleeding were significantly lower in the zanubrutinib group than in the ibrutinib group, and the risk for infection was similar in both groups; zanubrutinib group had a higher incidence rate of neutropenia. In summary, chemotherapy can be used as the first-line treatment for WM, and the most common treatment regimens include DRC and BR, which are selected according to the conditions of the patients. Moreover, BTK inhibitors can be used as the first-line treatment for WM. A direct comparison of the clinical trial results of zanubrutinib and ibrutinib has revealed that the former is less toxic and hence, is the preferred choice for treatment.

In Taiwan, the treatment options for WM are plasmapheresis for improving hyperviscosity, steroids (prednisolone is being used most commonly) and chemotherapeutic agents, which include alkylating agents (such as chlorambucil and drugs that have recently been included in the National Health Insurance, namely cyclophosphamide and bendamustine), anthracycline (only doxorubicin is being used), drugs targeting the central nervous system (CNS) (methotrexate [MTX] and cytarabine), and less commonly used targeted drugs (rituximab, bortezomib, ibrutinib, and zanubrutinib).

Owing to the lack of complete epidemiologic data on WM in Taiwan, the statistics from the National Taiwan University Hospital were used as the reference data. From 2011 to 2020, 55 patients were newly diagnosed with WM at National Taiwan University Hospital, of which 33 were male and 22 were female, with a median age of 65 years. It was difficult to assess PFS since clinical follow-ups and examinations were not performed regularly, and hence, only OS could be used as an indicator. The retrospective statistics showed that the 5-year OS rate was 60.6% and the 10-year OS rate was 49.5%.Hence, a longer observation period may be required to observe a significant difference. Finally, we found that 20% of the patients with WM died of causes other than the disease. Therefore, we aim to further examine the correlation between WM and other co-morbidities, for instance, whether WM is associated with cardiovascular or kidney diseases.

References

01. Talaulikar D et al., Intern Med J. 2017;47(1):35-49.
02. Dimopoulos MA et al., J Clin Oncol. 2007;25(22):3344-9.
03. Rummel et al., ASH 2019. Oral Presentation.
04. Treon SP et al., N Engl J Med. 2015;372(15):1430-40.
05. Treon SP et al., ICML 2019.
06. Buske C et al., ASH 2020.
07. Advani RH et al., J Clin Oncol. 2013;31(1):88-94.
08. Tam CS et al., Blood. 2019;134(11):851-9.
09. Dimopoulos MA et al., Blood. 2014;124(9):1404-11.
10. Tam CS. ASCO 2022.

MYD88 mutations and their detection using the AS-PCR method in Waldenström's macroglobulinemia

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The myeloid differentiation primary response 88 (*MYD88*) gene encodes a cytosolic adaptor protein that plays a vital role in the innate and adaptive immune responses mediated by the interleukin (IL) 1 receptor family and toll-like receptors.[1] In addition to its physiological role in the immune response, *MYD88* can function as an oncogene associated with lymphoma development and somatic mutations have been identified in numerous cases. The most common single nucleotide substitution mutation involves a change from T to C, resulting in an amino acid substitution from leucine to proline at position 265 (L265P).[2] Whole - genome sequencing has identified *MYD88*^{L265P} mutations in up to 90% of the patients with Waldenström's macroglobulinemia (WM).[3]

The L265P mutation makes the toll/IL-1 receptor domain of the mutated *MYD88* protein more active than the wild-type *MYD88* protein, which increases the formation of the "Myddosome" complex and downstream signaling.[4-5] Thus, the functional effects of *MYD88*^{L265P} include increased NF-κB activity, Janus kinase/signal transducer and activator of transcription signaling, and the production of proinflammatory cytokines, such as IL-6, IL-10, and interferon β, apart from the enhanced growth and survival of lymphoma cells.[4,6]

Only a small number of patients with WM (7%) lack *MYD88* mutations. These patients present a different genomic landscape, including other NF-κB-activating mutations, epigenomic dysregulation, and impaired DNA damage repair mechanisms, leading to inferior outcomes compared to those with *MYD88* mutations, especially with a shorter overall survival and higher risk of histological transformation.[7-10] These findings prompted us to consider the disease with the wild-type *MYD88* (*MYD88*$^{wild\text{-}type}$) genotype to be an entirely separate entity, and the presence of the *MYD88* mutation as a WM-defining feature.

Owing to the discovery of *MYD88* mutations in WM, Bruton tyrosine kinase (BTK) inhibitors have emerged as an important treatment option. Much of their efficacy is owing to the presence of this alteration, which has been shown to serve as a predictor of the response in patients treated with a BTK inhibitor-based regimen. The major response rate of WM to ibrutinib therapy was found to be substantially higher for *MYD88*^{L265P}-*CXCR4*$^{wild\text{-}type}$ (97%) and *MYD88*^{L265P}-CXCR4WHIM (68%), compared to that in patients with the *MYD88*$^{wild\text{-}type}$ genotype (0%).[10-11] Zanubrutinib, a second-generation BTK inhibitor, has demonstrated high-efficacy responses in patients with *MYD88*$^{wild\text{-}type}$ WM, including 27% of the excellent partial responses and 50% of the major responses.[12] The overall response rate was similar regardless of the genotype. However, the proportions of excellent partial response

and complete response were still different, as they were higher for patients with *MYD88*^{L265P}-*CXCR4*^{WHIM} (59%) compared to those with *MYD88*$^{wild\text{-}type}$ (25%) [13].

Allele - specific PCR (AS - PCR) - based methods are often used to detect single nucleotide polymorphisms (SNPs), because they offer the advantages of speed, simplicity, reliability, and sensitivity (Figure 1). AS - PCR - based methods for detecting *MYD88*^{L265P} using unsorted or CD19+ selected bone marrow samples showed that mutation prevalence varied from 86% to 93%, respectively, in WM.[14,15] At our institution, Tri-Service General Hospital,seventeen patients with suspected WM were tested for MYD88^{L265P} mutation,seven of whom were positive for *MYD88* gene mutations (41%) ,as shown in Table 1 and Figure 2. A novel, highly sensitive, and rapid detection method based on the quenching probe technique and AS-PCR has been reported by Nogami S and colleagues.[16]

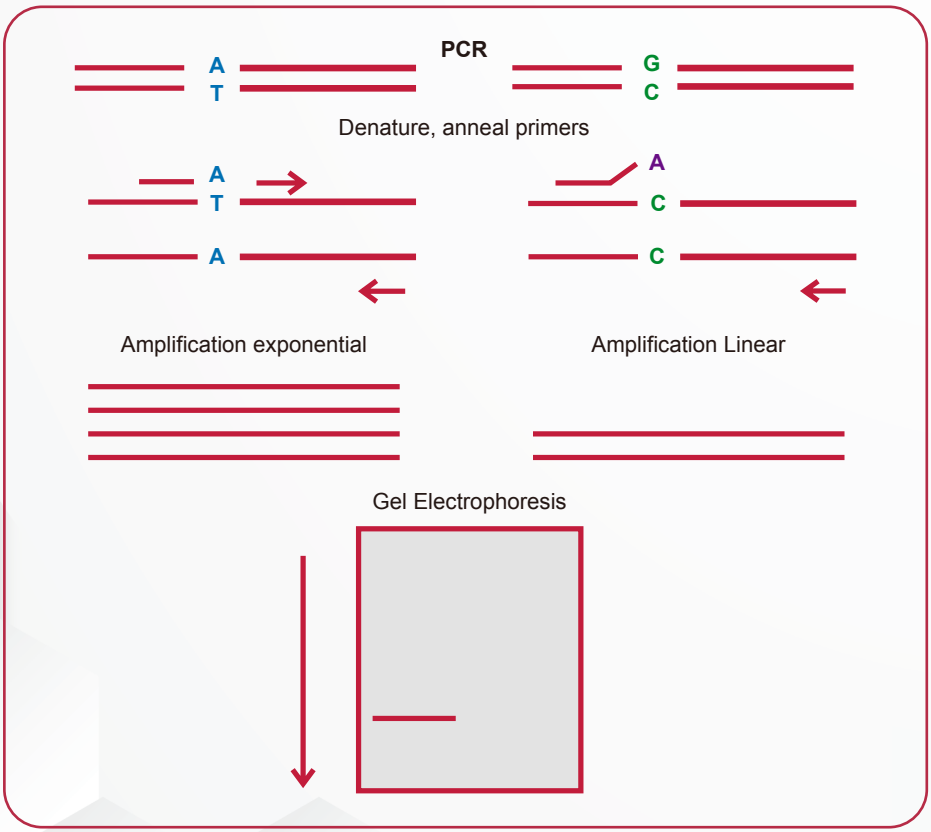

Figure 1. Allele - specific polymerase chain reaction (AS - PCR) - based methods

AS-PCR	Forward (mutant)	5'-gigcccatcagaagcgccc-3'
	Forward (wild-type)	5'-gigcccatcagaagcgect-3'
	Reverce	5'-gacgtgtcigtgaagttggcatctc-3'

Table 1. Sequences of the primers and probe design to detect *MYD88* mutation

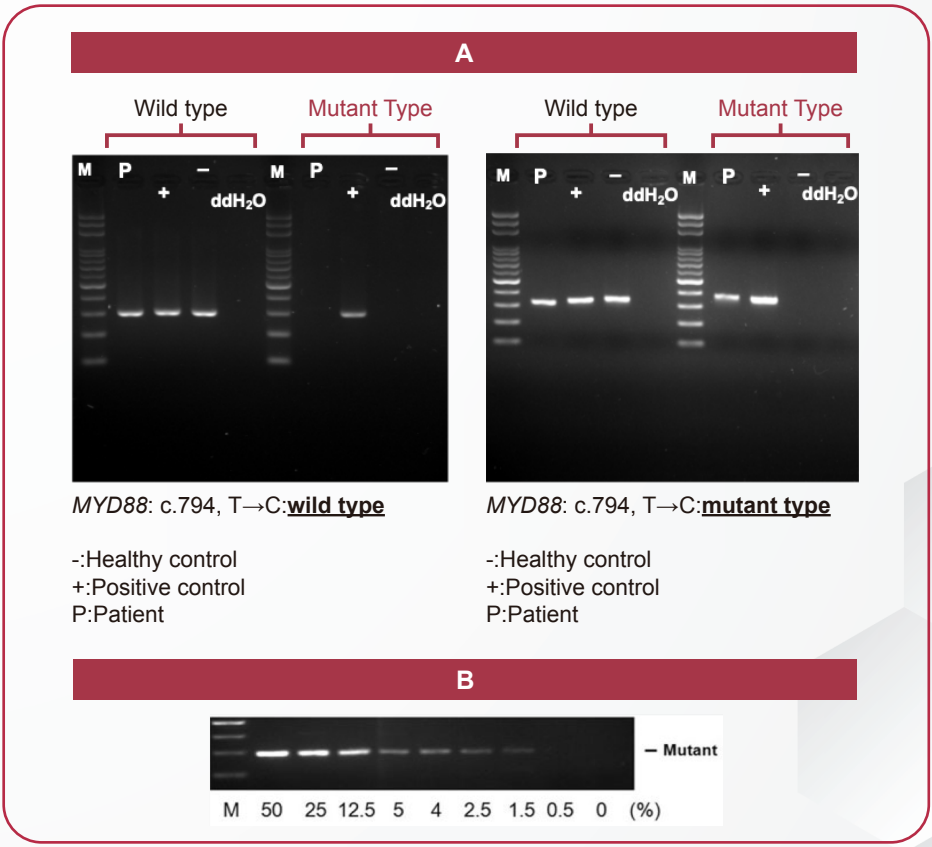

Figure 2. Agarose gel-based conventional AS-PCR assay for detection of *MYD88*^{L265P}. (A) Left side is a *MYD88*$^{wild\text{-}type}$ patient whose result show only band in wild type. Right side is a heterozygous *MYD88*^{L256P} patient whose result show band in both wild type and mutant. (B) Sensitivity of the conventional AS-PCR assay was established by serial dilutions of DNA.

The National Comprehensive Cancer Network Guidelines for WM include *MYD88*^{L265P} testing of the bone marrow and a genomic-based treatment approach to symptomatic treatment-naïve and relapsed or refractory WM.[16] Concordantly, the last international workshop on a WM consensus panel did not recommend the use of ibrutinib monotherapy in patients with *MYD88*$^{wild\text{-}type}$.[17] While the absence of *MYD88* mutations in patients with WM has been associated with a higher risk of transformation into aggressive lymphomas, resistance to certain therapies and shorter overall survival, the results of the ASPEN study demonstrated that zanubrutinib monotherapy can induce high quality responses in this population.[18] In light of this, the Chinese experts consensus on BTKi recommended zanubrutinib as one of the treatment options for patients with *MYD88*$^{wild\text{-}type}$.[19]

References

01. Medzhitov R et al., Mol. Cell. 1998;2:253–8.
02. Varettoni M et al., Blood. 2013;88:2522–8.
03. Treon SP et al., N. Engl. J. Med. 2012;367:826–33.
04. Ngo VN et al., Nature. 2011;470:115–9.
05. Rousseau S et al., Front. Cell. Dev. Biol. 2016;4:50.
06. Yang G et al., Blood. 2013;122:1222–32.
07. Treon SP et al., Blood. 2014;123:2791–6.
08. Treon SP et al., Br. J. Haematol. 2018;180:374–80.
09. Zanwar S et al., Am. J. Hematol. 2020;95:274–281.
10. Hunter Z.R et al., Blood. Adv. 2018;2:2937–46.
11. Treon SP et al., N. Engl. J. Med. 2015;373:584–6.
12. Dimopoulos MA et al., Blood. Adv. 2020;4:6009–18.
13. Trotman J et al., Blood. 2020;136:2027–37.
14. Xu L et al., Blood. 2013;121:2051–8.
15. Jiménez C et al., Leukemia. 2013;27:1722–8.
16. Treon SP et al., J. Clin. Oncol. 2020;38:1198–208.
17. Castillo JJ et al., Lancet. Haematol. 2020;7:e827–e837.
18. Tam CS et al., Blood. 2020;136(18):2038-50.
19. Song Y et al., Experimental Hematology & Oncology. 2023;12:92.

Waldenström's Macroglobulinemia - a Patient with Conscious Disturbance

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Clinical pearls

- According to a report of Mayo Clinic, it is uncommon for hyperviscosity to occur with levels of the monoclonal immunoglobulin below 4000 mg/dL.
- Hyperviscosity may be associated with thrombosis, hemorrhage, visual disturbance, neurologic and cardiac symptoms.
- Appropriate treatment for underlying disease resulting in hyperviscosity is important, and plasma exchange may be required and effective if significant or emergent symptoms occur.

Patient profile

Case presentation

- The patient was a 75-year-old male, who had history of gastrointestinal bleeding related to gastric ulcer ten years ago. Laboratory data obtained at that time at Chang Gung Memorial Hospital revealed mild anemia (hemoglobin [Hb] 7.4 g/dL), normal white blood cell (WBC) count (5800/uL) and mild thrombocytopenia (platelet count $13.3*10^9$/L), but no further evaluation for the thrombocytopenia had been done.
- The patient was found loss of consciousness on the road and admitted to the emergency department at a local hospital. Brain computed tomography (CT) reported no specific finding, but significant anemia (Hb 5.7 g/dL) and marked splenomegaly were found.
- On arrival to the emergency department, the patient's coma scale was E3V4M5, with ability to speak his name but disoriented. After blood transfusion and intravenous fluid resuscitation, he became fully awake.
- The patient experienced general malaise for a few months and weight loss within three months before this episode; dizziness on a chronic basis with no vertigo and blurred vision for several years presumed to result from cataract.
- Although no definite diagnosis was made, steroids were given at that time.
- The patient was then transferred to Chang Gung Memorial Hospital for further evaluation and treatment. Combining results of peripheral blood (PB) smear, bone marrow biopsy and serum immunofixation electrophoresis, hyperviscosity syndrome due to IgM monoclonal gammopathy was suspected; however, the serum viscosity result was unavailable at that time.

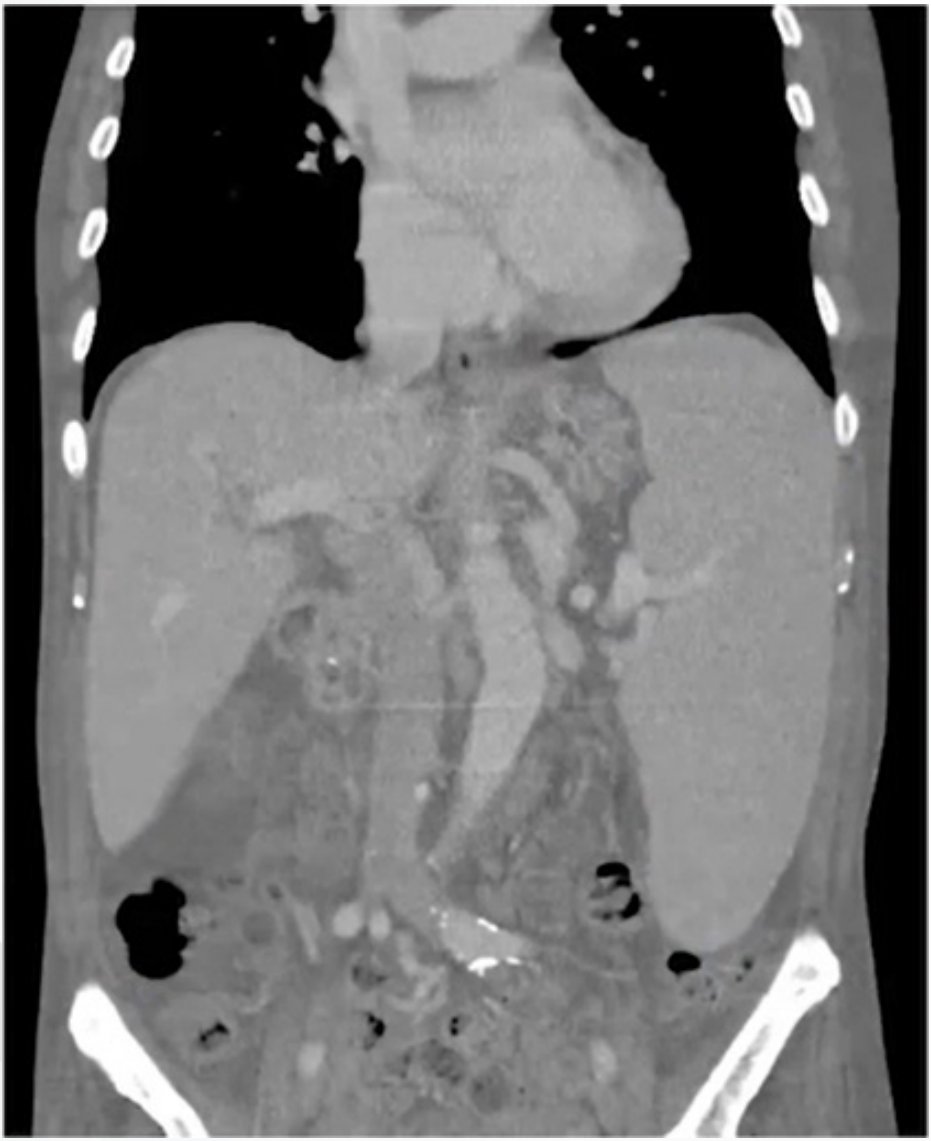
Non-hematological medical history

- Hypertension, under good control.

