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CASE REPORT

A Case of Waldenström's Macroglobulinemia Detected by the "Negative Creatinine" Alarm of Biochemical Results

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SUMMARY

Background: **Test results and outliers are of great significance to disease diagnosis, especially in some inconspicuous hematological diseases. This report presents a case of Waldenström's macroglobulinemia diagnosed following abnormal biochemical test results.**
Methods: **The laboratory of our hospital conducted a review of the patient's specimen due to a negative creatinine value, despite normal reagents, quality controls, and instrument status. It was found that the specimen was non-lipemic, but it became turbid immediately after the addition of distilled water. Subsequent tests were carried out based on multiple abnormal findings. Biochemical tests were additionally performed, including blood immunoglobulin and serum protein electrophoresis. The presence of serum M protein was detected.**
Results: **The diagnosis of Waldenström's macroglobulinemia was confirmed through consultation between the clinical physician and the laboratory physician.**
Conclusions: **In clinical practice, it is not uncommon for test results to be abnormal. The role of laboratory workers is to quickly and accurately identify the causes of these abnormalities, so that clinicians can promptly diagnose patients and proceed with subsequent treatments.**
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KEYWORDS

Waldenström's macroglobulinemia, B-cell non-Hodgkin's lymphoma, hyper-IgM syndrom, immune system hypoplasia

INTRODUCTION

B-cell non-Hodgkin's lymphoma (B-NHL) refers to a group of malignant tumors originating from B lymphocytes in the lymphatic system. Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia, LPL/WM, is a rare indolent mature B-cell lymphoma that accounts for less than 2% of non-Hodgkin's lymphomas. LPL/WM is characterized by the presence of lymphoplasmacytic infiltration of the bone marrow and lymph nodes, as well as hyper-IgM syndrom caused by abnormally high levels of IgM, which can lead to increased

blood viscosity, which may in turn lead to poor blood flow. This high level of IgM leads to increased blood viscosity, which may lead to poor blood flow. In addition, patients may exhibit fatigue, weight loss, easy bleeding, visual disturbances, and neurological symptoms. The pathogenesis of LPL/WM is complex and involves the interaction of multiple signaling pathways and molecular events. It mainly includes: MYD88 mutation, CXCR4 mutation, and immunoglobulin heavy chain abnormality. Genetic mutations, environmental factors, poor lifestyle, and immune system hypofunction can affect the development of LPL/WM. However, it is worth noting that LPL/WM has no specific morphological, immunophenotypic, and genetic alterations, so the diagnosis of LPL/WM is an exclusive diagnosis, which needs to be closely combined with the clinical manifestations and pathological findings for comprehensive diagnosis. This article reports an adult case of Waldenström's macroglobulinemia found due to abnormal testing. After being admitted to our hospital, the patient achieved a better clinical outcome, and the diagnostic and therapeutic process of the patient is now reported as follows.

CASE PRESENTATION

Clinical information

The patient, male, 76 years old, was admitted to the hospital with back pain and limitation of movement caused by a fall on the previous day. During the illness, the patient was clear and poorly refreshed, with a fair diet and sleep. There was no nausea, vomiting, dizziness, headache, or syncope. Urination and defecation were normal, and there had been no significant change in weight recently. Self-medication during the self-reported period, a specific effect that is ominous. Past medical history: history of hypertension for 12 years, usually taking Baxin Tong, the effect is ominous. He denied hepatitis B, hepatitis C and other liver diseases, tuberculosis, coronary heart disease, diabetes mellitus, and was admitted to the emergency department of our hospital in October 2022 due to fatigue for 3 days with fever for one day, and then transferred to the respiratory department for treatment of pneumonia, with the specific course of treatment unknown.

