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CASE SERIES

Two Cases of Macroglobulinemia with Elevated Serum CA125: Case Reports and Literature Review

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Abstract: Waldenström macroglobulinemia (WM) is a relatively rare hematological malignancy characterized by serum monoclonal IgM gammopathy and bone marrow infiltration of lymphoma cells (small B lymphocytes, plasmacytoid lymphocytes, or plasma cells). Elevated CA125 is most seen in ovarian cancer or some benign diseases such as pelvic inflammatory disease and endometriosis. No cases of WM combined with elevated CA125 have been reported so far. Here, we report two rare cases of WM with abnormally high CA125 at the onset of illness. Patient 1 had a nine-year history of pulmonary shadow with a moderately increased CA125 level. Subsequently, she was diagnosed with WM-related lung involvement by biopsy. Patient 2 presented with WM manifestation and a significantly elevated CA125 level of unknown significance. Based on bone marrow smear results and serum IgM levels, the diagnosis of WM was established in both patients. After rigorous physical examination, imaging screening, and pathological biopsy, any underlying disease associated with elevated CA125 in both patients was excluded. CA125 and IgM levels decreased with effective treatment for WM, suggesting that abnormally elevated CA125 was related to the progression of macroglobulinemia. Suspicious WM patients with elevated serum CA125 of unknown significance need to be alert to a special manifestation of macroglobulinemia. More clinical concern is needed. At the same time, the clinician could monitor the patient's serum CA125 level changes to assist in the judgment of the efficacy of the original disease. This report extends the understanding of WM and the application of CA125.

Keywords: macroglobulinemia, CA125, monoclonal IgM gammopathy, B-cell tumor, case report

Introduction

Waldenström macroglobulinemia (WM) is a relatively rare malignancy, accounting for 1–2% of hematological malignancies.[1] It is a mature B-cell neoplasm characterized by bone marrow infiltration of lymphoma cells and elevated serum monoclonal IgM. The diagnosis of WM should exclude other differential diagnoses for small B-cell lymphoma associated with plasma cell differentiation. Common clinical features include anemia, thrombocytopenia, hepatosplenic, lymphadenopathy, and hyperviscosity.[2]

Glycoantigen 125 (CA125) is the most used biomarker for monitoring epithelial ovarian cancer and differential diagnosis of pelvic masses. Although elevated CA125 can occur in benign or malignant diseases, including several hematological disorders, the relationship between serum CA125 level and WM progress has not been found. Here, we report two rare WM patients with elevated serum CA125 levels for the first time. The follow-up medical history of the patients highlighted the possible association between CA125 and WM.

Case Presentation

Patient 1

A 73-year-old female with shortness of breath was presented to the respiratory department of our hospital in March 2022. Blood cell count screening and peripheral blood smear showed rouleau erythrocytes, with 8% of abnormal lymphocytes.

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Reflex tests were ordered for immuno-proliferative disease. Immunofixed electrophoresis reported IgM-λ monoclonal immunoglobulin. Bone marrow smear showed a 2% infiltration of lytic plasma cells (shown in Figure 1A). Then, the patient was admitted to the hematology ward because of suspected WM. She had a nine-year history of pulmonary shadow. And three years ago, on physical examination, she was found to have abnormally elevated serum CA125 [Reference range (RI): ≤35U/mL]. Ultrasound found moderate to high echogenicity in the uterine cavity and suspected uterine fibroids. Hysteroscopic diagnostic scraping was performed in March 2021, and postoperative pathology suggested endometrial mesenchymal-like tissue. No further treatment was followed (shown in Figure 2A).

Relevant examinations were performed after admission, and the results are shown in Table 1. Bone marrow smear showed a 6% infiltration of lytic plasma cells. A bone marrow biopsy showed no significant abnormalities. Bone marrow immunophenotyping revealed an abnormal phenotype of B cells (shown in Table 1). Lymphoproliferative disease (LPD) mutation gene screening revealed no abnormal mutations in the MYD88 L265P or CXCR4 S338X genes. Fluorescence in situ hybridization (FISH) testing for multiple myeloma (MM) was not abnormal. PET-CT did not show other sites of involvement, and the patient had no associated clinical manifestations, so MM and other B-LPD could be largely ruled out.