Laboratory findings

- Laboratory data obtained on the first day of patient's admission to Chang Gung Memorial Hospital showed:
  - Hb 9 g/dL, mean cell volume (MCV) 99 fL, platelet count 9.8*10^3/μL.
  - Creatinine 0.8 mg/dL.
  - Normal Ca, Na, K levels.
  - Normal C-reactive protein (CRP) level.
- Laboratory data obtained while the patient's conscious disturbance episode during admission showed:
  - Arterial blood gas: pH 7.44, CO_2 22.1 mmHg, O_2 66 mmHg, HCO_3 19.5 mmol/L, saturation 95% (FiO_2 32%)
  - Sugar 166 mg/dL
  - Na 144 mEq/L, K 4.6 mEq/L
  - Ammonia and calcium levels were not checked.

Image findings



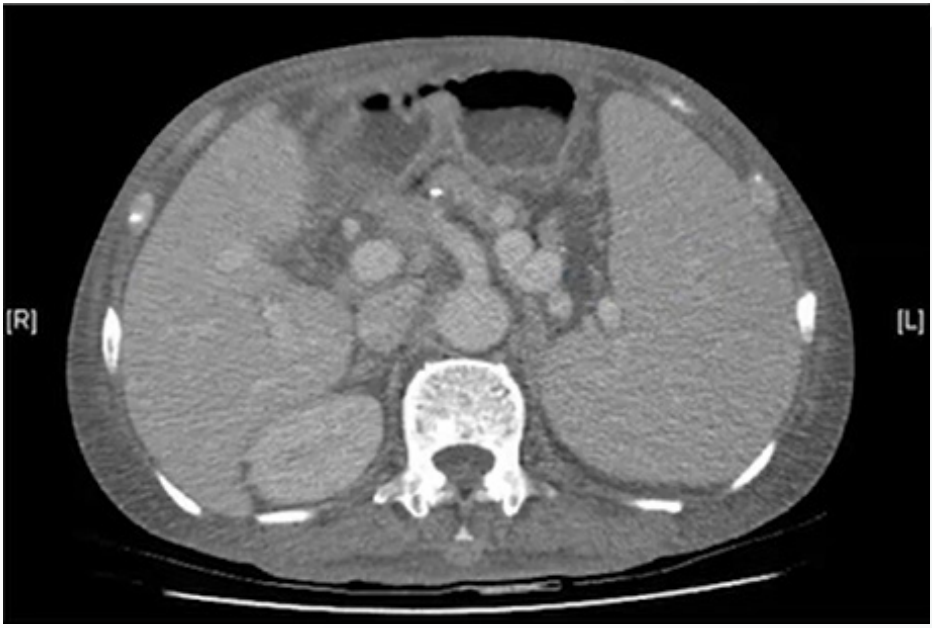


Figure 1-2. Abdominal CT obtained at Chang Gung Memorial Hospital showed marked splenomegaly.

Additional laboratory data

Peripheral blood smear

Marked rouleaux formation.

Bone marrow biopsy

Lymphoplasmacytic infiltrates.

Serum immunofixation electrophoresis

IgM monoclonal gammopathy 11100 mg/dL (reference range 40-230 mg/dL).

MYD88 and *CXCR4* mutation status assessment

Not done.

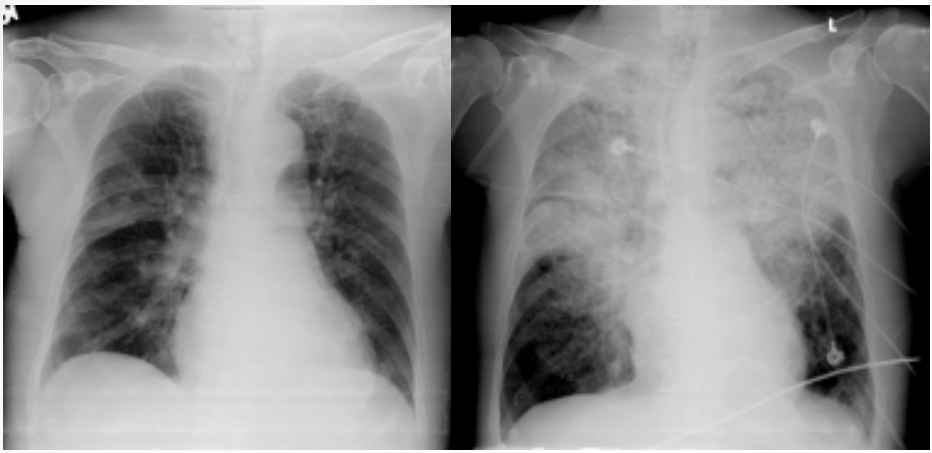


Figure 3-4. Chest radiograph obtained on the first day (left) and the fourth day (right) of admission found significant patchy infiltration of bilateral lung compared to baseline.

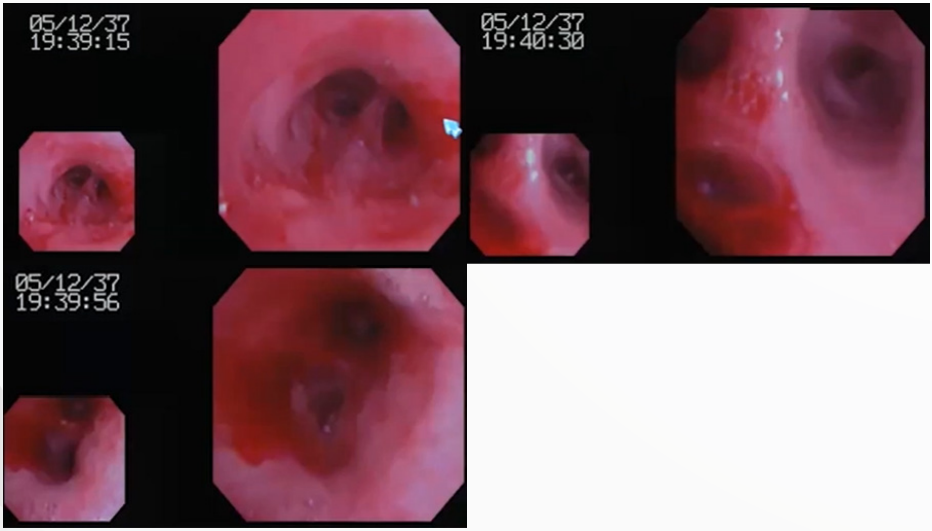


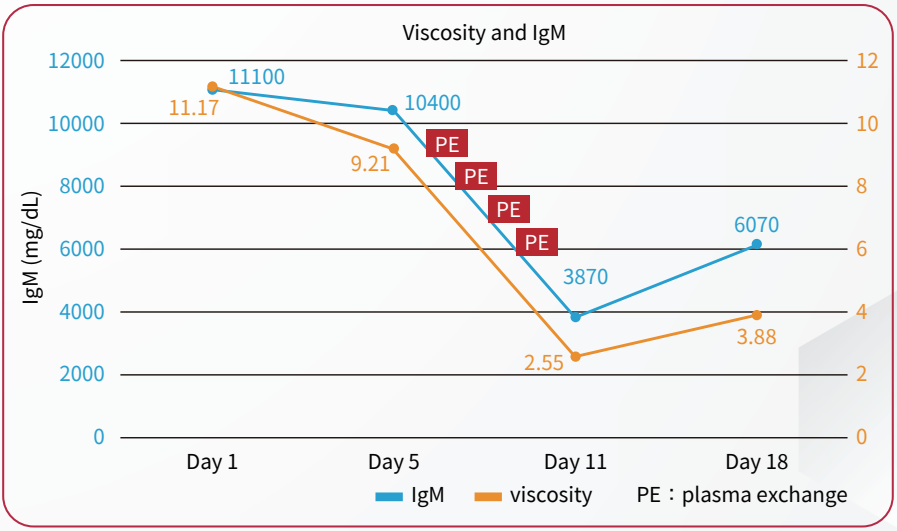
Figure 5—7. Bronchoscopy showed:

- Hyperemic mucosa.
- Blood found in RB3, LB2 orifices.
- No endobronchial lesion.
- Lavage: pink, frothy fluid.
- Culture: negative for microorganism growth.

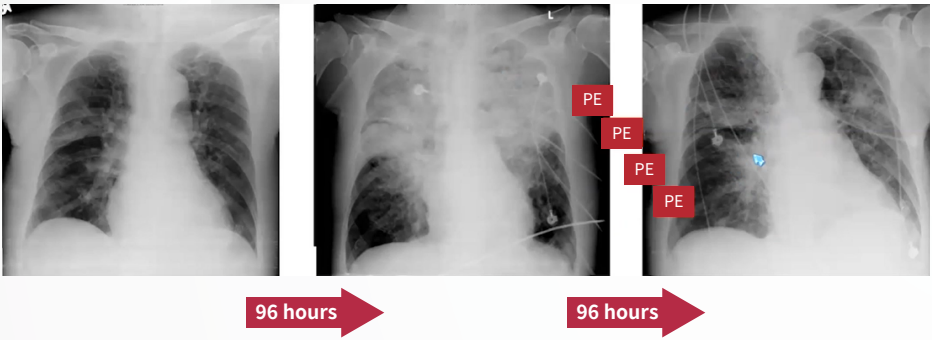
Treatment and Clinical course

- Steroid (prednisolone) was continued and chlorambucil was added because of his albumin/globulin ratio reversal.
- The patient's consciousness was clear at admission, but on the fourth day of admission, he had cough and exertional dyspnea, and was found unconscious but dyspneic at night.
- The laboratory data showed mild anemia (Hb 9.5 g/dL) and mild thrombocytopenia (platelet count $120*10^3/\mu L$), normal hepatic and renal functions, with no electrolyte disturbance or significant hyperglycemia. Arterial saturation 95% and respiratory alkalosis with metabolic compensation were found by arterial blood gas test. Serum viscosity test was ordered but no available result was reported.
- The patient received endobronchial intubation and was admitted to intensive care unit (ICU). The results of bronchoscopy showed hyperemic mucosa but with no evidence of inflammation or infection.

Treatment assessment



- On the patient's fifth day of admission, reports of IgM levels and viscosity became available and hyperviscosity status was confirmed. The patient received plasma exchange for four times, and his IgM level and viscosity dramatically decreased. Although mild elevated IgM and viscosity were observed after plasma exchange completed, the patient did not experience any clinical symptoms.



- The patient's chest radiography showed marked improvement of the infiltration over bilateral lung, suggesting it was more likely to be caused by hyperviscosity.

Discussion

- Common causes of acute confusion can be categorized to infection (sepsis, encephalitis, meningitis, etc.), withdrawal (alcohol, sedative hypnotics), acute metabolic (acidosis, electrolyte disturbances, hepatic/renal failure), trauma (head), central nervous system (CNS) diseases (hemorrhage, cerebrovascular accidents, seizures, tumor, vasculitis), hypoxia (acute hypoxia, chronic lung disease, hypotension), deficiencies (vitamin B12, thiamine, etc.), environmental (hypo/hyperthermia, endocrinopathies), acute vascular (hypertensive emergency, subarachnoid hemorrhage, thrombosis), toxin/drugs and heavy metal.[1]
- In the patient of this case, no conclusive findings except anemia and splenomegaly were reported right after his first episode of conscious disturbance at the local hospital. However, his second conscious disturbance episode occurred during admission at Chang Gung Memorial Hospital was caused by hypoxia, which may have resulted from infection or hyperviscosity-associated circulatory disturbance.
- Viscosity is a measure of a fluid' s resistance to flow and can be measured in absolute value where the unit is centipoise (cP), or in relative value units, where the value of water is set at 1.0, and the relative viscosity of serum is 1.7 in this measurement system.
- In a report of Mayo Clinic, hyperviscosity syndrome was observed in 13.5% of patients. The analysis showed that IgM > 4600 mg/dL (hazard ratio, 3.1 [1.3-8.9]; p< 0.0013) and viscosity > 2.2 cP (hazard ratio, 7.6 [3.2-20.5]; p < 0.0001) were independent predictors of development of hyperviscosity. It was uncommon for hyperviscosity to occur with levels of the monoclonal immunoglobulin below 4000 mg/dL. Thus, the policy concluded from the

report was not to measure the viscosity level below these immunoglobulin levels unless there are compelling symptoms or physical findings.

- Hyperviscosity may induce hemorrhage, visual disturbance, neurologic or cardiac symptoms. In the patient of current case, his blurred vision and general malaise were possibly associated with hyperviscosity. His first conscious disturbance may have been primarily associated with impaired cerebral blood flow caused by hyperviscosity, and the second conscious disturbance episode which resulted from hypoxia, was also contributed by mucosal hemorrhage (pulmonary hemorrhage) and heart failure with high output (pulmonary edema).
- The patient in current case was diagnosed approximately 20 years ago, when prednisolone plus chlorambucil were commonly used for Waldenström's Macroglobulinemia (WM). In recent decade, the most frequently used regimens for these patients are rituximab plus bendamustine (BR) at Chang Gung Memorial Hospital.

References

01.Smith J et al., Rosen's Emergency Medicine Concepts and Clinical Practices. 7th ed. Philadelphia, PA: Elsevier; 2010:1367-73.

Waldenström's Macroglobulinemia - a Patient Who Underwent Autologous Peripheral Blood Stem Cell Transplantation

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黃威翰 醫師

Clinical pearls

- The efficacy and safety of Bruton tyrosine kinase (BTK) inhibitors for the treatment of Waldenström's Macroglobulinemia (WM) have been demonstrated in several pivotal studies.
- BTK inhibitors are good non-chemotherapeutic options for certain group of patients with WM.
- *MYD88* and *CXCR4* mutation status assessments are recommended for patients with WM, especially those categorized as high-risk group, to predict the effectiveness of immunochemotherapy and BTK inhibitors.

Patient profile

Case presentation

- A 45-year-old male patient had history of coronary artery disease (CAD) and under regular follow up in the cardiology clinic.
- The patient complained frequent epistaxis, gingival bleeding, and dizziness in July 2018. No significant abnormality was found by cardiac examinations, but anemia and thrombocytopenia were noticed. He was then referred to hematology clinic for further evaluation.
- In our hematology clinic, atypical lymphocytes and decreased renal function were also noticed. High total protein level, albumin/globulin ratio reversal resulted from extremely high immunoglobulin (Ig) M level, and mild elevated β2-microglobulin were observed.
- Both abdominal echography and computed tomography (CT) showed liver nodules and splenomegaly, but no significant FDG uptake was found by positron emission tomography (PET). Referring to all the reports from imaging and bone marrow studies, WM or lymphoplasmacytic lymphoma (LPL) with indolent nature was diagnosed.

Laboratory findings

CBC & PLT		
WBC	6.23	$*10^3/\mu L$
RBC	3.15	$*10^6/\mu L$
Hb	8.5	g/dL
Ht	26.6	%
MCV	75.8	fL
MCH	24.2	pg
MCHC	32.0	%
PLT	139	$*10^3/\mu L$

Figure 1. Laboratory data obtained in cardiology clinic in July 2018 showed anemia and thrombocytopenia of unknown cause.

B2 MG	3819	ng/mL
ALT (GPT)	11	IU/L
T-bil	0.3	mg/dL
D-bil	0.1	mg/dL
LDH	173	U/L
TP	15.8	g/dL
Albumin	3.6	g/dL
GLO	12.2	g/dL
BUN	22	mg/dL
UA	11.5	mg/dL
CRE	1.8	mg/dL
WBC DC		%
N.band	3.0	%
N.seg.	59.0	%
Lym.	30.0	%
Mono.	3.0	%
Eosin.	1.0	%
Baso.	0.0	%
Aty.Lym.	4.0	%

HBs Ag	Negative
s/c value	0.21
Anti HCV	Negative
s/c value	0.08

Figure 2. Laboratory data obtained in hematology clinic in July 2018 revealed:

- Atypical lymphocytes.
- No hepatitis B or C infection.
- High total protein level, albumin/globulin ratio reversal.
- Decreased renal function.
- Mild elevated β2-microglobulin level.