Diagnosis and treatment on the day of admission

The results of the radiological X-ray were lumbar spondylolisthesis, lumbar 1 vertebral instability, and compression changes in the thoracic 11, 12 lumbar 1 vertebral compressive changes, no nausea, vomiting, headache, etc., with “lumbago” as the diagnosis of spinal surgery. The biochemical results of the routine renal function examination revealed a negative creatinine value of -134.9/μmol/L, suggesting that attention should be paid to the investigation of the technical reasons and the status of the specimen. Albumin 25.1 g/L↓, globulin 57.3 g/L↑, inverted ratio of albumin and globulin; glucose 11.4 mmol/L↑; potassium 3.39 mmol/L↓; urea 13.26 mmol/L↑, eGRF 52.35 mL/minute↓, cystatin C 1.43 mg/L↑, creatinine 89.2 μmol/L↑. Hemoglobin 111 g/L↓, eryth-rocyte count 3.17 x 10^{12}/L↓, erythrocyte pressure volume 0.299 L/L↓; mean hemoglobin volume 35.0 pg and concentration 371 g/L↑, C-reactive protein 188.45 mg/L↑ and high sensitivity C-reactive protein concentration > 10.00 mg/L↑. CT examination of the vertebral body showed a compression fracture, lumbar vertebral anterior protrusion enlarged, and the spinal canal was narrowed. Stenosis, with lumbar disc herniation, lumbar osteoporosis, and vertebral marginal osteophytes.

Based on the above laboratory results, the negative creatinine value caught the attention of the examiner, so the examiner dealt with this anomaly by first immediately checking the reagents, quality control, and instrument status to make sure they were all normal. Subsequently, the normal response curve comparison, add the sample and R1 reagent absorbance is very high, add R2 reagent after the reaction of the absorbance is not as high as before, the difference in absorbance is negative, resulting in negative results, similar to the reaction curve of the lipohematocrit specimen. The original state of the specimen was checked, and it was found that the serum appearance of the specimen was normal, with no abnormalities such as lipemia, hemolysis, or jaundice etc. In addition, it was found that creatinine had not been detected in 2021 when he visited our hospital by inquiring about his medical history. After adding distilled water to the specimen, it was found that the specimen immediately became very turbid, and the same turbidity occurred when the creatinine test reagent was replaced, so the specimen was immediately taken to a dry chemistry instrument to test for normal creatinine. In addition to the above results, the examiner also found several abnormal values, specific manifestations, such as: biochemical liver function albumin level decreased, globulin abnormally high, the proportion of albumin inverted, while the liver function of several other indicators is normal, the blood calcium is also abnormally high. Examiner thus raised questions, the elderly hypercalcemia is due to enhanced osteolysis caused by the rest of some indicators of abnormal liver function, to exclude the impaired, and what may be the cause? In response to various questions, the examiner first checked the routine blood indicators, found hemoglobin 111 g/L and red blood cell count of 3.17 * 10^{12}/L are reduced, suggesting mild anemia, blood smear red blood cell cord-like arrangement, hyperviscosity. In response to this abnormality, biochemistry was added to blood specific protein, serum immunoglobulin IgM was up to 40.5 g/L, IgG was slightly reduced, IgA was normal, and then serum protein electrophoresis was carried out. It was observed that there was an abnormal increase of immunoglobulin M, abnormal increase of γ-globulin, and high sharpness of γ-region zone of serum protein electrophoresis (Figure 1). Immunofixation electrophoresis was also performed, and the electrophoretic typing

was monoclonal IgM-Kappa type.
The clinician was immediately contacted to inform him of the findings in the current laboratory tests as well as the precipitation that immediately appeared when the patient's serum was dropped into a test tube of distilled water, consulted the patient about the test as it was found to be a rapid screening test for macroglobulinemia, and recommended that the hematologist be contacted for a consultation and refinement of the relevant laboratory tests. The relevant laboratory tests were as follows: laboratory findings: serum free light chain Kappa was increased and the ratio was also elevated, and the K/λ ratio was also slightly higher in urine (Table 1). Routine analysis of urine showed weakly positive urine protein test, negative protein this week, blood β2 microglobulin close to normal level, coagulation function fibrin degradation product 17.83 μg/L, D-dimer 5.7 mg/L. Monoclonal immunoglobulin IgM was increased, protein electrophoresis was suggestive of M protein, serum fixed electrophoresis detected IgM-κ, bone marrow puncture showed that there were nucleated cells with active proliferation (Figure 2), and plasma cells were 3.5%. Immunohistochemical plasma cells: CD138 15%+, CD19 12%+, CD20-, CD56-, CD117-, CD3-. Imaging findings: lumbar spine CT suggested osteoporosis, lumbar 1 vertebral compression fracture, compressive changes. Interstitial changes in both lungs, inflammation of the lower lobe of the right lung, moderate pleural effusion on the right side, and enlargement of the left ventricle. Clinical manifestations: anemia, hemorrhage, bone pain, hypercalcemia, significantly elevated blood viscosity, pulmonary infection, and peripheral neuropathy. After a multidisciplinary consultation, the patient was finally diagnosed with Waldenström's macroglobulinemia.