Meeting all significant criteria (bone marrow infiltration of lymphoma cells, serum monoclonal IgM elevation, exclusion of other lymphomas), the diagnosis of WM was established. To identify the nature of lung shadow, the patient underwent a CT-guided percutaneous puncture lung tissue biopsy in April 2022. Lung puncture pathology revealed highly proliferative lymphoid tissue with small to medium-sized lymphocytes and a few additional scattered plasma-like cells. Combined with the immunohistochemical findings [Bcl-2 (+), Bcl-6 (scattered +), CD3 (partial +), CD5 (partial +), CD10 (-), CD20 (+), CD21 (+), CD23 (-), Cyclin D1 (scattered +), Ki-67 (index 25%), SOX11 (-), CD19 (+), CD38 (partial +)], the patient's lung shadowing was consistent with inert small B-cell lymphoma. PET-CT results returned multiple uptake-enhancing solid shadows in both lungs, and hematologic involvement was considered. Combined with the above findings, WM-related lung involvement was confirmed.

In May 2022, patient 1 started chemotherapy with the DRC (dexamethasone, rituximab, cyclophosphamide) regimen for three courses. The patient was intolerant to cyclophosphamide with persistent nausea and vomiting, so she was changed to the RB chemotherapy (rituximab, bendamustine) regimen. After four courses of treatment, both IgM and CA125 levels decreased significantly (shown in Figure 3A), and a repeat chest CT showed a significant reduction in the solid shadow in the lungs (shown in Figure 4). Long-term follow-up was maintained in the outpatient department.

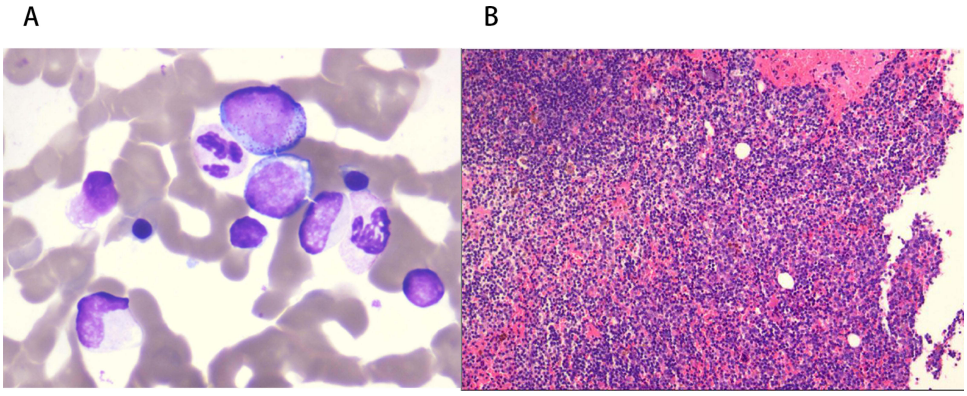

Figure 1 Picture of the patient's bone marrow smear or biopsy. (**A**): The bone marrow smear of patient 1. Under high magnification, these lymphoid plasma cells are small and irregularly shaped; the nucleus is round, lymphatic, and eccentric; the cytoplasm is abundant and dark grey-blue (Wright-Giemsa stain. Magnification×400). (**B**): The bone marrow biopsy of patient 2. Under low magnification, lamellar lymphocyte infiltration is seen (Wright-Giemsa stain. Magnification×100).

