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Secondary light chain amyloidosis with Waldenström's macroglobulinemia and internodal marginal zone lymphoma: A case report and literature review

A complex case of small B-cell lymphoma

Abstract

BACKGROUND

The co-existence of Waldenström's macroglobulinemia (WM) with internodal marginal zone lymphoma (INMZL) is rare and often associated with poor prognosis.

CASE SUMMARY

We present a Chinese female patient who developed secondary light chain amyloidosis due to WM and INMZL, and provide opinions on its systemic treatment. A 65-year-old woman was diagnosed with WM 6 years ago and received Bruton tyrosine kinase inhibitor monotherapy for 2 years. Her INMZL was confirmed due to left cervical lymphadenopathy. The patient presented with signs of edema in both lower limbs 1 year ago, and was diagnosed with secondary light chain amyloidosis. Treatment with the BC regimen (rituximab 375 mg/m^2 monthly for 6-8 courses, and bendamustine 90 mg/m^2 per day * 2, monthly for 6 courses) was initiated, but not tolerated due to toxic side effects. Bortezomib-based therapy including bortezomib, dexamethasone, and zanubrutinb was given for two months. The edema in both lower limbs was relieved and treatment efficacy was evaluated as partial remission.

CONCLUSION

A detailed clinical evaluation and active identification of the etiology is recommended to avoid missed diagnosis and misdiagnosis.

Key Words: Waldenström's macroglobulinemia; Internodal marginal zone lymphoma; Secondary light chain amyloidosis: Case report

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Core Tip: Waldenström's macroglobulinemia (WM) is a lymphoplasmacytic lymphoma, and internodal marginal zone lymphoma (INMZL) is another rare subtype of clinically inertial non-Hodgkin's lymphoma. We report a rare case of secondary light chain amyloidosis due to WM and INMZL. We also retrieved related articles indexed in PubMed. Bortezomib-based therapy including bortezomib, dexamethasone, and zanubrutinb was administered for two months, and treatment efficacy was evaluated as partial remission. Treatment should be based on the patient's physiological age, life expectancy, and tolerance to treatment. Therefore, we recommend detailed clinical evaluation and active identification of the etiology to avoid missed diagnosis and misdiagnosis.

INTRODUCTION

Waldenström's macroglobulinemia (WM), accounting for 2% of non-Hodgkin's lymphomas, is a lymphoplasmacytic lymphoma that secretes immunoglobulin M (IgM). WM is an inertial lymphoma, but most patients eventually progress and require new drugs to improve their prognosis. Internodal marginal zone lymphoma (INMZL) is another relatively rare subtype of clinically inertial non-Hodgkin's lymphoma (NHL), most commonly seen in adults, with a mostly atypical presentation. It can easily be misdiagnosed in the early stage as its symptoms are nonspecific in patients suffering

from comorbid WM and INMZL. The purpose of this report is to describe our pathological observations and review the literature in order to improve our understanding of the disease, to avoid misdiagnosis and provide evidence on clinical prognosis and treatment.

CASE PRESENTATION

Chief complaints

A 65-year-old woman was admitted to a local hospital due to increased blood sedimentation during physical examination 6 years ago.

History of present illness

The patient was admitted to our hospital due to signs of edema in both lower limbs, tachycardia, and lymphadenectasis 1 year ago.

History of past illness

She was admitted to a local hospital due to increased blood sedimentation during physical examination 6 years ago without pain and discomfort. Fever, splenomegaly, lymphadenopathy, and musculoskeletal complaints were absent, and she was subsequently diagnosed with WM but did not receive treatment due to the absence of symptoms. However, regular review was performed as recommended by the doctor. She was a non-smoker and denied a history of alcohol intake. Approximately three years later, she presented with weakness and lymphadenectasis, and bone marrow aspiration indicated that the proportion of lymphocytes was significantly higher, a small number of which were suspected to be plasmacytic lymphoma cells.