Image findings

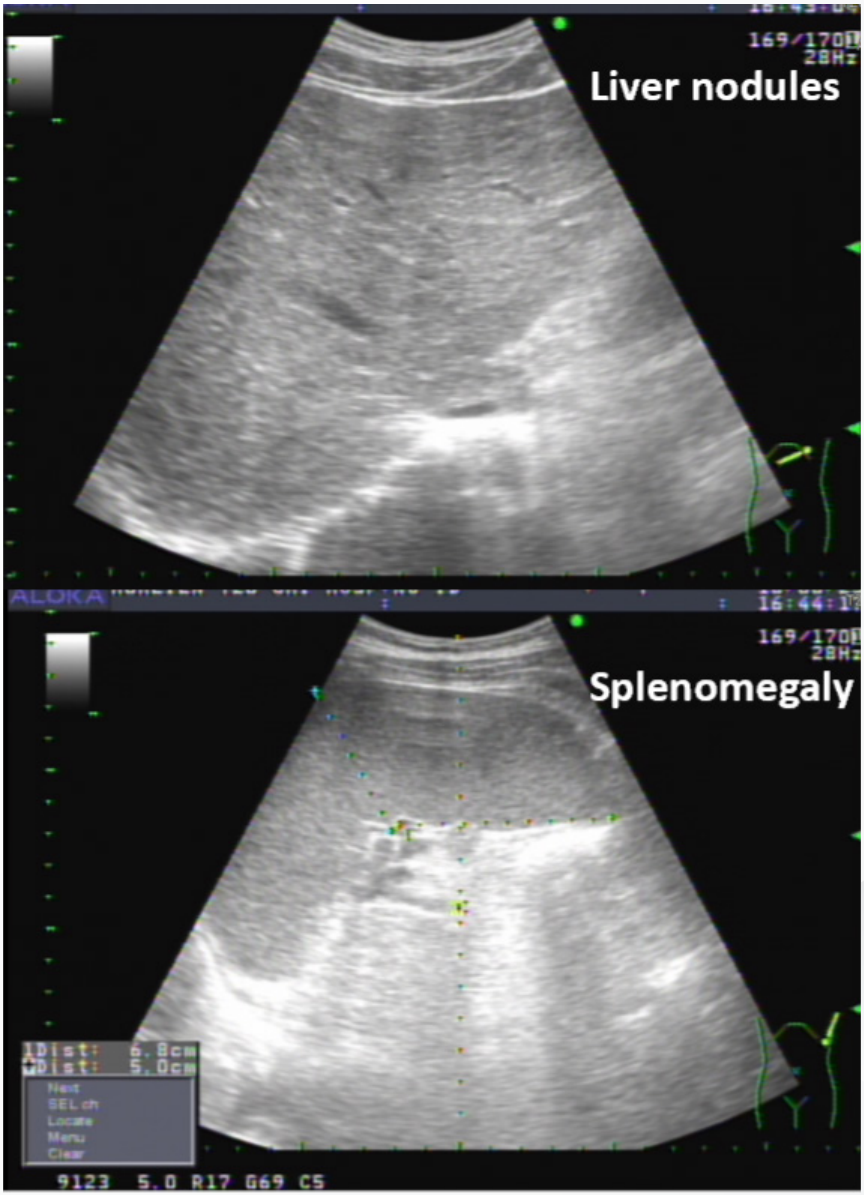


Figure 3-4. Abdominal echography found liver nodules and splenomegaly.

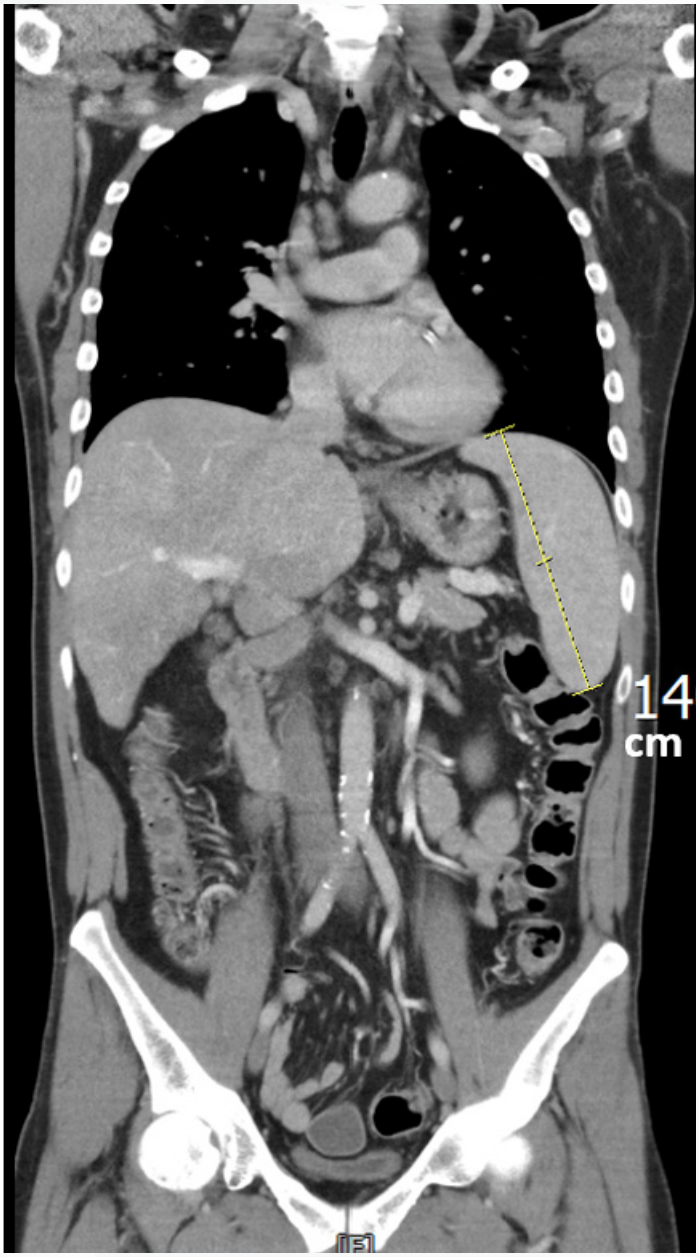


Figure 5. CT showed liver nodules and splenomegaly (diameter 14 cm).

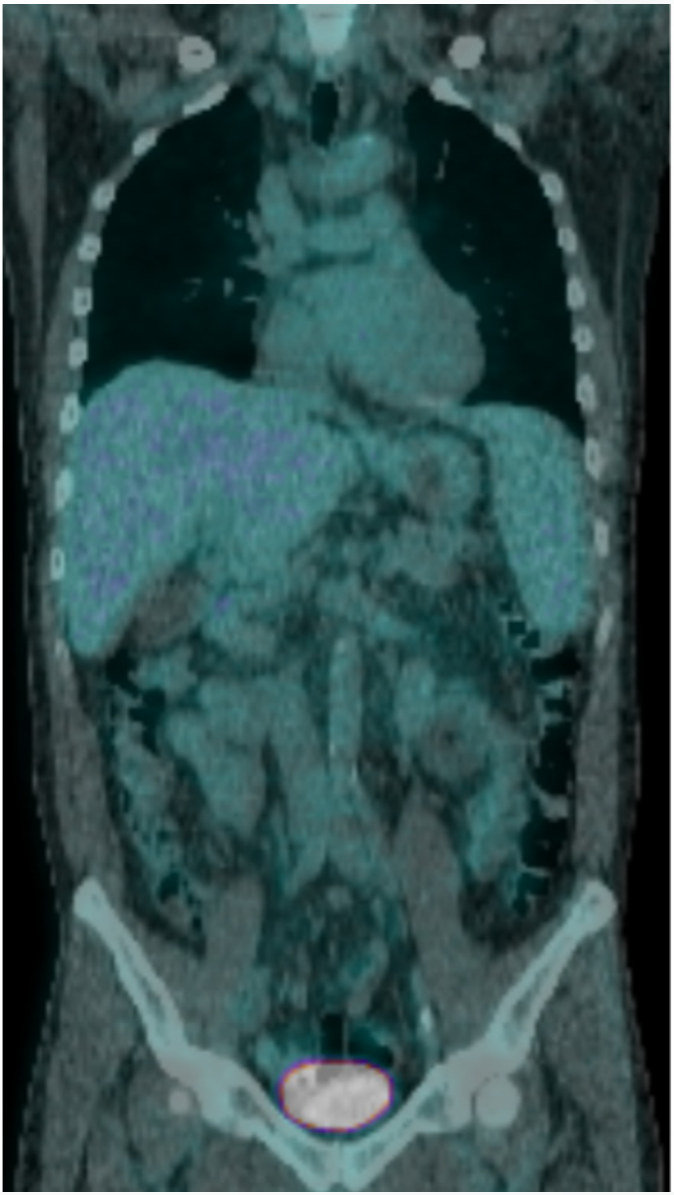


Figure 6. PET did not reveal any site with significant FDG uptake.

Diagnostic process

Serum immunofixation electrophoresis

Ig A	41	mg/dL
IgM	12200	mg/dL
IgG	410	mg/dL
M - protein	62.7	%
M - protein	9910	mg/dL
Free Ig K/L		
FKLC	151	mg/L
FLLC	6.63	mg/L
FK/FL ratio	22.78	

Figure 7.

- Markedly elevated IgM and mild decreased IgG levels.
- Mild increased free κ light chain.

Bone marrow smear

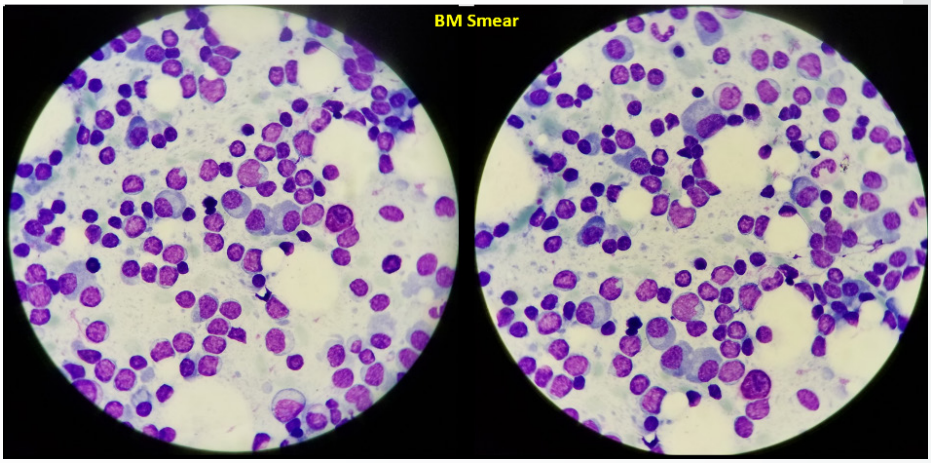


Figure 8-9. Bone marrow smear showed more than 20% of small lymphocytes with scattered plasmacytoid/plasma cells.

Bone marrow biopsy report:

- Hypercellular marrow (70% cellularity) with multifocal varying sized atypical lymphocytes, plasmacytoid lymphocytes, and plasmacytic aggregates.
- A few Dutcher bodies were also noted.
- IHC stain shows κ(+++), λ(-), CD20 (+++) and CD138 (+++); diagnostic of LPL.
- Large size transformation of some tumor cells is also noted.

Bone marrow flow cytometry

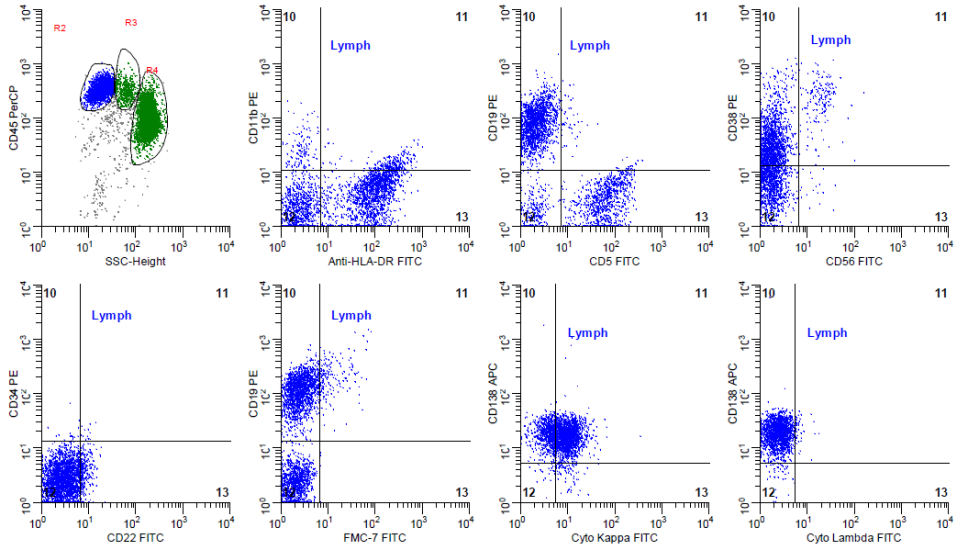


Figure 10-17. Bone marrow flow cytometry results showed:

- 20% B cells, with CD19+, CD20+, DR+, CD138+, cyto-Kappa light chain restriction.
- Compatible with WM/LPL.

MYD88 and *CXCR4* mutation status assessment

Not done.

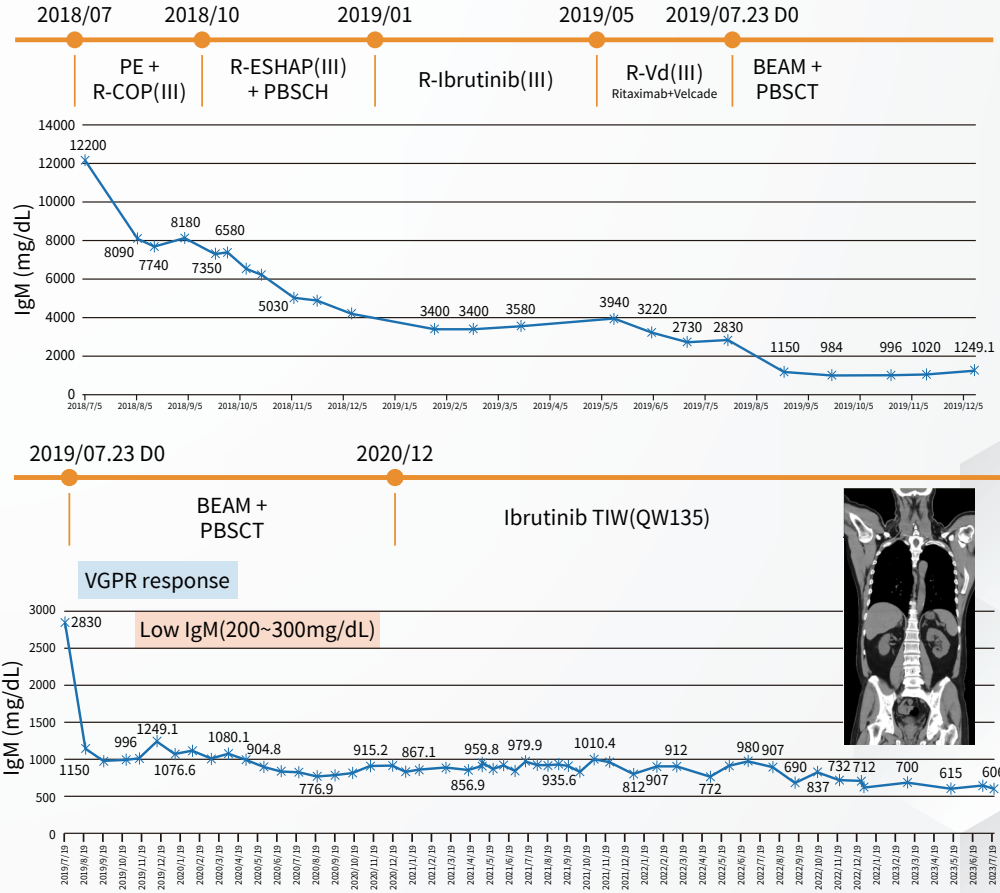
Treatment and Clinical course

- After plasma exchange (PE) once, three cycles of rituximab, cyclophosphamide, vincristine, prednisolone (R-COP) were given, but the patient's IgM level did not response significantly.
- Following R-COP, the patient received three cycles of rituximab, etoposide, methylprednisolone, high-dose cytarabine and cisplatin (R-ESHAP), and his IgM level decreased to 4000 mg/dL. He received peripheral blood stem cell harvest, followed by compassionate ibrutinib plus rituximab for three cycles and rituximab and bortezomib (RVd) for two cycles.
- In May 2019, the patient's IgM level decreased to below 3000 mg/dL. Autologous peripheral blood stem cell transplantation (PBSCT) was

performed in July 2019. After PBSCT, the patient's IgM level was approximately 1000 mg/dL, achieving very good partial response (VGPR).

- However, no significant reduce of the patient's IgM level was observed several months after PBSCT. Considering the financial burden, ibrutinib every other day was initiated from December 2020. His IgM level decreased gradually to approximately 600 mg/dL in July 2023.

Treatment assessment



- The patient's IgM level did not decrease to normal range under several chemo-immunotherapy regimens.
- After PBSCT, VGPR was achieved but his IgM level remained relatively high.

- Ibrutinib was initiated, and his IgM level decreased gradually.
- CT done in March 2023 showed resolved splenomegaly.

Treatment and Clinical course

- If the patient in current case was considered symptomatic, he had three risk factors based on The International Prognostic Scoring System for WM (IPSSWM) -- hemoglobin (Hb) $\leq$ 11.5 g/dL, β2-microglobulin > 3 mg/L, and M protein > 7.0 g/dL, and was classified as high risk group; even using asymptomatic WM patient risk calculator developed by Dana-Farber Cancer Institute, the patient was still classified as high risk group by his bone marrow infiltration, IgM, β2-microglobulin, and albumin levels, and the median progression time was estimated to be 1.8 years.[1,2]
- The results of iNNOVATE study showed that compared to rituximab alone treatment, ibrutinib-rituximab combination had significantly superior progression survival (PFS) rate (68% vs. 25%) at 54 months; ASPEN study also indicated that zanubrutinib treatment had comparable PFS with that of ibrutinib.[3-6] Both studies demonstrated that BTK inhibitors may be effective for high-risk WM patients, like the patient in this case.
- In the patient of current case, because of his young age and high-risk disease, the treatment goal was set to be complete response, in terms of the IgM level reduce to normal value. After using ibrutinib following autologous PBSCT, the patient's IgM level gradually decreased, but did not reach to normal value. Because the patient was unwilling to undergo the genetic test of *MYD88* and *CXCR4*, the effectiveness of BTK inhibitors was not predictable, thus, bendamustine plus rituximab(BR) or other novel therapies may be considered if disease progression.

References
01.Morel P et al., Blood. 2009;113(18):4163-70.
02.https://www.awmrisk.com.
03.Buske C, et al. Blood. 2020; 136(suppl.1):24-6.
04.Dimopoulos MA et al., N Engl J Med. 2018;378(25):2399-410.
05.Tam CS et al., Blood. 2020;136(18):2038-2050.
06.Tam CS et al. ASCO 2020. Oral Presentation.

Waldenström's Macroglobulinemia - a Patient with Persistent Constitutional Symptoms

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Clinical pearls

- Waldenström's macroglobulinemia (WM) can be difficult to diagnose because of its diverse clinical presentation. Clinicians should be aware of the clinical symptoms and laboratory abnormalities of WM.
- Although immunoglobulin (Ig) M concentration is often used to assess patients' treatment response to WM, some patients' symptoms may not improve while their IgM decreasing. Medication change should be considered.
- For patients unwilling to receive chemotherapy, Bruton tyrosine kinase (BTK) inhibitors like zanubrutinib can be a good option for the first line treatment of WM.