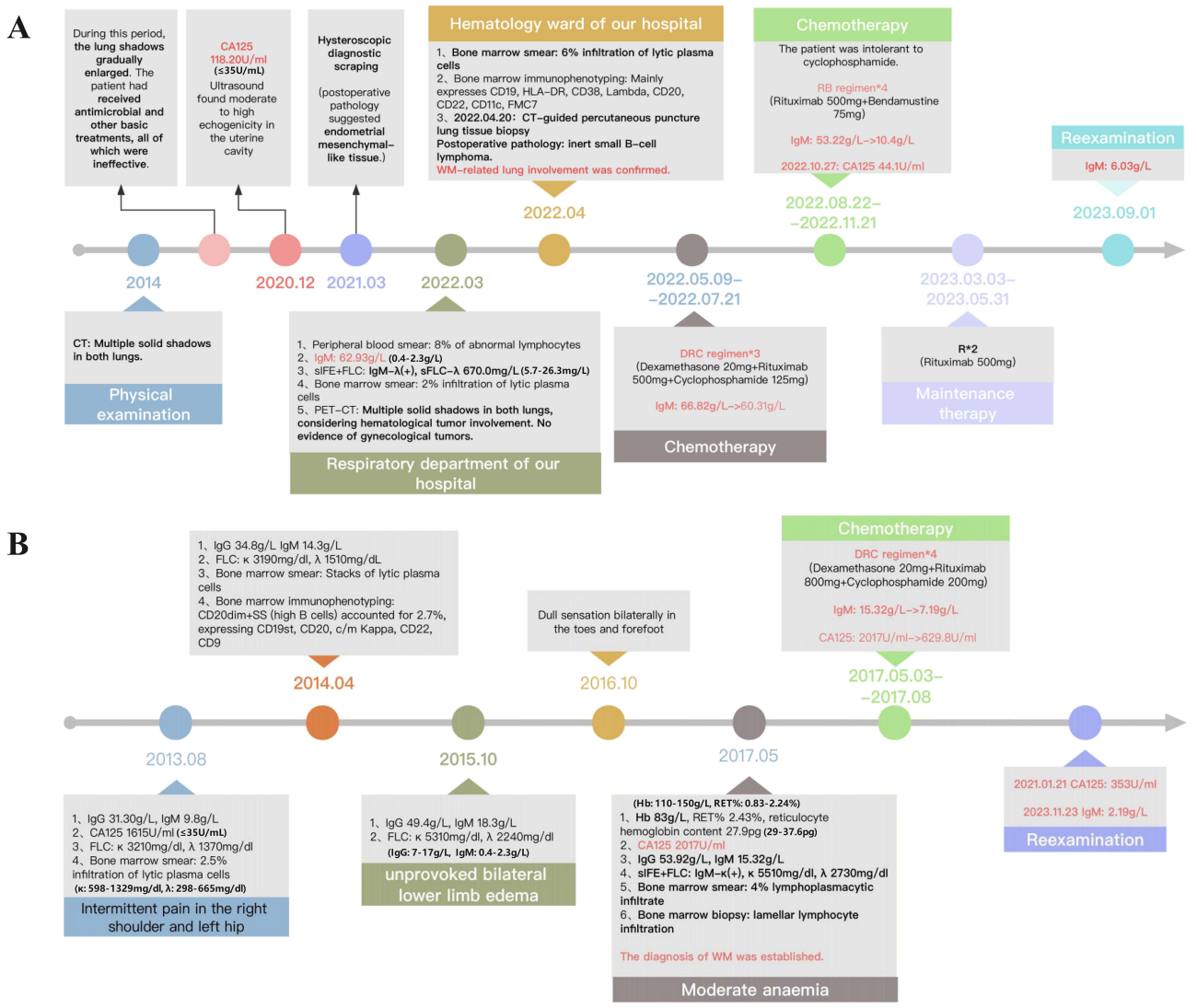

Figure 2 Timeline of patient progression. (**A**): Timeline of patient 1; (**B**): Timeline of patient 2. Reference ranges for each test are in parentheses.
Abbreviations: CT, Computed Tomography; sIFE, serum immunofixation electrophoresis FLC, free light chain; sFLC-λ, serum free light chain of type λ; λ, serum free light chain of type λ; κ, serum free light chain of type κ; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IgM-λ, IgM λ-type M protein; IgM-κ, IgM κ-type M protein; CA125, glycoantigen 125; Hb, hemoglobin; RET%, percentage of reticulocytes; DRC, dexamethasone+rituximab+cyclophosphamide; RB, rituximab+bendamustine; R, rituximab; WM, Waldenström macroglobulinemia.

Patient 2

A 69-year-old male with anemia visited the hematology department in May 2017. In August 2013, he had intermittent pain in the right shoulder and left hip. An outpatient examination at an outside hospital found serum immunofixation was positive for IgM-κ M protein. Quantifying serum protein gave IgG 31.3g/L (RI: 7–17g/L), IgM 9.8g/L (RI: 0.4–2.3g/L), κ light chain 3210mg/dl (RI: 598–1329mg/dl), and λ light chain 1370mg/dl (RI: 298–665mg/dl). Outpatient tracing of the fusion gene (RT-PCR) returned a positive result for the L265P mutant phenotype of the MYD88 gene. Outpatient consideration of possible macroglobulinemia. The patient's right shoulder and left hip pain did not progress after that and was not treated. Two years later, he presented with unprovoked bilateral lower limb edema, light in the morning and heavy in the evening, which was not treated. Then, he developed a dull sensation bilaterally in the toes and forefoot one year before admission (shown in Figure 2B). During these years, he had elevated serum CA125 in several physical examinations [1615U/mL-2017U/mL (RI: ≤35U/mL)].