Serum protein electrophoresis demonstrated significantly dark stained bands in the Y region, a negative P53 mutation by fluorescence in situ hybridization, and normal karyotype of the chromosome. Bone marrow biopsy indicated an increased proportion of heterogeneous lymphocytes with an abnormal cell population accounting for 14.03% of the nucleated cells in the flow cytology of bone marrow, and abnormal B

lymphocytes expressing CD19, CD20, CD79b, CD23, CD200, CD1d, sIgM, sIgD, cLambda, and partially expressing CD5 and CD38. Bone marrow immunophenotyping indicated that abnormal cells accounted for approximately 14.03% of the nucleated cells, and abnormal B lymphocytes expressed CD19, CD20, CD79b, CD23, CD200, CDId sIgM, sIgD, and cLambda. Despite the absence of the MYD88 L265P mutation, the diagnosis of WM was made based on the above results, and the patient received Bruton tyrosine kinase inhibitor monotherapy for 2 years.

Personal and family history

The patient denied a family history of malignant tumors.

Physical examination

On physical examination, her vital signs were as follows: Body temperature, 36.3°C; blood pressure, 118/70 mmHg; heart rate, 82 bpm; respiratory rate, 19 breaths/min. She was pale and had signs of edema in both lower limbs on examination.

Laboratory examinations

The patient was admitted to our hospital due to signs of edema in both lower limbs, tachycardia, and lymphadenectasis 1 year ago. Complete blood counts revealed moderate anemia (80 g/dL). Biochemical tests demonstrated hypoproteinemia (16.8 g/L), normal lactate dehydrogenase (128.4 U/L), and increased IgM (36.60 g/L) and light chain λ (5.82 g/L). Serum beta-2-microglobulin (4.79 mg/L) was also above the normal level (Table 1). Bone marrow smears showed an increased ratio of mature lymphocytes (68.0) and flow cytometry analysis of the bone marrow revealed abnormal cells that were HLA-DR+, CD19+, CD20+, and CD79b+, strongly suggesting a mature B-cell neoplasm. Serum protein electrophoresis demonstrated an "M" component of 21.83 g/L with a severe immunoparesis with band typing as IgM kappa (serum IgM 41.20 g/L) (Figure 1).

Imaging examinations

Positron emission tomography-computed tomography (F-18 Fluorodeoxyglucose PET/CT) confirmed a maximum standardized uptake value of 2.9 in the bilateral submandibular, bilateral cervical, bilateral axillary, mediastinal, and bilateral inguinal multiple lymph nodes.

Further diagnostic work-up

An allele-specific polymerase chain reaction (PCR) assay was carried out to detect the MYD88 L265P mutation and the mutation frequency was 29.2% (sequencing depth 1,890 X). Immunohistochemical staining was carried out on bone marrow (BM) biopsies which showed lymphocytosis (75%), indicative of lymphoplasmacytic lymphoma involvement in the BM. Bone marrow fluid specimens were cultured and analyzed for 20 midphase cells, five of which showed karyotypes with partial short arm deletion of chromosome 1, suspected partial short arm deletion of chromosome 4, and one missing of chromosome 6, with an additional marker chromosome attached.

A left cervical lymph node biopsy was performed on December 1, 2021. Histological examination of the biopsy specimens using hematoxylin and eosin staining demonstrated proliferation of predominantly small sized abnormal lymphoid cells, and these cells were MUM1 (multiple +), CD138 (-), Kappa (individual +), CD20 (multiple +), PAX5 (+), CD3 (few +), CD56 (scattered +), Cyc1in D1 (one), CD79a (multiple +), CD21 (FDC shrinkage), CD5 (few +), and Ki67 (GC+, scattered + around), and Congo red (+/-) on immunohistochemistry (Figure 2). Epstein–Barr virus-encoded small RNA in situ hybridization was negative. The PCR-IG gene rearrangement test (400bp) showed the following: IgHV-FR1(-), IgHV-FR2(-), IgHV-FR3(-), IgK-Vk-Jk(+), and IgK-Kde+INTR-Kde(+). Remarkably, the patient showed edema, hypoproteinemia, increased plasma creatinine, 3+ urine protein, and 7233.20 mg total protein in a 24-h urine collection. The results of the left cervical lymph node biopsy stained with Congo red were positive/negative for amyloid, the results of the BM biopsy stained with Congo red were negative; therefore, amyloidosis complicated by renal injury was

suspected, which required fat aspiration and a renal biopsy for confirmation, but the patient refused.