Patient profile

Case presentation

- 67-year-old male patient
- In November 2018, this patient visited gastrointestinal clinic because of epigastric distention and postprandial epigastric pain for one month. Symptom-relief medications were prescribed.
- In September 2019, he visited neurologic clinic with complaints of poor sleep and five-kilogram body weight loss within one year. Sleep apnea was suspected at that time.
- In April 2021, he visited family medicine clinic, complaining bilateral leg swelling for two weeks, six- to seven-kilogram body weight loss, poor appetite, and exertional dyspnea. Cardiac echography revealed no specific finding; laboratory data showed mild microcytic anemia.
- In May 2021, fever for four days with throat lump sensation occurred, and this patient visited gastrointestinal clinic again because of ten-kilogram body weight loss within the past 18 months and anemia. No specific finding was reported by gastric endoscopy and no hepatosplenomegaly was seen by abdominal echography.
- This patient visited hematology clinic two days after his visit to gastrointestinal clinic. Intermittent night fever for six months, ten-kilogram body weight loss within the past 18 month, and bilateral leg edema for one month were complained.
- WM was diagnosed by bone marrow biopsy.

Physical examination

No lymphadenopathy over neck, axillary, and inguinal area

Laboratory findings

	WBC (10^3/μL)	Hb (g/dL)	Platelet (10^3/μL)	MCV (fL)	Fe (ug/dL)	Iron sat.	TIBC	Ferritin (ng/ml)
110/4/20	9.7	8.1	336	78.8	19	11.2%	169.26	379

	Bun (mg/dL)	Cre (mg/dL)	Alb (g/dL)	TP (g/dL)	AST (IU/L)	ALT (IU/L)	T-bil (mg/dL)	LDH (IU/L)
110/4/20	19	0.81	2.65	7.2	36	35	0.4	90

	WBC (10^3/μL)	Neu(%)	Lym(%)	Mono(%)	Hb(g/dL)	Platelet (10^3/μL)	MCV	ESR (mm/hr)
110/4/20	9.1	77.1	11.7	10/7	8.8	428	79	>140

Image findings (computed tomography [CT])

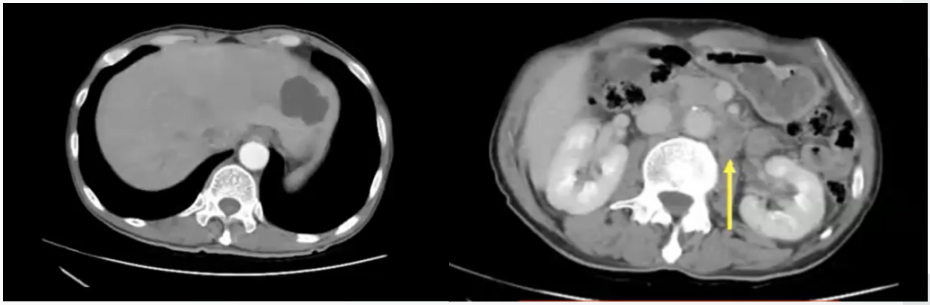


Figure 1-2. Abdominal CT images before treatment (in May 2021)

- Lymphadenopathy in left para-aortic region

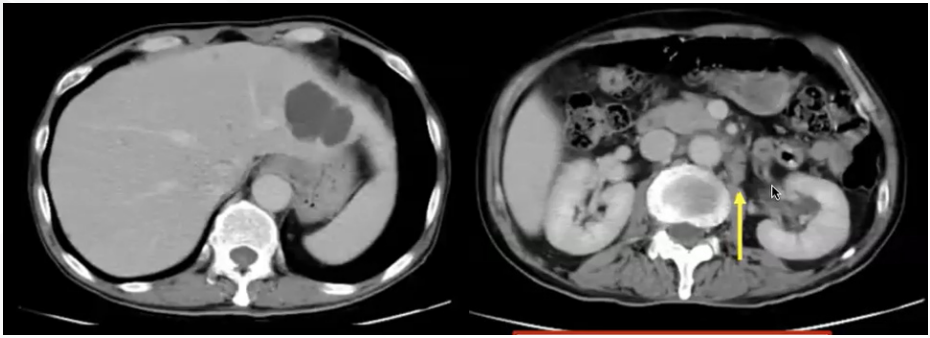


Figure 3-4. Abdominal CT images after treatment (in November 2021)

- Slightly improvement of lymphadenopathy

Pathological findings (bone marrow smear)

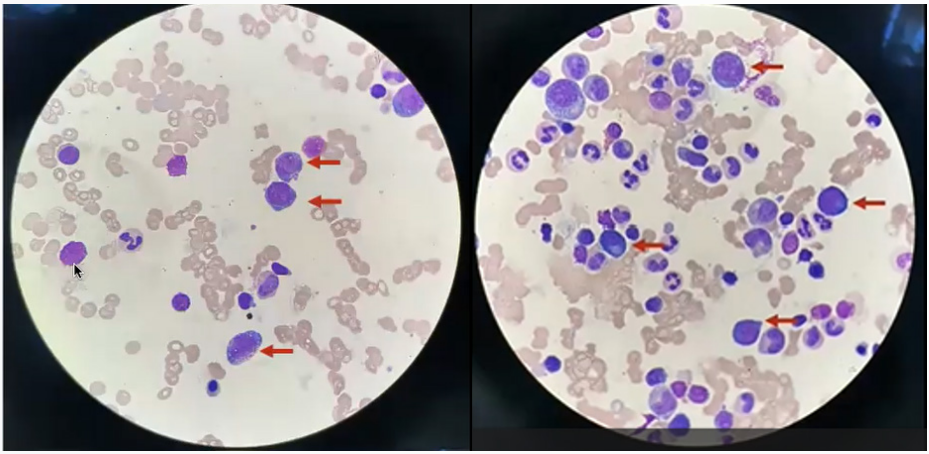


Figure 5-6. Small lymphoid cells with plasmacytic differentiation

Diagnostic process

Pathology reports

- Mildly hypercellular marrow (cellularity: 70—75%) with focal aggregation of small lymphoid cells with clumped chromatin and scanty cytoplasm
- Focal plasmacytic differentiation was also seen.
- Immunohistochemical study showed CD3-, CD5-, CD10-, CD20+, CD138 (scattered), kappa (scattered) and lambda+.
- Compatible with WM

Serum electropheresis findings

IEP:		A monoclonal lgMK is detected in the blood	
IgG	(mg/dL)	1230	(Serum:751-1560;CSF:0.48~5.86)
IgM	(mg/dL)	1540	(46-304)
Free kappa (serum)	(mg/L)	901	(3.30-19.4)
Free lambda (serum)	(mg/L)	21.6	(5.71-26.30)
Kappa/Lambda (serum)		41.7	(0.2601.65)

MYD88 and *CXCR4* mutation status assessment

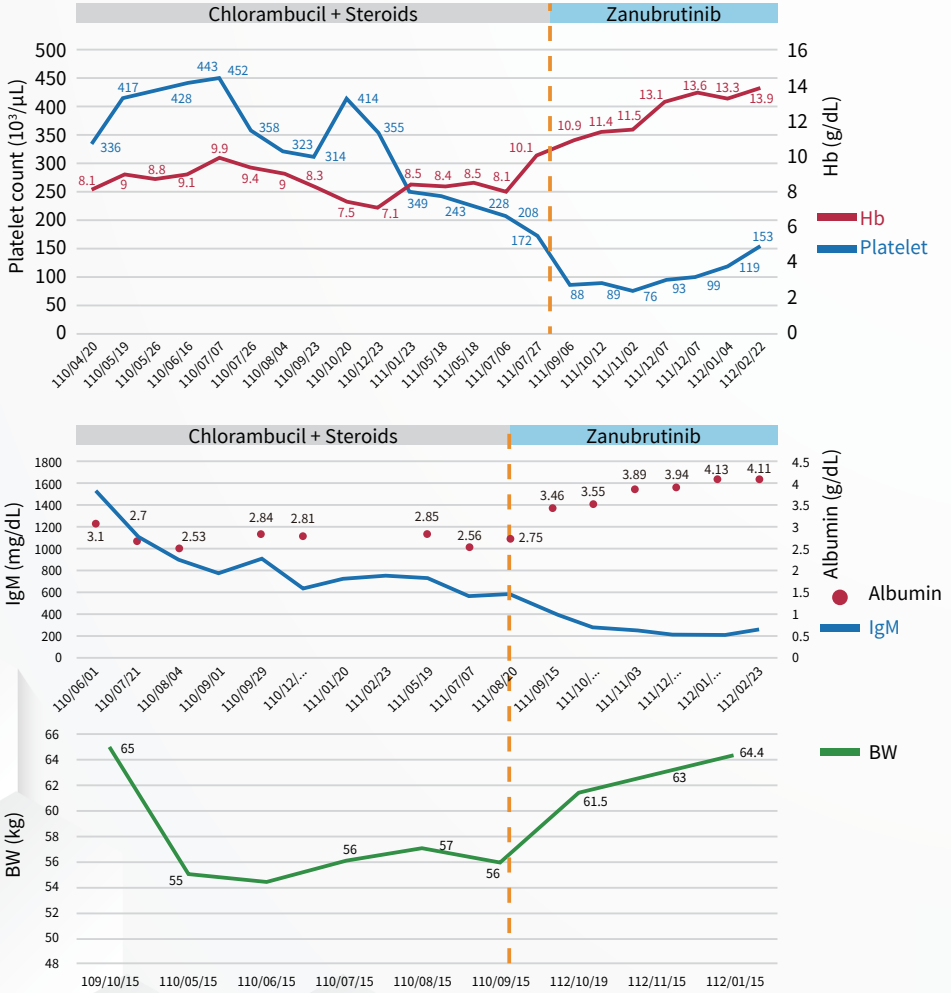
Not done.

Treatment and Clinical course

- Because of this patient's anemia and B symptoms, treatment with prednisolone 5 mg twice per day (BID) and chlorambucil 2 mg per day (QD) was started in June 2021.
- The patient's IgM level decreased after chlorambucil treatment, however, his hemoglobin (Hb) and albumin level, and body weight did not improve regardless of the treatment. Intermittent blood transfusion was needed.
- In August 2022, this patient started to receive zanubrutinib 160 mg BID in the compassionate use program.

- After three-month treatment of zanubrutinib, this patient's Hb level increased to 13 g/dL; albumin concentration and body weight also improved gradually. No more fever or night sweating was complained after zanubrutinib treatment.
- Mild skin rash and itching occurred during zanubrutinib treatment. Topical steroid was prescribed for symptom relief.

Treatment assessment



Discussion

- Before this patient came to hematology clinic, he had visited many clinics of different subspecialties for help, and it took almost two years from the patient's first complaint of body weight loss to confirming diagnosis of WM. WM can be difficult to diagnose because of its diverse clinical presentation.
- This patient's WM was classified as intermediate/high risk by International Prognostic Scoring System for WM (IPSS WM) due to lack of data of β2 microglobulin level, and as high risk by French score, with five-year overall survival (OS) rate of 25%.[1]
- In the China Medical University Hospital, the most used therapy for WM is oral cyclophosphamide, followed by chlorambucil and BR (bendamustine, rituximab). Many patients respond to chlorambucil well, achieving good improvement on IgM level, and with no significant side effects.
- Although the patient's IgM level significantly decreased after the first line treatment with chlorambucil and steroids, there was no improvement on his constitutional symptoms including low grade fever and poor appetite.
- IgM concentration is often used as a marker of treatment response for WM. However, in this patient, his IgM level decrease was incompatible with other persistent constitutional symptoms, which meant his WM was not under good control and medication change should be considered.
- BR was suggested as the second line treatment for this patient, but he hesitated to receive chemotherapy. He experienced symptom resolution during the first two weeks of zanubrutinib treatment, and his body weight and albumin level increased subsequently.
- BR is an immunochemotherapy with relatively less side effects, but the infection risk for elder patients, and the possibility of developing secondary malignancy for younger patients should be taken into consideration.

References
01.Morel P et al., Blood. 2000;96(3):852-8.

Waldenström's Macroglobulinemia - with Central Nervous System Involvement (Bing Neel Syndrome)

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李思慧 醫師

Clinical pearls

- Bing Neel syndrome is a relatively rare manifestation of Waldenström's macroglobulinemia (WM) and should be differentiated with hyper viscosity syndrome.
- Morphology of cerebrospinal fluid smear is the gold standard for diagnosing Bing Neel syndrome, and magnetic resonance imaging is the most ideal for Bing Neel syndrome workup.
- Bruton tyrosine kinase (BTK) inhibitors have shown central nervous system penetrating properties and are preferred regimen for Bing Neel syndrome.

Patient profile

Case presentation and Medical history

- 59-year-old male patient, with no notable systemic disease except history of amphetamine abuse 20 years ago.
- In 2016, the patient went to a local hospital, with chief complaint of 12 kg body weight loss during the past 4 months and dizziness.
- Anemia and multiple lymphadenopathy were noted; lymph node biopsy showed B cell lymphoma with plasmacytic differentiation. Immunohistochemistry (IHC) stains results: CD5-, CD10-, CD20+, CD23+ (focal), CD79a+, CD138+, cyclinD1-, IgM (immunoglobulin M)+(focal), BCL-2+.
- The patient received oral corticosteroids for several weeks but was sent to the emergency room (ER) due to conscious disturbance.
- IgM 7010 mg/dL was found at ER. Under the impression of hyperviscosity syndrome, the patient was transferred to National Taiwan University Hospital (NTUH) for further treatment.
- After 2 courses of plasma exchange, the patient's consciousness slightly improved (from completely no response to responding to name calling) and total protein level dropped from 9.5 g/dL to 7.9 g/dL.
- However, a general tonic-clonic seizure happened two days later. No tumor nor hemorrhage/ischemia was found by brain computed tomography (CT). Magnetic resonance imaging (MRI) was not performed because the patient was too agitated and could not remain still during the examination.

Laboratory findings

WBC (10^3/μL)	RBC (10^6/μL)	Hb (g/dL)	MCV (fL)	PLT (10^3/μL)	Blast (%)	Promyl (%)
21.66	2.85	8.4	90.5	225	+	1.0

Myelo (%)	Meta (%)	Band (%)	Seg (%)	Eos (%)	Baso (%)	Mono (%)
2.0	1.0	2.0	74.0	0	0	10.0

Lym (%)	Aty. Lym (%)	Normobl	Alb (g/dL)	TP (g/dL)	BUN (mg/dL)	Cre (mg/dL)
9.0	1.0	1.0/100 WBC	2.6	9.5	24.9	0.7

AST (U/L)	ALT (U/L)	T-bil (mg/dL)	Na (mEq/L)	Ca (mEq/L)	UA (mg/dL)	LDH (U/L)
20	18	0.44	129	2.27	5.6	122

Ammonia (umol/L)	IgM (mg/dL)	IgA (mg/dL)	IgG (mg/d)	Beta-2 microglobulin (ng/mL)	IFE
36	6360	<26.60	603.00	6530	Dense band of IgM/ kappa monoclonal gammopathy

Pathological findings (cerebrospinal fluid [CSF] and bone marrow smear)

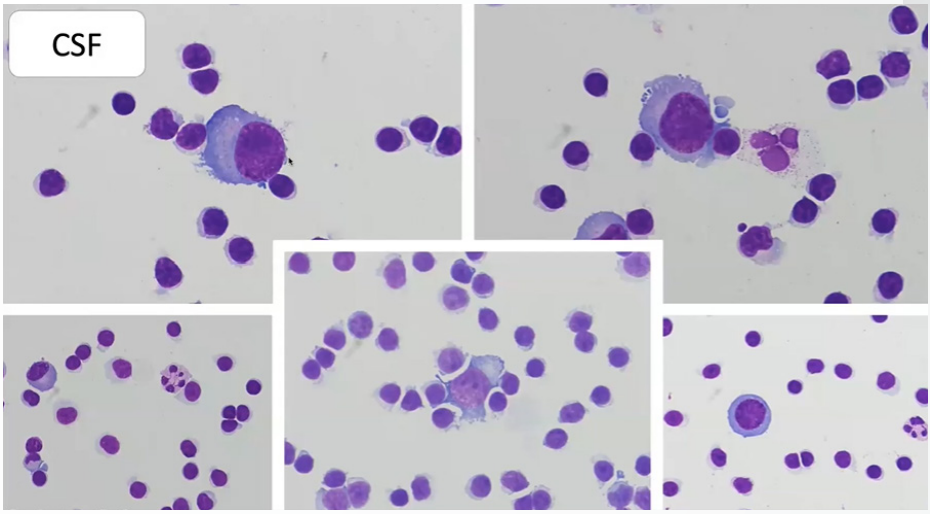
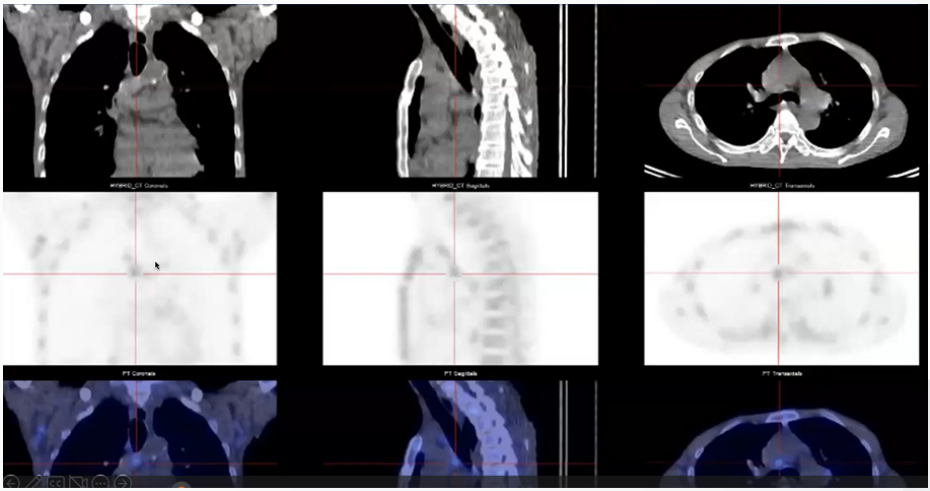


Figure 1-2. Small to medium size lymphoplasmacytic cells infiltration with scattered bizarre cells.