Table 1 Characteristics of Patients with WM Time of Onset

Characteristic	Patient 1	Patient 2
Demographic		
Age	73	69
Gender	Female	Male
First presentation	Pulmonary shadow	Intermittent pain in the right shoulder and left hip
CA125 (≤35U/mL)	135.0	2017.0
β2-microglobulin (0.7–1.8mg/L)	3.7	4.46
LDH (0–250U/L)	194	114
Serum albumin (35–52g/L)	34	29
Whole blood cell analysis		
WBC (3.5–9.5×10^9/L)	5.75	6.76
LY% (20–40%)	41.0	37.2
NEUT% (50–75%)	38.4	43.9
MONO% (3–8%)	4.7	13.9
HGB (110–150g/L)	112	83
PLT (100–350×10^9/L)	271	257
Monoclonal gammopathy		
IgM (0.4–2.3g/L)	62.93	15.32
Type of M protein	IgM–λ	IgM–κ
sFLC–λ (5.7–26.3mg/L)	670.0	2730
sFLC–κ (3.3–19.6mg/L)	10.1	5510
sFLC–κ/λ (0.26–1.65)	0.015	2.018
Bone marrow smear/biopsy	6% lymph-plasma cell infiltration seen in bone marrow	Lamellar lymphocyte infiltration seen in bone marrow
Immunophenotype	Mainly expresses CD19, HLA-DR, CD38,Lambda, CD20,CD22,CD11c,FMC7	CD20dim+SS (high B cells) accounted for 2.7%, expressing CD19st, CD20, c/m Kappa, CD22, CD9
MYD88 L265P mutation	Wild type	Wild type
PET-CT	No other lesions were detected	Nodule in the lower lobe of the left lung, a possible benign lesion
Lung lesions	Inert small B cell lymphoma	Nodule in the lower lobe of the left lung
Anemia	No	Yes
Peripheral neuropathy	No	Yes
Others	Hysteromyoma	Bilateral lower limb edema

Note: Reference ranges for each test are in parentheses.
Abbreviations: CA125, glycoantigen 125; LDH, lactate dehydrogenase; WBC, white blood cell; LY%, percentage of lymphocytes; NEUT%, percentage of neutrophils; MONO%, percentage of monocytes; HGB, hemoglobin; PLT, platelet; IgM, Immunoglobulin M; sFLC-λ, serum free light chain of type λ; sFLC-κ, serum free light chain of type κ; sFLC-κ/λ, serum free light chain ratio.

Relevant examinations were performed after admission; the results are shown in Table 1. PET-CT suggested increased central bone marrow metabolism; no lymph node enlargement or extranodal lesions were seen. Bone marrow smear showed a 4% lymphoplasmacytic infiltrate. Bone marrow biopsy shows lamellar lymphocyte infiltration (shown in Figure 1B). The immunohistochemistry revealed CD20 (+), CD79α (+), CD23 (+), CD56(NK-1) (-), CD5 (-), Cyclin D1 (scattered+), CD15 (partial+), MPO (partial+), CD235a (partial+), Ki-67 (index 40%), CD3 (partial+), CD38 (partial+), CD138 (partial+), Bcl-2 (+). In conjunction with the patient's history and immunohistochemistry results, the physician