DISCUSSION

WM is usually inert, irreversible, and has wide clinical heterogeneity [1]. WM is a rare disorder characterized by the presence of abnormal cold-precipitated globulins in the plasma, which tend to precipitate at low temperatures. Symptoms include anemia, bleeding tendencies, skin purpura, hyperviscosity, Raynaud's phenomenon (fingers and pigmentation turning white and purple in the cold), arthralgia, neurological symptoms, renal involvement, and hepatosplenomegaly. According to the World Health Organization (WHO) classification system, Waldenström's macroglobulinemia is defined as lymphoplasmacytic lymphoma with monoclonal pentameric IgM protein [2]. The consensus expert panel recommendations of the Second International Symposium on Waldenström's macroglobulinemia (WM) stated that the following clinical and pathologic criteria are required for the diagnosis of WM: Bone marrow biopsy (BM) is required to document the presence of a clonal lymphoplasmacytic cell-like infiltrate and the presence of IgM monoclonal serum [3]. Laboratory findings: anemia, blood smear with cord-like arrangement of erythrocytes, low albumin level, high globulin level, and inverted white globulin ratio. Monoclonal immunoglobulin IgM was increased, protein electrophoresis suggested M protein, serum fixed electrophoresis detected IgM-Kappa type, bone marrow aspiration showed active proliferation of nucleated cells, and plasma cells accounted for 3.5%. Immunohistochemical plasma cells: CD138 15%+, CD19 12%+, CD20-, CD56-, CD117-, CD3-. Imaging findings: CT of lumbar spine suggested osteoporosis, compression fracture of lumbar 1 vertebral body, compressive changes. Interstitial changes in both lungs, inflammation of the lower lobe of the right lung, moderate pleural effusion on the right side, and enlargement of the left ventricle. Clinical manifestations: anemia, bone pain, hypercalcemia, significant elevation of blood viscosity, pulmonary infection, peripheral neuropathy. In addition, WM should be differentiated from several other types of monoclonal IgM diseases, such as IgM-type MGUS, primary IgM-type MGUS-associated disease, and IgM-type multiple myeloma.
LPL/WM cells are thought to be derived from late-maturing B cells. Therefore, clonal B cells are seen in the peripheral blood of patients with WM, and rarely are there increased numbers of lymphocytes. The cells of patients with WM usually show chromosomal abnormalities, with approximately 50% of patients with confirmed WM having a deletion in the chromosomal structural domain 6q21e23. In addition, about 40% of patients with 6q deletions show a concomitant increase in the 6p gene. The chromosomal region of interest contains two important genes: one is TNFAIP3, which inhibits nuclear factor kappa B (NF-kB) signaling, and the other is PRDM1, a key regulator that plays an important role in the maturation process of B cells. The survival of WM cells is dependent on the process by which NF-kB is phosphorylated and then enters the nucleus of the cell [4]. WM patients are usually characterized by cytogenetic alterations as well as gene mutations. For example, the MYD88 L265P mutation, which is the most common in LPL/WM, is usually strongly associated with the development of the disease. CXCR4 mutations may also affect disease progression. The MYD88 mutant (MYD88Mut) can activate Bruton's tyrosine kinase (BTK), a process that occurs by inducing the transcription of hematopoietic cellular kinases. Subsequently, BTK further acts on the nuclear κ-factor light chain enhancer to promote survival signaling and modulate the activation of extracellular kinase (ERK) in the activated B cell 1/2 signaling pathway. Thus, it can promote the JAK-STAT3 signaling pathway by enhancing transcription factors such as NF-κB and mediate the production of inflammatory factors such as IL-6, IL-10, and IFN-β, thereby altering the microenvironment of tumor cell growth and promoting the development of WM by strengthening the viability of plasma cell-like lymphocytes as part of the autocrine cycle [5]. CXCR4 is a G protein-coupled receptor; knockdown or inhibition of CXCR4 and the addition of Gi protein inhibitors can

Table 1. Immunofixation electrophoresis.