Image findings (positron emission tomography/ computed tomography [PET/CT])



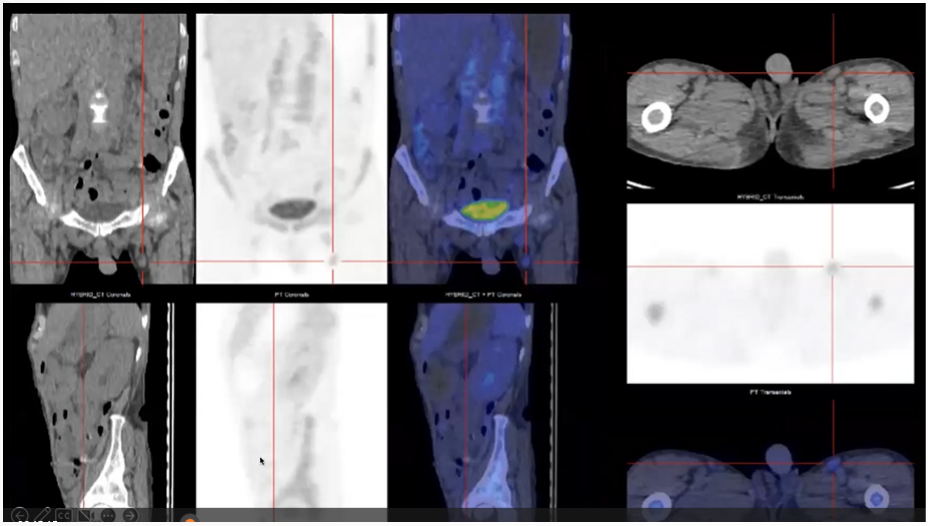


Figure 3-4. Multiple ambiguously enlarged lymph nodes.

Diagnostic process

Bone marrow examination reports

- Bone marrow smear: infiltration of small and mature lymphocytes (60%), plasma cells (2%), compatible with lymphoplasmacytic lymphoma (LPL) in the bone marrow.
- Bone marrow pathology: extensive lymphoid infiltrates of mixed small and large cells. IHC stains results: 90% CD79a+, 5-10% CD3+, and 10% CD138+ cells. The atypical cells are CD79a+, BCL2+ and BCL6-, CD23-, and indeterminate for CD10. These findings are compatible with, but not diagnostic for LPL.
- Bone marrow flow cytometry: clonal B cells around 60% with CD45+, CD19+, CD20+, CD22+, CD5-, CD10-, CD23-, FMC7+, CD25-, CD103-, CD138- and surface kappa light chain restriction.

MYD88 and *CXCR4* mutation status assessment

- Not done.

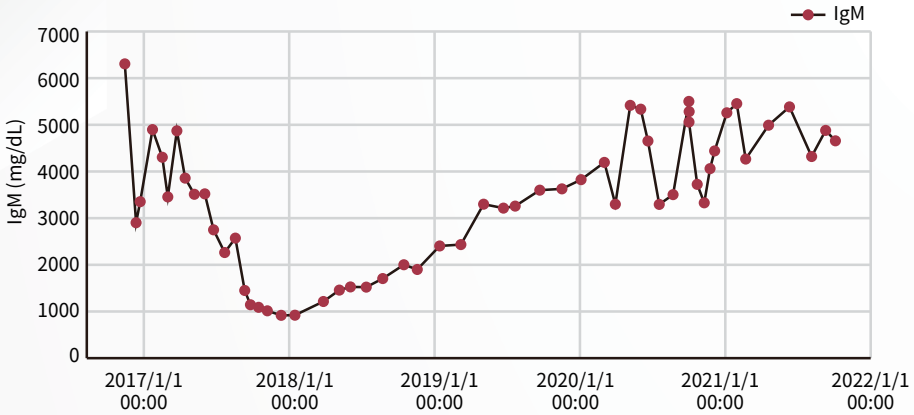
Diagnosis

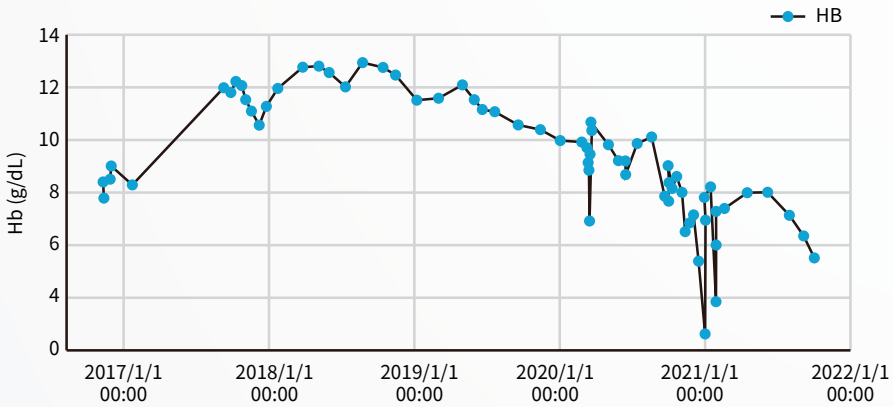
- WM, stage IV with involvement of bone marrow, central nervous system (CNS) (Bing-Neel syndrome), multiple lymph nodes, axial/appendicular bones and abdominal paraaortic region.
- International Prognostic Scoring System for WM (IPSSWM) score 2 (intermediate risk).

Treatment and Clinical course

- Consciousness improved (responded to questions appropriately but still agitated) after 1st cycle of high dose methotrexate (HD-MTX), cyclophosphamide (C), dexamethasone (D).
- The patient had received treatment with HD-MTX, DC, rituximab (R), bendamustine (B), bortezomib, cytarabine + etoposide (CyVE) and lenalidomide since 2016 to 2021.
- Regardless of a variety of treatment, abnormal lymphoplasmacytic cells were persistently found in CSF. Thus, the best response achieved was partial response (clinical symptoms improved without complete resolution).
- After treatment failure of lenalidomide, no other therapy was given and the patient has not come back for follow-up since 2021/10.

Diagnosis





Discussion

- Bing Neel syndrome is a relatively rare manifestation of WM.[1]
- Hyperviscosity syndrome is an important differential diagnosis for CNS symptoms in WM. For this patient, the CNS symptoms were not caused by high total protein level, but by direct lymphoplasmacytic cells infiltration to CNS.
- The gold standard for diagnosing Bing Neel syndrome is the morphologic presentation of CSF smear. Once large amount of lymphoplasmacytic cells seen in CSF, the diagnosis could be confirmed. CSF flow cytometry and immunofixation electrophoresis (IFE) may assist if morphologic presentation is not typical or indefinite.

- MRI is important for Bing-Neel syndrome workup; images of fluid attenuated inversion recovery (FLAIR), T1-wighted (contrast) and diffusion weighted imaging (DWI) sequences would be helpful to differentiate hyperviscosity syndrome and Bing-Neel syndrome.
- In 2016, treatment options for WM CNS involvement were limited; nowadays, Bruton's tyrosine kinase (BTK) inhibitors are recommended by many guidelines as the 1st line treatment for such patients.

References
01.Slides of Jorge Castillo. Dana-Farber Cancer Institute.

Waldenström's Macroglobulinemia - a Relapsed and Refractory Case with Bleeding as Initial Presentation

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卓士峯 醫師

Clinical pearls

- Waldenström's macroglobulinemia (WM) can cause diverse symptoms, including platelet dysfunction and coagulopathy, which may be resolved after treatment.
- For patients with relapsed/refractory WM, hematopoietic stem cell transplantation should be considered, especially for younger patients.
- After treatment failure of multiple immunochemotherapies and Bruton tyrosine kinase (BTK) inhibitors, drugs with different mechanism of action, such as B-cell lymphoma 2 (BCL2) inhibitors and mechanistic target of rapamycin (mTOR) inhibitors, could be used as the next-line therapy.

Patient profile

Case presentation

- 60+ year old male
- Chief complaints: frequent epistaxis and tinnitus
- Anemia, leucopenia, and coagulopathy were found by laboratory examination, along with hyperviscosity status due to high immunoglobulin (Ig) M level.
- Immunofixation electrophoresis (IFEP) showed serum IgM kappa monoclonal gammopathy.
- Bone marrow biopsy in 2010: lymphoplasmacytic lymphoma (LPL) compatible with WM.

Laboratory findings

2010/2/3	data
WBC (10^3/μL)	3.4
Hb (g/dL)	9.7
PLT (10^3/μL)	180
Lym (%)	32.4
Mono (%)	12.8
Bleedingtime	>10
PT	10.7/11.5
PTT	40.1/28.5

2010/2/3	data
ADP	10
Collagen	39
Ristocetin	0
Factor VIII	80%
Factor IX	39%
Factor XI	65%

2010/2/3	data
IgG (mg/dL)	800
IgA (mg/dL)	189
IgM (mg/dL)	9620
LDH (U/L)	76
Viscosity	9.85
B2M (ng/mL)	3110
Alb (g/dL)	2.82

Image findings

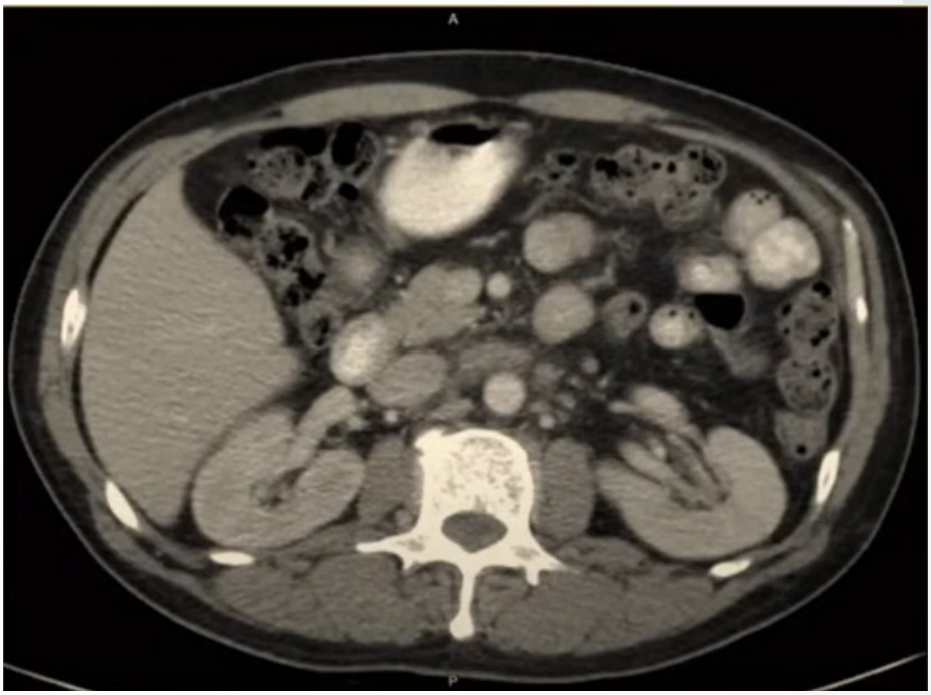


Figure 1. Abdominal computed tomography (CT) in 2010: no significant splenomegaly nor lymphadenopathy.

Diagnostic process

Pathology reports

- Bone marrow biopsy: hypercellular marrow (over 95%) filled with relatively uniform plasmacytoid cells with eccentrically located nuclei. These plasmacytoid cells are positive for lambda light chain and CD5. The morphology is compatible with WM.

MYD88 and *CXCR4* mutation status assessment

MYD88 L265P mutation

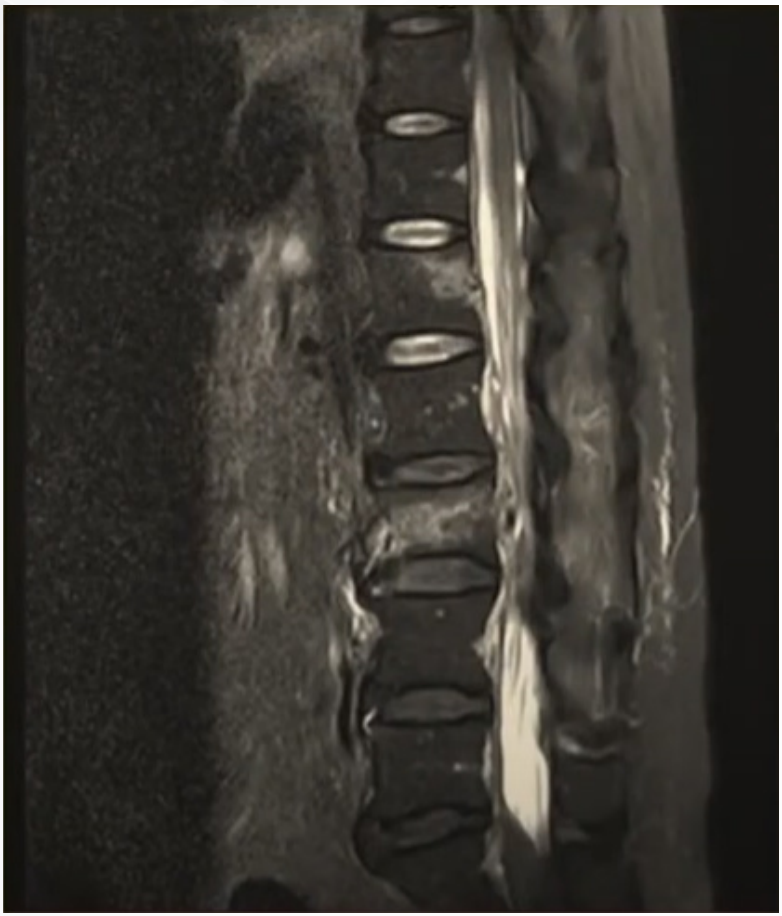


Figure 2. Lumbar spinal magnetic resonance imaging (MRI) in 2021.

- Vertebral compression fractures of L1 and L3.
- Bone marrow edema in vertebral bodies of L1 and L3 with enhancement.

Diagnostic process

Pathology reports

- Bone marrow biopsy: hypercellular marrow (over 95%) filled with relatively uniform plasmacytoid cells with eccentrically located nuclei. These plasmacytoid cells are positive for lambda light chain and CD5. The morphology is compatible with WM.

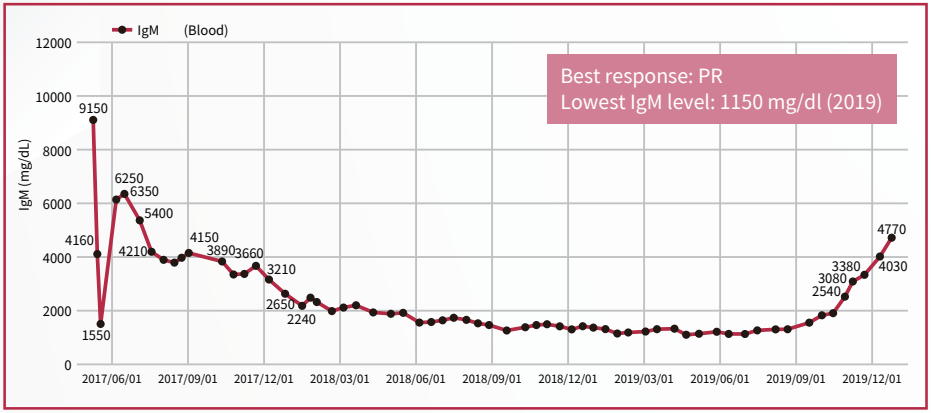
MYD88 and *CXCR4* mutation status assessment

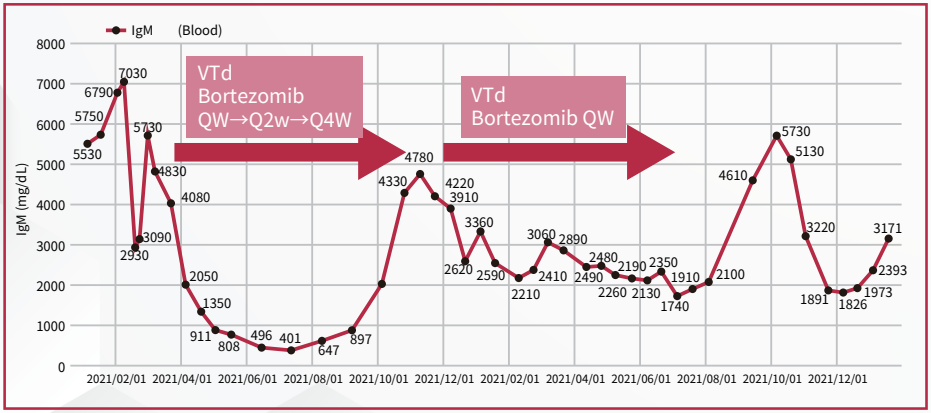
MYD88 (+)

Treatment and Clinical course

- Eight cycles of chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or COP (cyclophosphamide, vincristine, prednisone) were given within 2010-2011. Complete response (CR) was achieved, and the best IgM level was 750 mg/dL in 2013/5.
- Disease relapse was noted in 2014/9, with decreased WBC counts (3500/uL), anemia (Hb 10.6 g/dL) and high IgM level (7710 mg/dL). The patient received CHOP x 1, R (rituximab)-CHOP x 9 and R x 1, and achieved partial response (PR).
- However, the patient's IgM level gradually increased despite treatment, and the IgM level of 8030 mg/dL was noted, as well as LPL showed by the bone marrow biopsy in 2017/2.
- One cycle of modified R-CEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone) was given on 2017/4/14, but no response was seen. The patient's IgM level raised to 10400 mg/dL, so plasmapheresis were performed for several times, to correct the hyperviscosity status.
- After discussing with the patient, he started to use ibrutinib (self-paid) from 2017/4/27, and achieved best response of PR in 2019 (lowest IgM: 1,150 mg/dL).
- The disease started to progress again in the end of 2019. Rituximab x 2, BR (bendamustine, rituximab) x 2 were given but with poor responses. Two cycles of modified ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) were used, which only made the patient's IgM level decrease to below 5000 mg/dL for a few months.
- In 2021/2, the patient's IgM level increased to 7030 mg/dL, so the treatment was changed to VTd (bortezomib, thalidomide, dexamethasone). The response was good at first(the lowest IgM: 401 mg/dL), but recurrent LPL in lumbar vertebrae was found in 2022/8 .
- Although the disease seemed to be progressing, the patient still asked to keep current treatment with bortezomib(VTd) and refused hematopoietic stem cell transplantation.