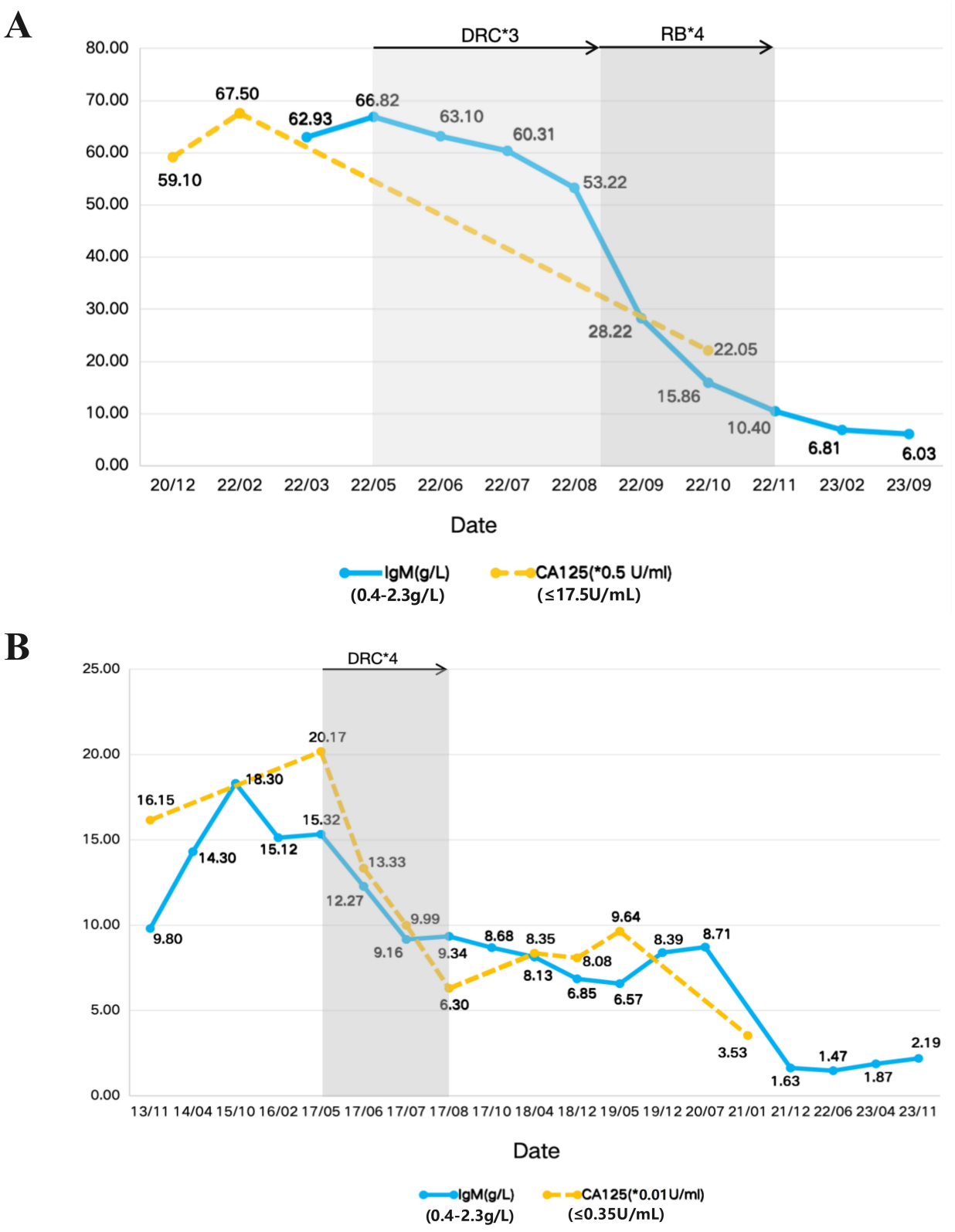

Figure 3 Response to treatment in two patients. (**A**) Treatment response of patient 1; (**B**) Treatment response of patient 2. * is a multiplication sign. Reference ranges for each test are in parentheses.

Abbreviations: IgM, Immunoglobulin M; CA125, glycoantigen 125; DRC, dexamethasone+rituximab+cyclophosphamide; RB, rituximab+bendamustine.