A. Patient's serum specimen.

The name of project	Project abbreviation	Outcome	Unit	Reference interval	Methodology
Light chain Lambda quantiative	λ-LC	1.08	g/L	0.90 - 2.10	scattering turbidimetry
Light chain Kappa quantiative	κ-LC	7.96↑	g/L	1.70 - 3.70	scattering turbidimetry

B. Patient's urine specimen.

Test	Test abbreviation	Outcome	Unit	Reference interval	Methodology
Urine light chain Kappa quantitative	Uκ-LC	138.00	mg/L		scattering turbidimetry
Urine light chain Lambda quantitative	Uλ-LC	11.10	mg/L		scattering turbidimetry
Urine light chain κ/λ ratio	Uκ/Uλ	12.432↑		0.750 - 4.500	calculation method

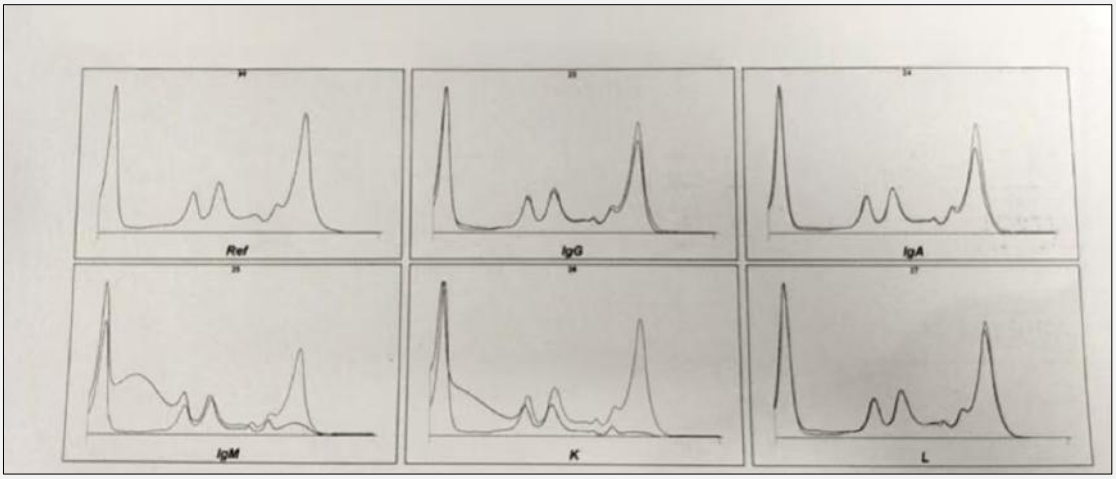

Figure 1. Results of serum protein electrophoresis.

Department of Spine, Surgery age: 76.

inhibit the migration and adhesion ability of WM cells, which highlights the importance of CXCR4 in the homing process of WM cells. In addition, WM cells possess the ability to express another chemokine receptor, VLA-4, which can directly interact with CXCR4 and thus activate the AKT and MAPK signaling pathways, which not only enhances cell survival but also enables them to circumvent the apoptotic process, thus promoting the progression of WM [6].

WM is a rare lymphoma that may exist in an asymptomatic phase in which patients may not require treatment or may require treatment due to the development of symptoms and complications from bone marrow or other tissue infiltration. The therapeutic approach to WM has evolved rapidly, with anti-CD20 monoclonal antibody-based combination therapies and Bruton's ty-