Treatment assessment: IgM level from ibrutinib treatment started





Discussion

- This patient's bleeding tendency may be secondary to immunoglobulin abnormality. After treatment for WM started, no bleeding episode was noted. There was no significant bleeding risk elevation during ibrutinib treatment.
- For this patient, VTd treatment was effective at first, but the depth of response and the disease-free duration seemed to be decreasing. According to The National Comprehensive Cancer Network® (NCCN®) guideline for WM/LPL, treatment recommendation for previously treated WM/LPL patients includes rituximab-based regimens.[1] However, this patient's CD20 expression on WM cells was weak, which might be the explanation to previous poor response to rituximab.
- The patient had received ibrutinib and experienced treatment failure. Thus, another BTK inhibitor or drugs with different mechanism of action should be considered for the next-line treatment.
- One study used venetoclax, a B-cell lymphoma 2 (BCL2) inhibitor, in previously treated WM patients, and an overall response rate (ORR) of 84% was achieved, while for patients received $\geq$ 3 prior lines of treatment, the ORR would be lower (63%). The median progression-free survival (PFS) for all patients was 30 months, with 12/24-month PFS rates of 83% and 80%, respectively. No difference in PFS on the basis of prior BTK inhibition.[2]
- Fludarabine and mTOR inhibitors might be considered for the next-line treatment.

References
01.NCCN Guideline Version 1.2023. Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma.
02.JJ Castilo et al., J Clin Oncol. 2022; 40(1):63-71.

Waldenström's Macroglobulinemia - a Patient Presenting with Anemia and Acute Renal Failure

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邱倫瑋 醫師

Clinical pearls

- For elder patients with anemia of unknown cause, bone marrow infiltrative diseases should be taken into consideration.
- Both Bruton tyrosine kinase (BTK) inhibitors and 4-6 cycles BR (bendamustine, rituximab) are recommended for treatment-naïve Waldenström's macroglobulinemia patients. Decision making should be based on patients' preference, side effects or other consideration.
- Early diagnosis of Waldenström's macroglobulinemia (WM) is important, which makes early and appropriate intervention possible, to prevent major organ damage.
- Specific genotype tests (*MYD*88 and *CXCR4*) would be helpful for early diagnosis of WM, treatment decision making and outcome prediction.

Patient profile

Case presentation and Medical history

- 67-year-old female patient, with history of hypertension and left breast cancer (treated with surgery and CAF [cyclophosphamide, doxorubicin, fluorouracil]).
- Patient came to hematology clinic due to chronic anemia of unknown cause, with associated symptoms including general malaise, fatigue, 2 kg weight loss within 6 months and sudden onset of anorexia, vomiting and drowsiness.
- Acute renal failure was found before bone marrow biopsy.

Physical examination

No palpable lymph nodes nor organomegaly.

Laboratory findings

Hb (g/dL)	Hct (%)	Platelet (10^3/μL)	WBC (10^3/μL)	Seg (%)	Lym (%)
7.1	21.6	161	8.38	73.2	22.4

BUN (mg/dL)	Cre(ml/min/1.73m^2)	Na (mEq/L)	K (mEq/L)	Ca (mEq/L)	P (mEq/L)
142	9.55	137	5.2	9.7	8.1

Total bilirubin (mg/dL)	AST (U/L)	ALT (U/L)	ALP (U/L)
0.2	13	10	94

Total protein (g/dL)	Albumin (g/dL)	Globulin (g/dL)	IgM (mg/dL)
8.9	3.9	5.0	3043

Protein electrophoresis (serum)	β2-microglobulin (ng/mL)
Monoclonal pattern of gamma-globulin	7413

Image findings

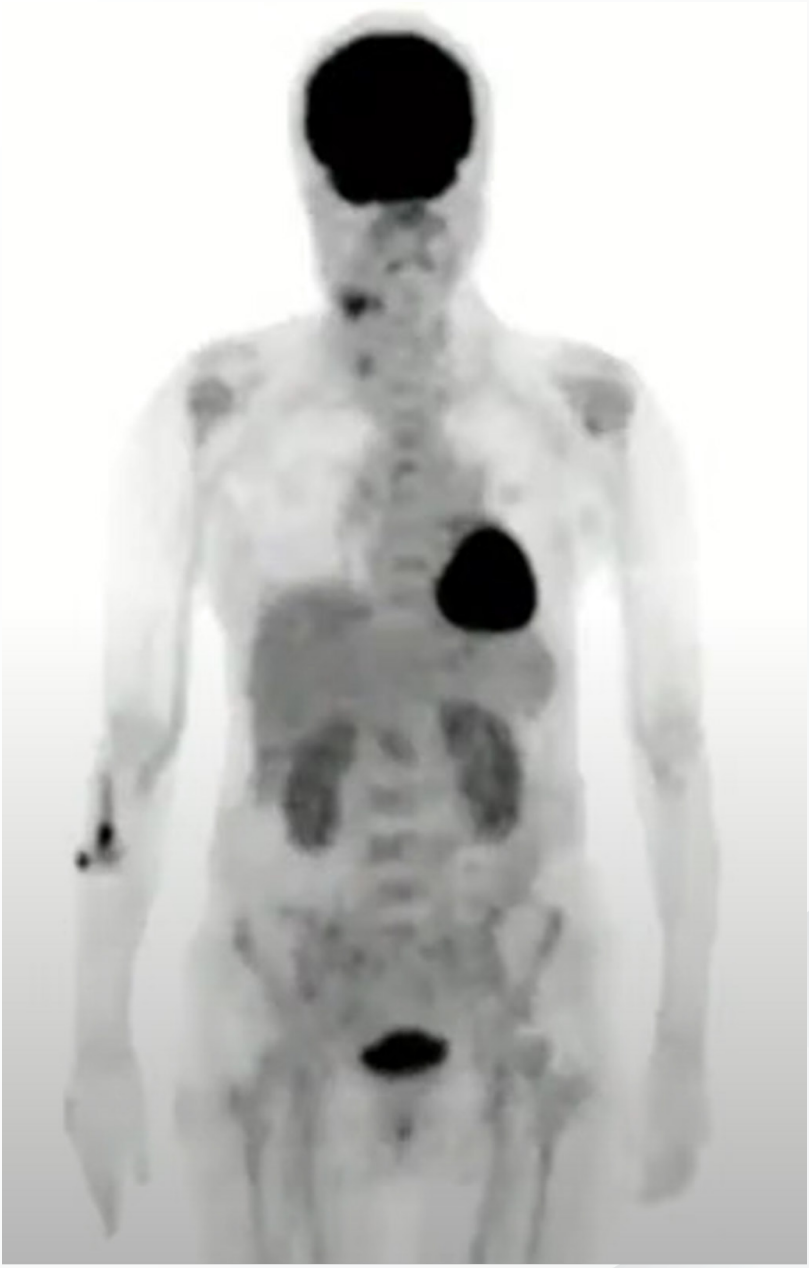

Figure 1. No significant lymphadenopathy nor organomegaly lesion.

Diagnostic process

Bone marrow examination reports

- Bone marrow biopsy: 80% cellularity with paratrabecular lymphoid infiltration. The atypical lymphoid cells display small to medium cell size, mild nuclear atypia and focal plasmacytoid feature. Immunohistochemistry (IHC) stains results: BCL2+, BCL6-, Kappa+, lambda-, Ki67 1-2%. Presentation compatible with follicular lymphoma or lymphoplasmacytic lymphoma (LPL).
- Bone marrow flow cytometry: abnormal cells of small to medium size present (2.87%). IgK+, IgL-, CD20++, CD19+++, CD5-, CD23++, CD10-, CD4-, CD8-, CD7-, CD3-, CD15-, CD34-, CD13-, HLA-DR(?), CD33-, CD64-, CD14-, CD16-, CD56-, CD71-, CD11b-, CD117-, CD38+, CD45+++.

MYD88 and *CXCR4* mutation status assessment

Not done.

Diagnosis

Combining the bone marrow pathology report (LPL), laboratory findings (monoclonal immunoglobulin [Ig] M) and clinical symptoms (anemia and acute renal failure), the diagnosis was WM.

Treatment and Clinical course

- Considering the patient's poor performance under acute renal failure status, as well as the cumulative dose of doxorubicin, 3 cycles of R-COP (rituximab-cyclophosphamide, vincristine, prednisolone) were given as 1st line therapy after 2-month recovery period.
- After R-COP treatment, the patient' s general condition including renal function improved, but IgM level increased to even higher than baseline. Hence, 3 cycles of R-CHOP (rituximab-cyclophosphamide, doxorubicine, vincristine, prednisolone) were given at acceptable doxorubicin accumulative dose.
- Complete remission (CR) was achieved after R-CHOP therapy: IgM level normalized and no more lymphoplasmacytoid cells seen in bone marrow.
- About 3 years later, WM relapsed with symptoms of anemia and increased globulin level. 4-6 cycles of BR (bendamustine, rituximab) were prescribed but discontinued after 3rd cycle due to severe urticaria and skin rash.

- After BR treatment, the IgM level normalized, and anemia resolved. Disease-free status persisted for about 7 years before the 2nd relapse.
- Since the patient was 77 years old at that time and previous adverse reactions to bendamustine, COP was used again for relapsed WM.
- The disease status remained stable during COP treatment. Zanubrutinib was initiated in August 2022 to achieve a better response.
- The patient keeps using zanubrutinib and regular follow-up till now.

Discussion

- Although this patient experienced acute renal failure and was diagnosed with WM, the causality could not be confirmed. The patient' s renal function completely recovered within 2 months after urgent hemodialysis, without using any other therapy such as steroids or anti-lymphoma agents; thus, this episode was less likely to be caused by IgM monoclonal gammopathy.
- For elder patients with anemia of unknown cause accompanying major organ damage, LPL and monoclonal gammopathy diseases should be included as possible differential diagnoses. Plasma total protein level and albumin/globulin ratio are good markers for a quick evaluation.[1]
- Once the diagnosis of WM is confirmed, International Prognostic Scoring System for WM (IPSSWM) can be used for risk evaluation. For this patient, the score would be 3 (high risk); however, her survival is much longer than the median survival of high-risk group (43.5 months).
- StiL trial demonstrated that median progression-free survival (PFS) of BR-treated patients was much longer than R-CHOP-treated group (70 vs. 28 months) for WM.[2] These survival data are very close to this patient, which means the results of StiL trial may be highly reproducible in real world.
- iNNOVATE study found ibrutinib + rituximab (IR) treated WM patients had better response rate, IgM reduction and PFS than placebo/R group.[3] ASPEN study indicated that for relapse/refractory WM, zanubrutinib had comparable efficacy, but less adverse effects than ibrutinib.[4]
- Based on Mayo Clinic Consensus for relapse/refractory WM needing treatment, both of Bruton's tyrosine kinase (BTK) inhibitors or 4-6 cycles of BR are recommended and the treatment decision should be based on patients' preference, side effects or other conditions.[1] If there is durable response from previous therapy (time-to-next therapy period > 4 years), repeating original therapy may be considered.[1] For this patient, repeating

BR may be effective; however, taking age and previous skin adverse effects into consideration, zanubrutinib may be the best choice currently.

References
01. Gertz MA., Am J Hematol. 2021;96(2):258-69.
02. Rummel MJ et al., Lancet. 2013;381(9873):1203-10.
03. Dimopoulos MA et al., N Engl J Med. 2018;378(25):2399-410.
04. Trotman J et al., Blood. 2020;136(18):2027-37.

Waldenström's Macroglobulinemia - a Patient with Hyperviscosity Syndrome

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Clinical pearls

- Plasma hyperviscosity is a rare complication of both monoclonal and polyclonal disorders associated with the elevation of immunoglobulins.
- Plasma exchange (PE) is a relatively safe treatment option for symptomatic hyperviscosity and for patients in risk of irreversible complications.
- The survival outcome of patients with Waldenström's macroglobulinemia (WM) appears to be unaffected by the development of symptomatic hyperviscosity.

Patient profile

Case presentation

- 71-year-old male patient, with history of stage IV diffuse large B cell lymphoma diagnosed in 2007, completing six cycles of rituximab plus cyclophosphamide, epirubicin, vincristine, prednisone (R-CEOP).
- This patient attended our clinic for regular follow-up. In 2021, he started to complain vertigo, several syncope episodes, and recurrent chest tightness.
- He visited cardiology clinic for evaluation; echocardiography revealed preserved global left ventricular systolic function (left ventricular ejection fraction 51%) with no evidence of pulmonary hypertension (pulmonary artery systolic pressure 26 mmHg), and 24-hour Holter results showed dominant sinus rhythm, heart rates within normal range (maximal heart rate 113 beats per minute, minimal heart rate 47 beats per minute).
- This patient also visited neurology clinic for survey, but no specific finding was reported by brain image examinations.
- In the meanwhile, progressive normocytic anemia (hemoglobin [Hb] decreasing from 14 to 9 g/dL) was noted, but no evidence of gastrointestinal bleeding was observed by endoscopy. After excluding cardiac and neurologic cause, hematologic disease related anemia was suspected to be responsible for this patient' s syncope.
- Based on laboratory data of immunoglobulin (Ig) M monoclonal gammopathy and extremely high IgM level, bone marrow biopsy was arranged to confirm the diagnosis of WM.

Non-hematological medical history

- Diabetes mellitus and dyslipidemia, under medical control

Laboratory findings

- Albumin / total protein: 4 / 10.3 (g/dL)

Image findings (whole body computed tomography [CT])

- Small para-aortic, aortocaval and retrocaval lymph nodes
- Borderline splenomegaly

Diagnostic process

Pathology reports

- Interstitial infiltration of small lymphocytes, accounting for approximate 70% of mononuclear cells.
- Positive for CD20, IgM and the myeloid cell nuclear differentiation antigen (MNDA), and negative for CD3, CD5, CD10, and IgG. Intermixed CD138 positive cells are seen, which showed kappa light chain restriction in kappa and lambda stain.
- Diagnosis: lymphoplasmacytic lymphoma (LPL).

Serum electropheresis findings

- Immunofixation electrophoresis (IFE) of serum revealed IgM kappa monoclonal gammopathy.
- IgG / IgA / IgM: 873 / 140 / 7040 (mg/dL)

MYD88 and *CXCR4* mutation status assessment

Droplet digital polymerase chain reaction (ddPCR) for bone marrow results:

- Positive for *MYD88* p.L265P
- Negative for *CXCR4* WHIM-like mutation

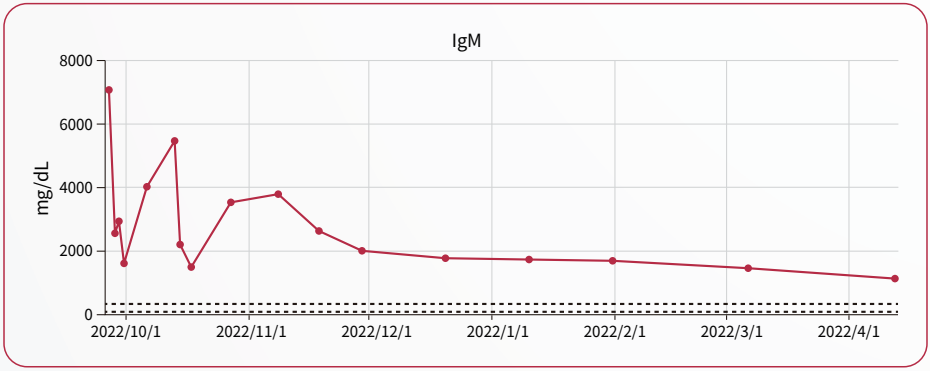
Diagnosis

Based on this patient's elder age and relatively high baseline lactate dehydrogenase (LDH) and β2 microglobulin levels, he was diagnosed with WM, revised international prognostic score for Waldenström's macroglobulinemia (rIPSSWM) 3 (high risk).

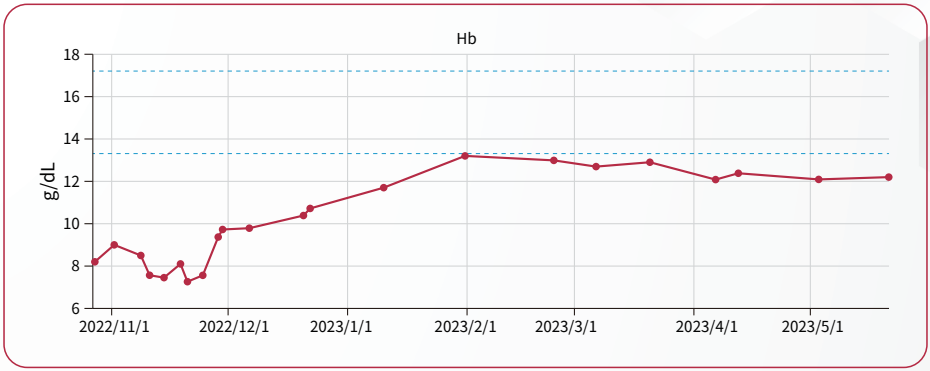
Treatment and Clinical course

- Because of this patient's high IgM level accompanying symptomatic hyperviscosity syndrome, plasma exchange was performed.
- This patient's WM was indicated for treatment owing to anemia and symptomatic hyperviscosity syndrome, so rituximab + bendamustine (BR) was initiated after plasma exchange.

Treatment assessment



- After completing the 2nd cycle of BR, his IgM gradually decreased to a steady low level.



- Following this patient's IgM level decrease, his Hb level gradually recovered to normal range.

Discussion

- Patients of WM may exhibit clinical features due to tumor growth or IgM dependent changes. In this patient, his anemia was resulted from tissue infiltration by tumor cells, and hyperviscosity syndrome caused by elevated serum concentration of monoclonal IgM.[1]
- Viscosity of a fluid is a measure of its resistance to flow based on shear stress, so large volume of serum ingredients, blood cells, and small vessel diameter would increase the resistance of blood vessels. Monoclonal gammopathy (including WM, rituximab induced IgM flare, myeloma), polyclonal gammopathy (some autoimmune or infectious diseases) and hematologic diseases associated with red or white blood cell increase, may result in hyperviscosity syndrome.
- Different structure of immunoglobulins may have impact on blood viscosity; IgG is a monomer, which is less likely to increase viscosity, and would cause symptomatic hyperviscosity at an average concentration of 9000 to 10000 mg/dL, on the other hand, as a pentamer, IgM is prone to increase viscosity at an average concentration of 5000 to 6000 mg/dL.[2]
- The symptom triad of hyperviscosity syndrome -- mucosal hemorrhage, visual disturbance, and neurologic signs, are caused by small vessel obstruction and secondary hemorrhage. Cardiovascular symptoms may also occur, like this patient.[2]
- When patients present highly specific symptoms suggesting hyperviscosity, measuring immunoglobulin and viscosity levels at first is recommended. Plasma exchange may be performed depending on risk of irreversible complications.[2]

- Based on results of univariate and multivariate model analyses, the most predictable factors for symptomatic hyperviscosity are serum viscosity and serum IgM level, instead of other clinical factors associated with tumor burden.[3]
- According to previous study, the occurrence of symptomatic hyperviscosity does not impact the overall survival for patients of WM if treated appropriately, and that may be the main reason that rIPSSWM does not include IgM level as a risk scoring factor.
- For patients with symptomatic WM, recommended treatment options include rituximab alone, rituximab-based chemotherapy, and Bruton tyrosine kinase (BTK) inhibitors. However, for patients with extremely high IgM level or suspected symptomatic hyperviscosity, rituximab alone therapy may cause IgM flare up in the first one to two treatment cycle. Thus, rituximab alone is not recommended for these patients.