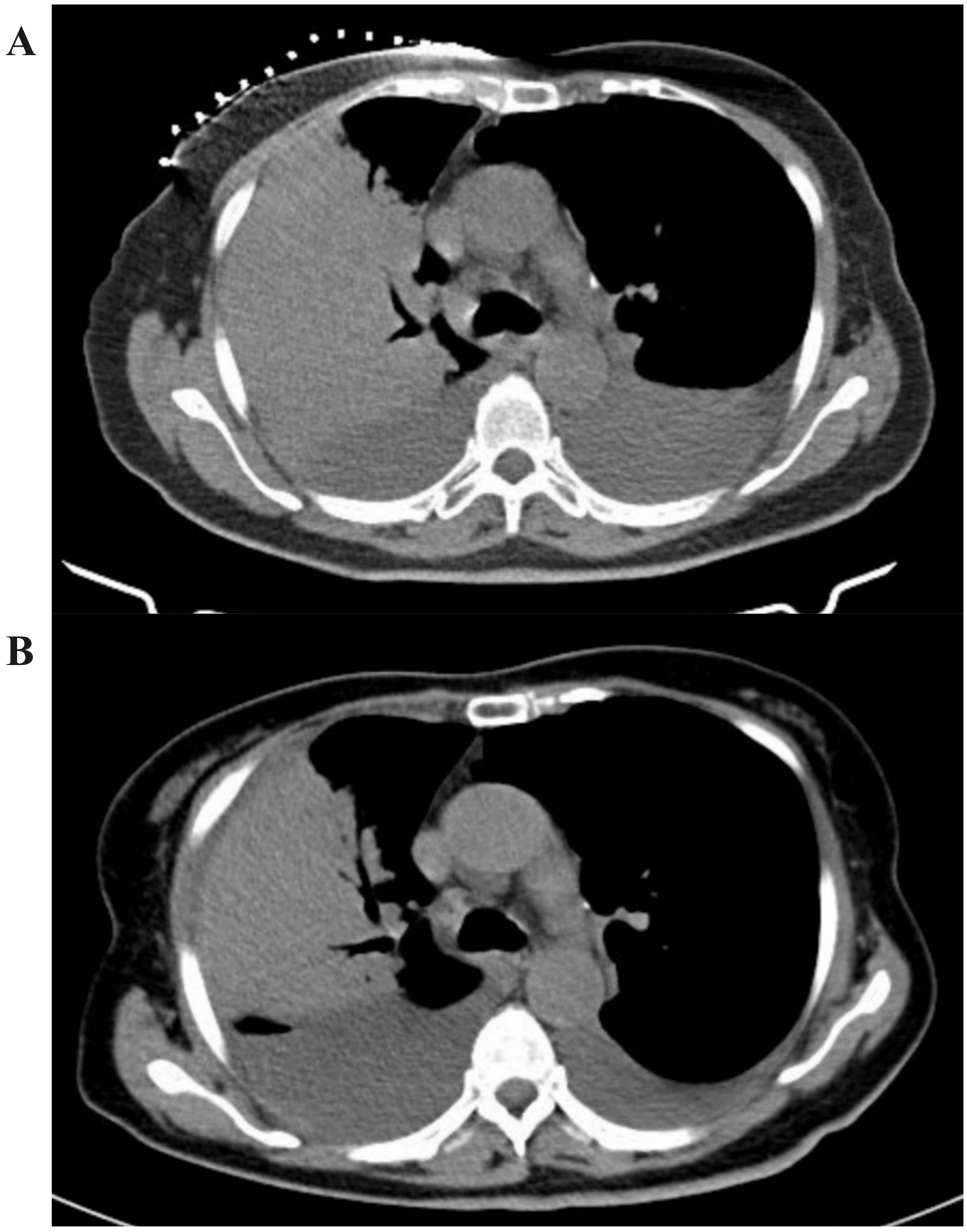

Figure 4 Enhanced CT scans of patient 1. (**A**) Before treatment; (**B**) After treatment.

considered lymphoplasmacytic lymphoma involving the bone marrow. Bone marrow immunophenotyping revealed an abnormal phenotype of B cells (shown in Table 1). Post-hospitalization review of bone marrow DNA sequencing was negative for MYD88 L265P and CXCR4 S338X mutations (shown in Table 1). No IgH (14q32) recombination and other abnormal signals were seen in the bone marrow FISH test.

Serum immunofixation electrophoresis confirmed the presence of monoclonal IgM in the peripheral blood, bone marrow biopsy showed lymphoplasmacytic infiltration, and bone marrow immunophenotyping was an abnormal B-cell phenotype. The patient's medical history was positive for a mutation in the MYD88 L265P gene. After ruling out MM and other diseases based on the clinical presentation and FISH test results, the clinician determined that the patient had a definitive diagnosis of WM. On May 13, 2019, he started chemotherapy with the DRC regimen. After four cycles of chemotherapy, serum CA125 and IgM levels were significantly reduced (shown in Figure 3B). The patient was followed up in the outpatient department after discharge.

Discussion

WM is a B-cell tumor characterized by a bone marrow lymphoplasmacytic infiltrate and elevated monoclonal immunoglobulin M (IgM). Males account for approximately 55–70% of all patients. Most patients' median age of onset is between 63 and 68 years.[3] The main diagnostic criteria for WM include the presence of monoclonal IgM in the serum, invasion of lymphoma cells in the bone marrow (regardless of number), and exclusion of other types of lymphoma. The two patients in this paper met all primary criteria of WM.