To investigate whether WM and INMZL in this patient had the same origin, we planned to perform immunoglobulin heavy chain (IgH) gene rearrangement analyses of the BM and lymph node using PCR of laser micro-dissected samples from a formalin-fixed paraffin-embedded section. However, as the patient still refused this assessment, we were unable to exclude the possibility of a composite lymphoma.

FINAL DIAGNOSIS

According to the patient's medical history combined with her test results, she was diagnosed with WM and INMZL, with concomitant amyloid renal damage.

TREATMENT

The patient was scheduled to receive the BC regimen (rituximab 375 mg/m^2 monthly for 6-8 courses, bendamustine 90 mg/m^2 per day * 2, monthly for 6 courses), but toxic side effects, allergic reaction, infection, and systemic reaction were observed after 2 courses. After the first chemotherapy course, the patient experienced mild diarrhea and low-grade fever for two weeks. Unfortunately, she developed moderate pleural effusion and dyspnea and was unable to lie flat, and then two chest drainage tubes were urgently placed in the bilateral pleural cavities for more than one month. Grade 1-2 myelosuppression was observed after chemotherapy and moderate fever which was treated with intravenous antibiotics. Thus, alternative therapy options were considered, and bortezomib-based therapy including bortezomib, dexamethasone, and zanubrutinb was administered for two months. The edema in both lower limbs was relieved and treatment efficacy was evaluated as partial remission.

OUTCOME AND FOLLOW-UP

The patient is still alive at the time of publication.

DISCUSSION

Jan Waldenstrom first described macroglobulinemia in 1944. WM is characterized by infiltration of the bone marrow with lymphoplasmacytic cells, excessive production of a monoclonal IgM protein, and associated clinical features such as anemia, lymphadenopathy, and serum hyperviscosity[1]. As an uncommon lymphoid neoplasm, WM has low morbidity, with an overall annual age-adjusted 3.8 cases per million persons per year. Therefore,WM is easily misdiagnosed as other B-cell lymphomas and monoclonal gammopathies of undetermined significance[2].

The patient in this report was diagnosed with WM and received Bruton tyrosine kinase (BTK) inhibitor monotherapy for 2 years. The treatment of WM has progressed from traditional treatment with benzodiazepine, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), and the FC (fludarabine, cyclophosphamide) regimen to new treatments based on rituximab, proteasome inhibitors, and BTK inhibitors[3]. Over the past 10 years, the proportion of patients on new treatment regimens has gradually increased in our center, and these patients receiving new treatments had significantly longer overall survival and progression-free survival than patients receiving traditional treatment. Zanubrutinib, a FDA-approved drug for WM, has demonstrated comparable efficacy in terms of hematologic response with improved side effects compared to other BTK inhibitors. Therefore, we chose this drug to treat our patient and achieved an improved short-term curative effect. The patient developed painless and progressive enlargement of superficial lymph nodes after 2 years of oral zanubrutinib treatment. WM can be combined with superficial lymph node enlargement, but the lymph nodes do not develop progressive enlargement. These symptoms suggested that the patient did not have WM alone, but had disease progression or transformation to other diseases; therefore, we carried out lymph node biopsies and other related tests.