References

01. Janz S. ISRN hematology, 2013, 815325.
02. Gertz MA. Blood. 2018;132(13):1379-85.
03. Abeykoon JP et al., Am J Hematol. 2018;93(11):1384-93.
04. Gertz MA. J Clin Oncol. 2022;40(23):2600-8.

Waldenström's Macroglobulinemia - a Patient with Hemolytic Anemia

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葉宗讓 醫師

Clinical pearls

- Although very uncommon, autoimmune hemolytic anemia (AIHA) caused by cold agglutinin disease can be the first clinical presentation of Waldenström macroglobulinemia (WM).
- For patients diagnosed with cold agglutinin disease, comprehensive survey should be performed to exclude underlying lymphoid malignancy, especially for older patient.
- There are many treatment options of different characteristics recommended for WM. Shared decision making may be helpful to find out the most suitable regimen for individual patient.
- A $\geq$ 90% immunoglobulin (Ig) M reduction means achieving very good partial response (VGPR) in WM, and observation until disease progression is recommended.

Patient profile

Case presentation

- 55-year-old male, with asthma and dyslipidemia history but not under regular follow-up or medication control.
- He visited chest clinic owing to dyspnea on exertion for two to three weeks. Considering his asthma history, inhaler was prescribed at first.
- However, significant anemia and indirect hyperbilirubinemia were found by laboratory tests. This patient was transferred to hematology clinic for further evaluation.
- In hematology clinic, further tests were performed, and AIHA was diagnosed. This patient was admitted to our hospital for further evaluation and treatment.
- Steroid was given for AIHA before final diagnosis concluded.
- During admission, cold agglutinin disease was confirmed, and secondary nature was suspected. Based on laboratory data, viral hepatitis and human immunodeficiency virus (HIV) infection and autoimmune disease were exclude; high immunoglobulin (Ig) M level was noticed.
- After confirming IgMκ restriction by serum immunofixation electrophoresis (IFE), bone marrow biopsy was arranged, and WM was diagnosed.

Physical examination

- No lymphadenopathy

Laboratory findings

DATE 2021/08/03	
WBC(10^3/μL)	6.03
RBC(10^6/μL)	2.34
Hgb(g/dL)	7.0
HcT(%)	21.8
MCV(fL)	93.2
MCH(pg)	29.9
MCHC(g/dL)	32.1
PLT(10^3/μL)	239
RDW-CV(%)	>18
NEUT(%)	71.6
EOSIN(%)	2.2
BASO(%)	0.3
LYMPH(%)	15.1
MONO(%)	10.8

DATE 2021/08/10	
WBC(10^3/μL)	4.13
RBC(10^6/μL)	2.46
Hgb(g/dL)	7.4
HcT(%)	24.2
MCV(fL)	98.4
MCH(pg)	30.1
MCHC(g/dL)	30.6
PLT(10^3/μL)	259
RDW-CV(%)	>18
Reticulocyte(%)	7.3
NEUT(%)	62.5
EOSIN(%)	7.5
BASO(%)	0.5
LYMPH(%)	16.2
MONO(%)	13.3

SGOT(U/L)	17
SGPT(U/L)	17
LDH(U/L)	208
Urea N(g/day)	21.6
Creatinine (mg/dL)	1.17
T-bil (mg/dL)	2.36

Figure 1-3. Laboratory data in Chest clinic (in August 2021) found hemolytic anemia.

DATE 2021/08/11	
WBC(10^3/μL)	6.03
RBC(10^6/μL)	2.34
Hgb(g/dL)	7.0
HcT(%)	21.8
MCV(fL)	93.2
MCH(pg)	29.9
MCHC(g/dL)	32.1
PLT(10^3/μL)	239
RDW-CV(%)	>18
Haptoglobin (mg/dL)	<7.0

D-Dimer (ng/mL)	6.03
Fibrinogen (mg/dL)	2.34
PTT P(sec)	7.0
PTT C(sec)	21.8
PT P(sec)	93.2
PT C(sec)	29.9
PT(INR)	32.1

AIHA survey	
Direct Antiglobulin test	Positive
Indirect antiglobulin test	Negative
Coomb's test Anti-IgG	Negative
Coomb's test Anti-C3d	Positive
Cryoglobulin	Negative
Cold agglutinin titer	2048X (+)

Figure 4-6. In hematology clinic and during admission, the diagnosis of cold agglutinin disease was confirmed.

Virus infection	
HBs Ag	Non-reactive
HBs Ab	Non-reactive
HBs IgG	Non-reactive
HCV IgG	Negative
HIV	Negative

Autoimmune titers	
Anti-CTD	< 0.03
ANA	< 1:40
C3	46.2
C4	2

Immunoglobulins		
Albumin (g/dL)	3.28	3.5~5.0
IgG (mg/dL)	894	540~1822
IgA (mg/dL)	104	63~484
IgM (mg/dL)	4500	22~240
Free κ (mg/L)	35.5	3.3~19.4
Free λ (mg/L)	10.7	5.71~26.3
K/λ	3.32	0.26~1.65

Figure 7-9. Further investigation for possible cause of secondary cold agglutinin disease showed:

- No viral hepatitis or HIV infection.
- No strong evidence of underlying autoimmune disease except mild decrease of C3, C4 level.
- High IgM level was found.

Image findings

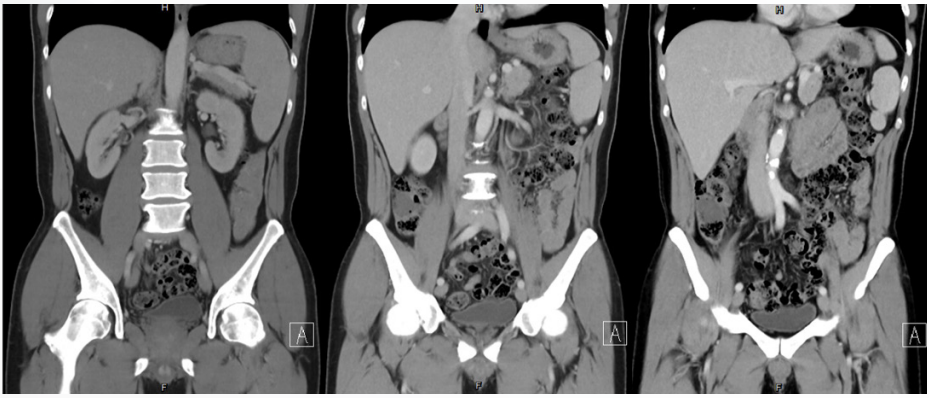


Figure 10-12. No splenomegaly or lymphadenopathy was seen on abdominal computed tomography (CT) images.

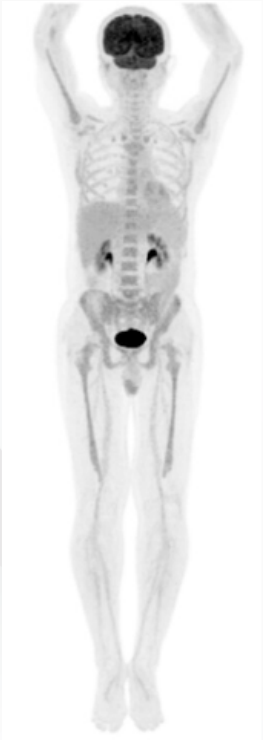
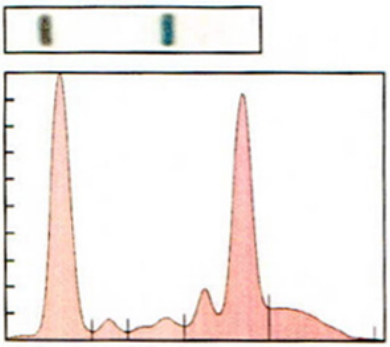


Figure 13. The positron emission tomography (PET) taken after diagnosis revealed some bone marrow uptake with no lymph node involvement.

Diagnostic process

Serum electropheresis findings

Protein electrophpresis



A/G	0.59
Albumin	37.20
Alpha 1	2.74
Alpha 2	5.13
Beta	43.78
Gamma	11.15

Immunofixation electrophpresis

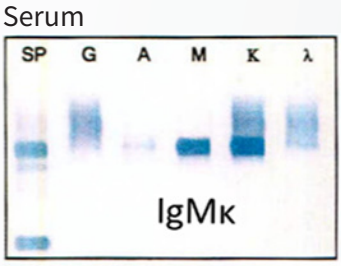


Figure 14-15. IgMκ restriction was found.

Pathology reports

- Bone marrow biopsy showed extreme hypercellularity (>95%) with diffuse infiltrates of small lymphocytes admixed with plasma cells, plasmacytoid lymphocytes and mast cells.
- Immunohistochemical stain results: the neoplastic cells are positive for CD20, CD138 and IgM, and negative for CD3, CD5, CD10, MNDA, IgG and CD34. Kappa light chain restriction was demonstrated by kappa and lambda stains.
- Diagnosis: compatible with lymphoplasmacytic lymphoma (LPL), WM.

MYD88 and *CXCR4* mutation status assessment

Not done.

Diagnosis

- AIHA, caused by cold agglutinin disease, secondary to WM.
- WM, Ann Arbor stage IV (with bone marrow involvement), diagnosed on 2021/08/17 by bone marrow biopsy, 2019 revised international prognostic score for Waldenström's macroglobulinemia (rIPSSWM) 1 (low risk).

Treatment and Clinical course

- Because this patient was not willing to receive injection chemotherapy regimen, rituximab + cyclophosphamide + dexamethasone (DRC) was chosen for treatment by shared decision making.
- Six cycles of treatment were completed between September 2021 to January 2022.
- His IgM level gradually decreased after DRC initiated, and his hemoglobin (Hb) level continuously increased from 7.2 to 13.2 g/dL during steroid and DRC treatment.
- Follow-up bone marrow biopsy done in January 2022 showed normal cellularity with no specific abnormality.
- In April 2023, there is a more than 90% IgM reduction (from 5340 to 323 mg/dL) of this patient, which means he had achieved very good partial response (VGPR) according to The National Comprehensive Cancer Network (NCCN) guideline for WM.

Treatment assessment

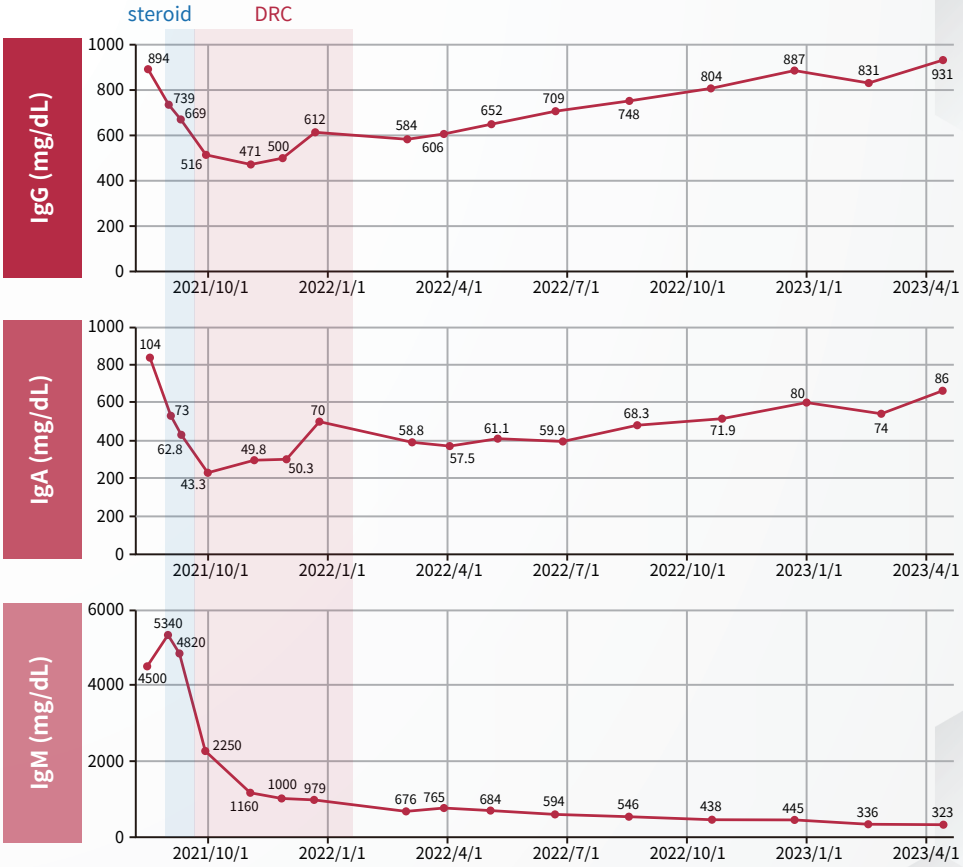


Figure 16-18. This patient's IgM level once increased while using steroid, but gradually decreased under DRC treatment. His IgG and IgA level also started to increase after treatment initiated.

Cold agglutinin titer	
2021/08/16	2048X
2021/09/09	4096X
2021/12/21	4096X
2022/01/14	256X
2022/03/01	16X

Figure 19. This patient's cold agglutinin titer significantly decreased after DRC treatment.

Treatment and Clinical course

- There are several differential diagnoses should be considered for AIHA with complement alone, including warm AIHA with subthreshold IgG deposition, cold agglutinin disease, paroxysmal cold hemoglobinuria, and drug induced AIHA. In this patient, he had no fever or other infection history before this AIHA episode, so cold agglutinin disease was highly suspected and confirmed by high cold agglutinin titer (2048X).[2]
- Cold agglutinin disease accounts for five percent of AIHA, and 90% is caused by IgM-mediated process. Cold agglutinin IgM molecules can be polyclonal or monoclonal; polyclonal antibodies are typically observed in the postinfectious setting, self-resolving and mostly in children, while monoclonal antibodies classically occur in older adults, and may be associated with an underlying lymphoproliferative disorder.[3,4]
- A cold agglutinin titer $\geq$ 64 is considered clinically significant. Cold agglutinin disease can also be classified as primary and secondary based on presence of underlying disease. In younger patients, the underlying causes of secondary cold agglutinin disease/syndrome are more likely to be infection or autoimmune disorder; in older patients, secondary cold agglutinin disease/syndrome may be associated with lymphoid malignancy, like aggressive non-Hodgkin lymphoma or WM.[3,4]
- A retrospective, multinational, observational study of 232 patients with cold agglutinin disease reported the prevalence rate of lymphoid disorder or malignancy is high: 27% for cold agglutinin disorder associated lymphoproliferative disorder, 14% for LPL/WM, 4% for marginal zone

lymphoma, 4% for small lymphocytic lymphoma, and 18% for unclassified lymphoproliferation or reactive lymphocytosis.[5] Thus, for patients diagnosed with cold agglutinin disease, comprehensive survey for underlying cause, especially lymphoid malignancy, is necessary.

- According to NCCN guidelines for WM/LPL version 1.2023, rituximab-based chemotherapy including rituximab + bemdamustine (BR), rituximab + cyclophosphamide + dexamethasone (DRC) and rituximab + bortezomib ± dexamethasone (BRD), and Bruton tyrosine kinase (BTK) inhibitors -- ibrutinib and zanubrutinib, are all recommended options of primary treatment options for WM. After discussing with this patient, DRC was chosen because of its all-oral regimen and fixed-duration characteristics.
- This patient achieved VGPR after six cycles of DRC treatment. Regarding IgM level, NCCN guideline defines complete response (CR) in WM as IgM in normal range, and disappearance of monoclonal protein by immunofixation. However, considering WM is a relatively indolent disease, observation until disease progression is recommended for patients achieving CR/VGPR after primary treatment, and second line treatment is only recommended for patients of partial/minor response with symptoms, and of no response/progressive disease.

References
01.Morel P et al., Blood. 2000;96(3):852-8.
02.ASH-SAP 2022.
03.Swiecicki PL et al., Blood. 2013;122(7):1114-21.
04.Uptodate.
05.Berentsen S et al., Blood. 2020;136(4):480-8.

Waldenström's Macroglobulinemia - a Patient with Anemia

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Clinical pearls

- Waldenström's macroglobulinemia (WM) demonstrates infiltration of the bone marrow by clonal lymphoplasmacytic cells and a monoclonal immunoglobulin (Ig) M gammopathy in the blood.
- The diagnosis of WM is based on an evaluation of a bone marrow biopsy specimen and analysis of the serum protein components.
- Treatment indications include the presence of systemic symptoms along with physical findings and/or cytopenias.
- Recommended initial therapy includes BR (bendamustine, rituximab) and Bruton tyrosine kinase (BTK) inhibitors. Choice of therapy is determined by patients' preference and safety consideration.