The most common clinical manifestation of WM is fatigue due to anemia, and progressive anemia is the common indication for starting treatment. Relatively rare manifestations include hyperviscosity syndrome[4] and peripheral neuropathy related to elevated levels of IgM.[5] However, most patients with WM present with non-specific systemic symptoms, and up to a quarter of patients may be asymptomatic at diagnosis. Patient 2 has anemia, skeletal pain, and peripheral neuropathy at admission, while Patient 1 has neither.

After rigorous physical examination, imaging screening, and pathological biopsy, any underlying condition associated with elevated CA125 in both patients was excluded. CA125 and IgM levels decreased with effective treatment, suggesting that abnormally elevated CA125 was related to the progression of macroglobulinemia (shown in Figure 3).

Asymptomatic WM patients with a combination of solid occupation from other sites, such as patient 1, are more likely to be missed or misdiagnosed. Patient 1 was found to have solid shadows in the lung in 2014. However, the definitive diagnosis and treatment have been delayed until 2022. Failure to make an early diagnosis and treatment resulted in progressive enlargement of the lung shadow. During this time, the patient had been treated symptomatically, such as antimicrobial for pulmonary shadowing, with poor results. After targeted chemotherapy in 2022, the solid shadows in the lungs shrank significantly (shown in Figure 4). Patients with an asymptomatic onset, like Patient 1 in this article, are highly susceptible to underdiagnosis. For these patients, abnormally elevated CA125 on physical examination can prompt the clinicians to conduct further tumor screening and reduce the probability of missing the diagnosis. This suggests to the clinicians that when a patient presents with a solid mass in the lung that is not responding well to treatment, other possibilities, like hematological disorders, should be considered.

Patient 2 was diagnosed with typical macroglobulinemia symptoms, while abnormally high results of CA125 were suspected as false positives. Various methods, including serial dilution, other reagents, polyethylene glycol PEG6000, heterophilic antibody blocking reagent, and Protein A/G agarose sedimentation, were all used to treat the samples to identify potential interference. The results of CA125 were proved truly high and excluded laboratory errors. Along with the effective treatment, the level of CA125 gradually decreased.[6] It is a rare case in WM, and we directed our attention to the relationship between WM and CA125.

Glycoantigen 125 (CA125), also known as tumor antigen 125 or mucin 16 (MUC16), is a mucin-type glycoprotein produced by the MUC16 gene. Elevated CA125 is most seen in epithelial ovarian cancer and can also be elevated in cervical, endometrial, liver, lung, and pancreatic cancers. In addition, elevated CA125 may be observed in physiological conditions (eg, menstruation, pregnancy) or benign diseases (eg, endometriosis, pelvic inflammatory disease, inflammatory peritoneal disease).[7]

The literature on the association of CA125 and WM is minimal. Only a few cases of hematological diseases with abnormally elevated CA125 have been reported, including multiple myeloma (MM), plasma cell disease, and plasma cell lymphoma. However, no cases of WM combined with elevated CA125 have been reported so far. The literature review of all cases is listed in Table 2. All four patients with MM started with bone pain, a common symptom of multiple myeloma.[8–11] The remaining five patients started with systemic symptoms common to malignancy, such as fever and weight loss.[12–15] Of the nine patients reported in the literature and the two mentioned in this article, nine were from the Asian region. That may be due to the more widespread clinical use of tumor markers in Asia. In all the cases, CA125 decreased significantly after combined chemotherapy.

The impact of high levels of CA125 on the prognosis of patients with hematological disorders has few reports. Russo et al investigated 221 newly diagnosed adult Hodgkin lymphoma (HL) patients with high CA125. They found that abnormally elevated CA125 significantly shortened the HL patients' event-free survival (EFS) and overall survival (OS) rates after long-term follow-up.[16] Due to the limited number of cases, the role of abnormally elevated CA125 on the