Internodal marginal zone B-cell lymphoma (INMZL), a rare condition that is diagnosed based on histology, accounts for fewer than 2% of all lymphoid neoplasms and approximately 10% of marginal zone B-cell lymphomas (MZL), according to the

American Society of Hematology[4]. The immunohistochemical and histopathological findings confirmed INMZL in our patient, with a high number of peripheral zone B cells expressing CD1d and secreting mainly IgM[4]. Due to similar laboratory results, differential diagnosis is particularly difficult between WM and INMZL that can secrete IgM. Although MYD88 mutations are present in the majority of patients with WM, they are not specific; MYD88 mutations are seen in 5% to 10% of patients with lymph node MZL[5]. The lymph node biopsy was dominated by small lymphocytes, with abundant cells, small size, and visible germinal center-like structures, and CD20+[6]. In the present case, the final diagnosis of INMZL was thus established and this was not an insignificant result.

The patient's INMZL diagnosis was established, but proteinuria, hypoproteinemia and bilateral lower extremity edema persisted. WM-related renal damage is clinically rare, mostly manifesting as mild to moderate M proteinuria with microscopic hematuria, renal insufficiency, and rare nephrotic syndrome, with less than 3% of WM patients progressing to end-stage renal disease[7]. The literature reports monoclonal immunoglobulin A-associated renal damage in about 81% of cases, including light chain amyloidosis (21.5%), non-amyloid glomerulopathy (33.0%) and tubulointerstitial lesions (26.5%), non-amyloid glomerulopathy (33.0%) and tubulointerstitial lesions (16.5%); lymphoma infiltration was the most common tubulointerstitial lesion (19%), other tubular lesions include tubulointerstitial nephropathy and light chain proximal tubulopathy[8].

Secondary light chain amyloidosis can occur in 10% to 15% of patients with multiple myeloma, as well as in patients with WM or INMZL. Primary light chain amyloidosis is distinguished from secondary light chain amyloidosis primarily by whether the patient can meet the relevant diagnostic criteria for the disease[9]. Our patient's diagnosis of amyloidosis was confirmed by examination, which may be secondary to WM or INMZL. MW-related renal impairment is rare, accounting for 5.1% to 8% of patients with MW, and is usually characterized by low to moderate M proteinuria with microscopic hematuria, renal failure, and nephrotic syndrome, with

less than 3% of patients with MW developing end-stage renal disease[10]. Although the patient did not have a renal puncture biopsy, we concluded that the patient had a combined renal amyloidosis by lymph node biopsy, and 24-h urine protein level greater than 0.5 g. We did not confirm this diagnosis by biopsy, which is a shortcoming in this case.

Chemotherapy with rituximab (R)-based regimens, such as RCD (rituximab + cyclophosphamide + dexamethasone) or bendamustine + R (BR), is preferred for those whose main symptom is WM-related hematocrit disorder or organomegaly, which can reduce tumor load more rapidly[11]. There are no effective treatment options for light chain amyloidosis due to NHL, which include rituximab monotherapy or combination radiochemotherapy regimens, or autologous stem cell transplantation modalities. However, after receiving BR treatment, this patient developed severe complete hematocrit disorder, massive pleural effusion, diarrhea, and infection, but lymph node enlargement did not subside and renal function did not improve, so after two courses of treatment, the regimen was discontinued. Dangien *et al* reported six cases of cutaneous marginal zone B-cell lymphoma combined with amyloidosis, one of which achieved complete remission after treatment with bortezomib[12]. Our patient achieved partial remission after switching to zanubrutinib and bortezomib for 8 wk as she could not tolerate the BR regimen.

CONCLUSION

WM combined with INMZL followed by amyloidosis is rare and the clinical presentation lacks specificity, requiring detailed clinical evaluation and active identification of the etiology to avoid missed diagnosis and misdiagnosis. Pathological biopsy is the gold standard for confirming the diagnosis of this disease. There is no effective treatment and zanubrutinib + bortezomib has shown partial efficacy, but the long-term prognosis is unknown. Regular follow-up and timely treatment are important to prolong the survival of patients.

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