Patient profile

Case presentation

- 60-year-old male.
- In September 2020, this patient visited other hospital because of frequent epistaxis for a period of time, and pancytopenia was found.
- He was transferred to our hospital, and the laboratory data showed pancytopenia (white blood count [WBC] 3.51*10^3/μL with 60% lymphocytes, hemoglobin [Hb] 6.2 g/dL, and platelet [PLT] count 55*10^3/μL).
- Peripheral blood and bone marrow aspiration revealed many eccentric, plasmacytoid cells with high nucleus-to-cytoplasmic (N:C) ratio. WM was diagnosed by bone marrow biopsy.
- Based on revise International Prognostic Scoring System for WM (IPSS WM), this patient's disease stage was very low risk.[1]

Past history

- Diabetes mellitus
- Hypertension
- Hyperlipidemia

Laboratory findings

DATE	20200904	20200928
WBC (10^3/μL)	3.51	3.82
RBC (10^6/μL)	1.74	1.51
Hb (g/dL)	6.2	5.7
Hct (%)	18.5	16.1
MCV (fL)	106.3	112
PLT (10^3/μL)	55	112
BLS (%)		
PRO (%)		
MY (%)		
BAND (%)		
NEUT (%)	20.0	30.0
LYM (%)	60.0	55.0

DATE	20200917
IgG (mg/dL)	783
IgA (mg/dL)	136.1
IgM (mg/dL)	5460.0
IgG4	
Free K (mg/L)	34.9
Free L (mg/L)	18.4
Free k/L RATIO	1.90

Image findings

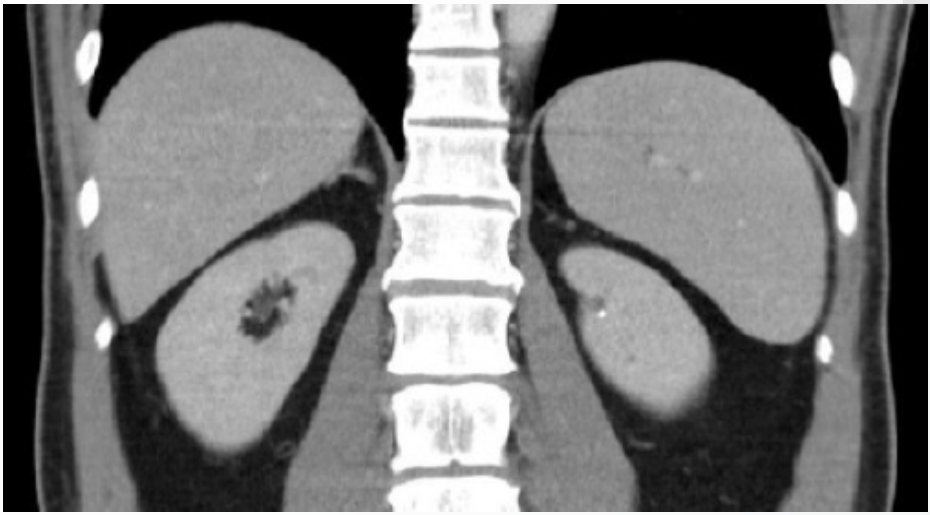


Figure 1.

- Mild splenomegaly.
- No lymphadenopathy.

Diagnostic process

Pathology reports

- CD20 (+, diffuse and more than CD 138), CD138 (+), CD117 (mildly increased mast cells infiltration), CD56 (-), cyclin D1 (-), kappa (+, more than lambda).

Serum electropheresis findings

- IgG/A/M: 783/136/5460 mg/dL, free kappa/lambda: 35/18 mg/L.
- IgM kappa monoclonal band.

MYD88 and *CXCR4* mutation status assessment

- Not done.

Treatment and Clinical course

- BR treatment was started on October 8th, 2020.
- During six cycles of BR treatment, this patient's IgM level decreased gradually, and the pancytopenia improved as well.

Treatment assessment

DATE	WBC (10^3/μL)	RBC (10^6/μL)	Hb (g/dL)	Hct (%)	MCV (fL)	PLT (10^3/μL)	BLS (%)	PRO (%)	MY (%)	BAND (%)	NEUT (%)	LYM (%)
20201007	4.91	1.28	4.5	13.3	103.9	57				1.0	13.0	81.0
20201012	1.1	1.80	6.2	18.5	102.8	120					76.0	18.0
20201014	1.15	2.18	7.3	22.0	100.9	101					72	16.0
20201016	1.12	2.49	8.8	25.6	102.8	239					78.0	12.0
20201019	1.61	2.36	8.1	24.4	103.4	255					70.0	12.0
20201021	1.64	2.28	8.1	24.1	105.7	194					66.0	14.0
20201106	2.12		9.8			224					80.3	7.5
20201123	3.13	2.98	11.5	30.9	103.7	279					54.0	32.6
20201203	2.57		11.7			229					58.0	28.4
20201216	1.64	3.18	11.4	31.8	100.0	213					60.3	16.5
20210101	2.78		11.0			301					71.9	10.8
20210118	3.56	3.14	11.2	32.7	104.1	216					77.6	5.9
20210128	4.15		11.8			309				1.0	77.0	11.0
20210210	1.11	3.25	11.7	33.0	101.5	244					40.0	24.0
20210310	4.15		12.1			249					73.0	12.0

20210317	3.36		13.2			304			83.9	4.8
20210406	3.1	3.62	12.9	36.9	101.9	145		1.0	74.0	12.0
20210526	3.92	4.36	14.7	43.2	99.1	345			72.5	15.3
20210825	5.14	4.80	15.2	44.9	93.5	183			78.0	14.0
20211020	6.49	4.77	14.7	45.8	96.0	347			75.9	14.3
20211028	6.06		14.3		96.3	235			82.0	9.9

DATE	IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)	IgG4	Free K (mg/L)	Free L (mg/L)	Free k/L RATIO
20201123	754	106.5	1858		19.9	12.8	1.55
20210129	758	94.7	888.4				
20210526	817	116.6	796.7		19	13	1.46
20210825	852	121.5	718.0		20	15.9	1.26
20211020	832	119.8	554.0		20.7	14.1	1.47
20220111	807	116.0	429.6		20.3	14.6	1.39
20220415	838	114.6	442.0		16.8	16	1.05
20220611	893	126.1	513.4		17.5	15.7	1.11
20220908	860	124.7	491.5		16.8	16	1.05
20221109	961	146.7	559.1		15.8	15.6	1.01
20230104	877	150.1	594.2		20.1	17.8	1.13

Discussion

- According to World Health Organization (WHO) criteria for lymphoplasmacytic lymphoma (LPL), WM International workshop criteria, and Mayo Clinic criteria, the key to diagnosis of WM is demonstration of bone marrow infiltration by lymphoplasmacytoid lymphocytes, accompanying IgM monoclonal gammopathy and exclusion of other small B cell neoplasms.[2-5]
- Anemia and/or cytopenia are the most common clinical presentation in symptomatic WM. The median of IgM level among WM patients is 3480 mg/dL.[6]
- WM is relatively indolent, and symptomatic disease is the indication to start treatment. Anemia (Hb $\leq$ 10 g/dL) and thrombocytopenia (PLT < $100*10^3/\mu L$)) are both laboratory indications for initiation of therapy. Thus, initiation of treatment for this patient's WM was indicated.[6]
- BR regimen showed 95% overall response rate (ORR), 69-month progression-free survival (PFS) and 90.4% 5-year overall survival (OS) rate for subjects with WM in StiL study,[7] and demonstrated better efficacy than DRC (dexamethasone, rituximab, cyclophosphamide) and BDR (bortezomib, dexamethasone, rituximab) regimens in a retrospective study.
- BTK inhibitors, including ibrutinib and zanubrutinib, are also effective for WM.[9,10] In Aspen study, compared to ibrutinib, zanubrutinib treatment achieved better, faster and longer response but with less atrial fibrillation and hypertension adverse events.[10]
- BR and BTK inhibitors $\pm$ rituximab are both recommended for treatment-naïve WM patients with bulky disease, cytopenia, or immediate IgM reduction required. Whereas BR is fixed-duration, and BTK inhibitors are continuous therapy.[6]
- In Taiwan, our National Insurance had approved BR but not BTK inhibitors as the first line therapy for WM. Choice of therapy is determined by patients' preference (cost, compliance) and safety consideration. BR was chosen as the first line therapy for this patient.
- High IgM concentration (higher than 4000 or 5000 mg/dL) tend to cause hyperviscosity syndrome, and sometimes, rituximab treatment may be followed by IgM flare up. Prophylactic plasmapheresis before rituximab usage may be indicated for patients with high IgM level. This patient did not receive plasmapheresis and his IgM level decreased significantly after the first cycle of BR treatment; however, if any symptom of hyperviscosity occurred, plasmapheresis should be performed promptly.

References
01.Kastritis E et al. Leukemia. 2019;33(11):2654-61.
02.Owen RG et al., Semin Oncol. 2003;30(2):110-5.
03.NCCN Clinical Practice Guidelines in Waldenström's Macroglobulinemia Version 1. 2023.
04.Kapoor P et al., JAMA Oncol. 2017;3(9):1257-65.
05.Kapoor P et al., JAMA Oncol. 2017;3(9):1257-65_supplement.
06.Dimopoulos MA et al., Blood. 2019;134(23): 2022-35.
07.Rummel MJ et al., Lancet. 2013;381(9873):1203-10.
08.Abeykoon JP et al., Am J Hematol. 2021;96(8):945-53.
09.Treon SP et al., N Engl J Med. 2015;372(15):1430-40.
10.Tam CS et al., Blood. 2020;136(18):2038-50.

Waldenström's Macroglobulinemia - a Patient with Pancytopenia

高雄長庚醫院
廖碧涵 醫師

Clinical pearls

- The frequency of follow-up for asymptomatic patients with Waldenström's macroglobulinemia (WM) is based on the risk classification.
- The treatment for WM should be started if clinical symptoms appear and/or immunoglobulin M level > 6000 mg/dL.
- Single rituximab therapy could be reserved for elder patients. BR (bendamustine, rituximab) and Bruton kinase inhibitor (BTK) inhibitors (ibrutinib, zanubrutinib) are both recommended primary therapies for symptomatic WM.
- Detecting *MYD88* and *CXCR4* mutation status would be helpful for prognosis prediction and treatment decision.

Patient profile

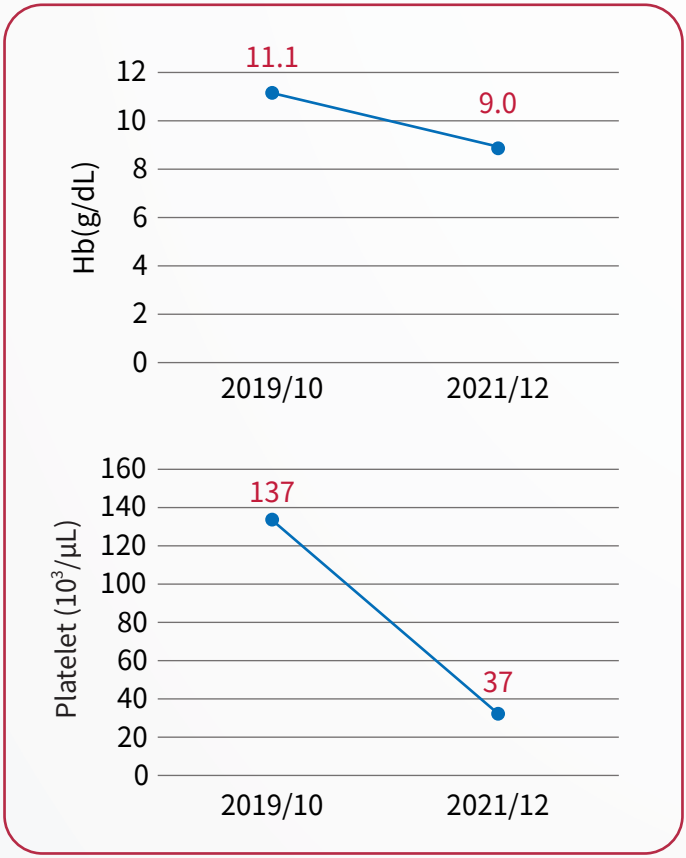
Case presentation

- 75-year-old male, referred from local hospital to our hematologic clinic.
- Chief complaint: pancytopenia found in health examination, data of 2019/6 showed hemoglobin (Hb) level 12.5 g/dL, white blood cell (WBC) counts 3.8 * 10^3/μL (segments 37%, lymphocytes 54%), platelet counts 99*10^3/μL.
- Peripheral blood smear revealed mild lymphocytosis with normal lymphocyte subset.
- No past nor current hepatitis A, B or C infection was found; abdominal echogram showed no splenomegaly.
- Under the impression of asymptomatic and mild pancytopenia without decrease of specific cell lineage, keeping observation under regular follow-up was decided in 2019/10.
- Between 2019-2021, the patient's WBC and platelet counts fluctuated, but Hb level decreased gradually from 12.5 g/dL to 9.0 g/dL.

Past history

- Hypertension
- Chronic kidney disease stage III
- Valvular heart disease

Laboratory findings



Bone marrow aspiration findings

- Hypercellularity (80%-90%).
- Lymphoid cells: 29.4% of total nuclear cells; mostly small lymphocytes with abnormal, plasmacytoid morphology.
- Normal bone marrow chromosome karyotype.

Image findings (computed tomography [CT])

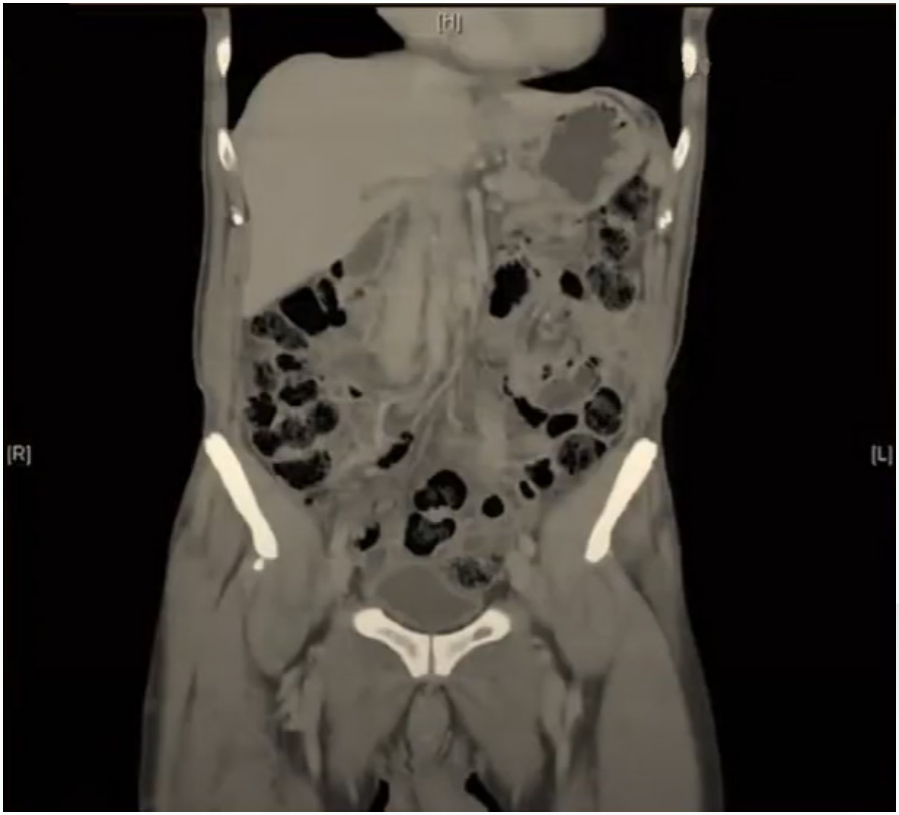


Figure 1. No organomegaly nor lymphadenopathy

Diagnostic process

Pathology reports

- Bone marrow biopsy: 95% cellularity with adequate amounts of megakaryocytes. Diffuse infiltration of small lymphocytes with clear cytoplasm. Immunohistochemistry (IHC) stains results: CD10-, CD20+, CD23-, CD3-, CD5+, cyclin D1-, Ig (immunoglobulin) D+ (focally), MNDA-, SOX11-, CD25-, CD123-, annexin A1-. Low grade B-cell leukemia/lymphoma is considered.

Protein electropheresis & immunofixation findings

M protein	2300 mg/dL
Immunofixation electrophoresis	IgM chain, Kappa light chain
IgG	570 mg/dL
IgA	28.4 mg/dL
IgM	3720 mg/dL
Free light chain Kappa	49.14 mg/L
Free light chain Lambda	11.29 mg/L
Free light chain K/L	4.35
β2-microglobulin	3324.93 ng/mL
Albumin	3.7 g/dL

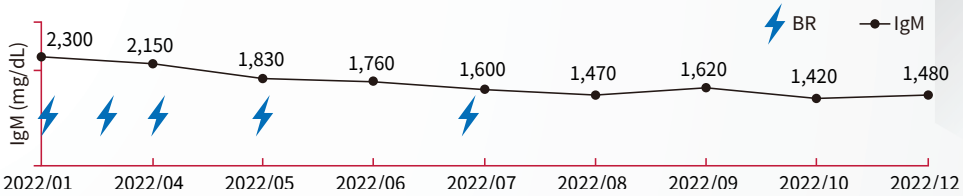
MYD88 and *CXCR4* mutation status assessment

Not done.

Diagnosis

- Based on the patient' s clinical course, pathological morphology and IHC results, and IgM monoclonal gammopathy, the diagnosis concluded was Waldenström's Macroglobulinemia (WM).
- Revised International Prognostic Scoring System for WM (R-IPSSWM) score 1 (low risk)[1].

Treatment assessment: IgM level



Discussion

- WM is usually an indolent disease with a median survival of 5-10 years. About 50% of WM patients are asymptomatic while diagnosed, just like this patient. Watchful waiting could be considered for those asymptomatic WM patients.
- Pan-B-cell antigens (CD19, CD20) and CD25, CD27, IgM together with CD22+dim are biomarkers that commonly express on WM abnormal cells. CD5 are sometimes positive. However, this patient's bone marrow biopsy results showed CD5+ but CD25-, which is atypical for WM.
- According to The National Comprehensive Cancer Network® (NCCN®) guideline for WM/lymphoplasmacytic lymphoma (LPL), calculating asymptomatic WM risk score to predict the median time to progression is recommended. Follow-up frequency should be determined based on risk classification.[2] This patient's risk score was 4.5291, and the predicted median time to progression was 1.8 years (high risk group).
- The treatment for WM should be started if clinical symptoms appear.[2] For this patient, the treatment was started mainly because of progressive pancytopenia (Hb level was below 10 g/dL before treatment).
- The first line therapies for WM recommended by NCCN guideline includes BR, VRd (bortezomib, dexamethasone, rituximab) and Bruton's tyrosine kinase (BTK) inhibitors (ibrutinib, zanubrutinib).[2] For WM with certain significant symptoms, Mayo Clinic recommends using BR x 4-6 cycles or BTK inhibitors as first line therapy; for elder patients or minor symptoms, single agent rituximab is acceptable.[3]
- One study indicated that in WM patients, BR has significantly higher major response rate (92% vs. 83%, p=0.05) and complete response rate (20% vs. 2%, p<0.001) than ibrutinib. However, the 4-year progression survival rates of those two treatments were similar (72% vs. 78%, p=0.14).[4] Thus, BR is a fixed-duration and relatively inexpensive therapy, but has similar efficacy as ibrutinib, which makes a good choice for patients who can tolerate immunochemotherapies well.R-COP for next option.

References
01. Kastritis E et al., Leukemia. 2019;33:2654-61.
02. NCCN Guideline Version 1.2023. Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma.
03. Mayo Clinic Recommendation.
04. 2022 ASCO; Abstract 7566.

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