Table 2 Literature Review Profile Checklist

The Year of Publication	Country	Age	Gender	Previous history	Symptom Before Diagnosis	Diagnosis	Tumor Markers	Chemotherapy Regimens	Therapy Response
Case 1 2010	China	73	Male	NA	Lumbago	Light chain MM	CA125: 548.1μg/L	MP+Thalidomide +Ibandronate*5	CA125 ↓
Case 2 2009	China	53	Male	NA	Back pain	IgE MM	CA125: 1292.3U/mL	VAD*1+DVD/4w*7	IgE ↓ 、CA125 ↓
Case 3 2016	United States	55	Female	History of localized cervical cancer; post hysterectomy	Back pain	IgG-κ MM; pelvis plasmacytoma	CA125: 500U/mL	DTPACE	CA125 ↓
Case 4 2008	Spain	73	Female	Hypertension	Bone pain in the right coxofemoral area	IgG-λ MM; secondary plasma cell leukemia with liver metastases	CA125: 361U/mL CA15-3: 2205U/mL	CTX+DXMS	CA125 ↓ 、CA15-3 ↓
Case 5 1997	Japan	63	Female	NA	Weight loss, fever, generalized lymphadenopathy	IgG-λ type extramedullary plasmacytoma	CA125: 8710U/mL	VCR+MP+CTX	CA125 ↓ 、IgG ↓
Case 6 1997	Japan	73	Male	NA	Lumbago	IgG-λ type plasma cell leukemia	CA125: 3895U/mL	MCNU+CHOP	IgG ↓ 、CA125 ↓
Case 7 2005	China	53	Male	NA	Persistent high fever	Malignant lymphoma	CA125: 1686U/mL	CHOP	CA125 ↓
Case 8 1997	Japan	53	Male	NA	High fever, malaise, weight loss	Ki-1 anaplastic large cell lymphoma	CA125: 3090U/mL	CHOP	CA125 ↓、IL-6 ↓、LDH ↓
Case 9 1994	Kingdom of Saud Arabia	69	Female	NA	Pyrexiamediastinal mass	Ki-1 anaplastic large cell lymphoma	CA125: 4657U/mL	CTX +doxorubicin +VCR+PED	CA125 ↓ 、LDH ↓

Note: NA: No previous history ↓: Decrease in the levels of test indicators +: combination therapy *: multiplication sign.

Abbreviations: MM, multiple melasma; IgE, Immunoglobulin E; IgG, Immunoglobulin G; IgG-κ, IgG κ-type M protein; IgG-λ, IgG λ-type M protein; CA125, glycoantigen 125; CA15-3, cancer antigen 15–3; IL-6, Interleukin-6; LDH, lactate dehydrogenase; DTPACE, dexamethasone+thalidomide+cisplatin+doxorubicin+cyclophosphamide+etoposide; MP, melphalan+ prednisone; VAD, vincristine+ adriamycin+ dexamethasone; DVD, liposomal doxorubicin+ vincristine+ dexamethasone; CHOP, cyclophosphamide+ adriamycin+ vincristine+ prednisone; MCNU, ranimustine; CTX, cyclophosphamide; DXMS, dexamethasone; PED, prednisone; VCR, vincristine.

prognosis of WM patients is unclear. WM is an inert disease with relatively slow disease progression. Most patients have a median survival of up to 10 years.[17] In this report, patient 1 had a nine-year interval between the discovery of pulmonary infiltration and the definitive diagnosis of WM. Patient 2 was diagnosed with WM in 2013 and has survived for ten years. Both patients achieved a median survival of 10 years, suggesting that WM with elevated serum CA125 did not significantly affect the OS of WM patients.

The exact mechanism of CA125 elevation in hematological disorders is unknown. One theory postulates that abnormally elevated serum CA125 is secreted by the tumor cells.[10,12,18] Another theory proposes that cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) secreted by lymphoma cells may lead to CA125 secretion by mesothelial cells, resulting in an abnormal increase in serum CA125.[19] More cases need to accumulate to explore the mechanism of CA125 in the progress of macroglobulinemia.

Conclusion

In conclusion, we report two rare cases of patients with WM combined with abnormally elevated CA125. This provides a clue to clinicians that when patients present with abnormally elevated serum CA125, they could be alerted to the possibility of hematologic diseases in addition to screening for solid tumors. At the same time, the clinician could also monitor the changes in the patient's serum CA125 level to assist in determining the efficacy of the treatment. Close collaboration between laboratory physicians and clinicians plays an essential role in diagnosing rare phenotypes of rare diseases.

Data Sharing Statement

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Consent for Publication

The Ethics Committee of Peking Union Medical College Hospital approved this study and the publication of case details under approval number K6200. Informed consent was obtained from both patients for publication of this case report and any accompanying images.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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