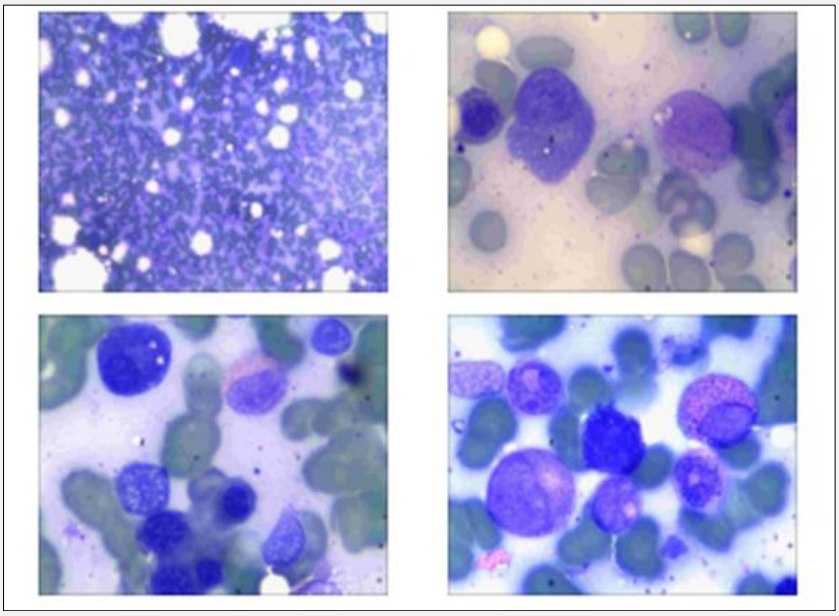

Figure 2. Bone marrow cytology.

rosine kinase (BTK) inhibitors predominantly being used [7]. The standard treatment regimen is to combine the anti-CD20 antibody rituximab with alkylating agents (Bendamustine, Cyclophosphamide), nucleoside analogs (Fludarabine, Cladribine), or proteasome inhibitors (Bortezomib, Carfilzomib, and Ixazomib) [8]. According to the NCCN Panel, plasma exchange therapy is recommended to be implemented first in patients with an urgent need for disease control, such as those with symptomatic hyperviscosity. After completion of plasma exchange, systemic therapy should then be rapidly initiated [9]. The prognosis of patients has improved over the past two decades with the introduction of more effective treatments. Rituximab-based immunochemotherapy (ICT) regimens are the mainstay of treatment for first-line and relapsed/refractory (R/R) WM, but they are associated with side effects. BTK inhibitors are part of the standard of care for patients with relapsed/refractory Waldenström's macroglobulinemia (WM) and for patients with WM who are not candidates for immunochemotherapy (ICT). Their effects are more profound and long-lasting, have a manageable safety profile, and are usually favorable compared to ICT regimens [10]. Both the FDA and the EMA approved ibrutinib as the first BTK inhibitor, which can be used alone or in combination with rituximab, thus revolutionizing the treatment of this disease [11]. Several therapeutic approaches, such as AKT inhibitors, BCL-2 inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and stem cell transplantation, also play an important role in the treatment of patients with WM. Al-though WM is a rare and currently incurable disease, a genome-based therapeutic strategy can already be conceptualized as our understanding of the underlying biological mechanisms of WM deepens. At the same time, with the emergence of new drugs in clinical development, it is expected that patients will achieve deeper efficacy, longer response times, and lower rates of toxic side effects. However, we must also be mindful of the potential for rising costs associated with new drugs, as well as their possible long-term safety concerns. Nonetheless, we continue to study WM in the hope that more cost-effective treatments will further improve the survival and quality of life of patients with WM [12].

In this case, the examiner first noticed that the patient's creatinine test result was negative and immediately checked the instrument, quality control, etc. It was found that everything was normal. Then it was suspected that the patient's specimen was a lipohematocrit specimen, and found that it was not a lipohematocrit specimen. Then the patient's blood samples were observed. The same patient's blood was drawn, and the amount of serum and plasma was very different and therefore immediately added distilled water to find out that the patient's specimen was turbid, and then replaced it with a dry one. The patient's creatinine test was normal according to the chemical reagent method. At the same time, the doctor also found that the patient's other biochemical indicators were abnormal, and finally, according to the analysis of routine blood and blood smear

results, plus serum protein electrophoresis, and ultimately lock the target protein - M protein. After finding the basis of the disease, he immediately contacted the clinician for consultation and made a correct diagnosis of the disease, i.e., Waldenström's macroglobulinemia. It is worth noting that due to the lack of specificity of WM, clinicians and patients are unable to detect and pay attention to it promptly, whereas the examiner has the convenience of seeing all of the patient's labs and can analyze every piece of data and report in depth, so the patient's diagnosis of the disease needs to be considered in many ways.

WM is a rare B-cell lymphoproliferative disease, this time through the introduction of a case of WM patient's clinical symptoms as well as diagnosis and treatment, at the same time summarize the review of the current status of the research of the disease and diagnosis and treatment progress, to promote the early diagnosis of this disease in the clinic and early treatment.

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Declaration of Interest:
Authors state no conflict of interest. All authors agree to the submission and that the manuscript has not been published in whole or in parts nor submitted anywhere else.

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