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A rare case of marginal zone lymphoma with severe rashes and literature review

A rare case of marginal zone lymphoma with severe rashes

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Abstract

BACKGROUND

Marginal zone lymphoma (MZL) is an indolent subtype of non-Hodgkin lymphoma (NHL), which is rare clinically with severe rashes as the initial symptom.

CASE SUMMARY

This study reports a case of MZL with generalized skin rashes accompanied by pruritus and purulent discharge. First-line treatment with rituximab combined with zanubrutinib had poor effects. However, after switching to obinutuzumab combined with zanubrutinib, the case was alleviated, and the rashes disappeared.

CONCLUSION

For patients with advanced stage MZL not benefiting from type I anti-CD20 monoclonal antibody combination therapy, switching to a type II anti-CD20 monoclonal antibody (mAb) combination regimen may be considered. This approach may provide a new perspective in the treatment of MZL.

Key Words: Marginal zone lymphoma, Mucosa-associated lymphoid tissue, Extranodal marginal zone lymphoma, Primary cutaneous marginal zone lymphoma, Rituximab, Obinutuzumab, Zanubrutinib

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Core Tip: This paper reports a case of MZL with generalized skin rashes accompanied by pruritus and purulent discharge. First-line treatment with rituximab combined with zanubrutinib had poor effects. However, after switching to obinutuzumab combined with zanubrutinib, the case was alleviated, and the rashes disappeared. Therefore, in patients with advanced stage MZL not benefiting from type I anti-CD20 monoclonal antibody combination therapy, switching to a type II anti-CD20 monoclonal antibody (mAb) combination regimen may be considered. This approach may provide a new perspective in the treatment of MZL.

INTRODUCTION

Marginal zone lymphoma (MZL) is a type of B-cell non-Hodgkin lymphoma (B-NHL) originating in the marginal zone of lymphoid follicles. MZL is the third commonest type of B-NHL after diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). MZL has low incidence, insidious onset, slow clinical progression and relatively good prognosis.

An epidemiological survey carried out in the United States in 2016 on 7460 patients diagnosed with non-Hodgkin lymphoma revealed that MZL accounted for 7% of all non-Hodgkin lymphomas[1]. Three subtypes have been proposed for MZL according to the site of origin, including extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), splenic marginal zone lymphoma (SMZL), and nodal marginal zone lymphoma (NMZL). Although all three subtypes are indolent

lymphomas, they have different clinical presentations, disease prognoses, and treatment options. According to the NCCN or CSCO guidelines, rituximab-based regimens are preferred for first-line treatment in advanced and symptomatic MZL cases. However, MZL cases with extensive and severe rashes at onset are rare, and no consensus on relevant treatment options is available.

CASE PRESENTATION

Chief complaints

A 63-year-old man presented with superficial lymphadenopathy for more than 4 mo and severe rashes for 3 mo.

History of present illness

Symptoms and signs began 4 mo ago, and the rashes recurred, gradually increasing in size and severity.

History of past illness

The 63-year-old man noticed a 1.5×1 cm mass on the right neck and a 2×1 cm mass under the right armpit 4 mo before admission, without overt causes. The patient experienced fatigue, poor appetite, acid regurgitation, heartburn, and nausea, but no vomiting, fever, or night sweats. A blood routine test at the local hospital revealed a platelet count of 55×10^9/L; a Color Doppler ultrasound examination revealed multiple enlarged lymph nodes throughout the body. A biopsy of the right cervical lymph node was performed at the local hospital, and pathological analysis showed a tendency toward B-cell non-Hodgkin lymphoma. Following the recommendations of the local hospital, the patient was orally administered 80 doses of a traditional Chinese medicine preparation, but the symptoms did not improve significantly. Three months before admission, the patient developed red maculopapular skin rashes on both lower limbs, which gradually expanded to cover the head, face, trunk, and limbs with ulceration and pus. The patient self-administrated prednisone acetate at 20 mg/day for

3 days, but the symptoms continued to worsen progressively. Consequently, the patient was admitted to our department for a definitive diagnosis of lymphadenopathy and rash etiology. Patient weight was unchanged before the first half-year of admission.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

Large areas of dark red rashes were observed on the face, chest, abdomen, back, and limbs, with some being ruptured and purulent, and others scabbed, without tenderness (Figure 1A-D). The patient had multiple enlarged lymph nodes that were palpable in the neck, clavicular region, axilla and inguinal region of both sides, with the largest one of approximately 3×2 cm found on the right neck. The lymph nodes were hard, mobile, nontender, and nonadherent to the surrounding tissues. No specific positive signs were observed in the heart and lungs. The abdomen was flat and soft. The liver was not palpable under the ribs, while the spleen was palpable 8 cm below the ribs without tenderness. The patient also had bilateral lower limb edema.

Laboratory examinations

Routine blood test revealed white blood cell count at 7.15×10^9/L, hemoglobin at 142 g/L, lymphocyte count at 1.85×10^9/L, and platelet count at 112×10^9/L.

Biochemical analysis showed alanine aminotransferase at 46.56 IU/L, aspartate aminotransferase at 46.90 IU/L, serum albumin at 24.47 g/L, and β2 microglobulin at 6.48 mg/L. No obvious abnormality was detected in blood urea nitrogen, serum creatinine, lactate dehydrogenase, electrolytes, immunoglobulin (Ig)A, IgG, IgM, infectious diseases (including HBV-DNA and HCV-RNA), antinuclear antibody spectrum and hematuria immunofixation electrophoresis.

Inflammatory indicators were: C-reactive protein (CRP), 44.84 mg/L; procalcitonin level and erythrocyte sedimentation rate, normal ranges.

Imaging examinations

To avoid hypersensitivity in the patient's skin due to enhancers, which would aggravate the rash symptoms, plain computed tomography (CT) of the neck, chest, abdomen, and pelvis was performed, revealing splenomegaly and multiple lymph nodes enlarged in the neck, clavicular region, axilla and inguinal region of both sides, as well as the mediastinum and retroperitoneal region (Figure 2A-D).

The pathological analysis of right cervical lymph nodes showed that the lymph node structure disappeared in most areas, with diffuse and consistent infiltration of small lymphocytes with predominantly small centroblasts. The cellular morphology suggested that atypia was not obvious; mitotic cells were rare, and a small number of lymphoid follicles remained locally, which indicated follicular implantation. Immunohistochemistry showed CD20 (diffuse +), CD3 (scattered low +), Ki67 (about 15%), CD10 (-), BCL-6 (-), CD5 (-), CD23 (-), CyclinD1 (-), MUM-1 (scattered low +), CD21 (low residual follicular dendritic reticulum), C-myc (-), BCL-2 (+), P53 (about 60%), and CD30 (scattered low +) (Figure 3A,3C-J). Skin pathology suggested mild hyperplasia of stratified squamous epithelium with parakeratosis, scattered T cell-dominated lymphocyte infiltration in the epithelium, focal erosion and small abscess formation, and T cell-dominated lymphocyte infiltration in tissues under the epithelium. Combined with immunohistochemical data, there was insufficient evidence to diagnose lymphoma (Figure 3B). Immunohistochemistry suggested CD20 (partial +), CD3 (majority +), CD5 (majority +), CD23 (dendritic cell +), CyclinD1 (scattered +), Bcl-2 (partial +), p53 (-), CD30 (-), Ki-67 (20% +), CD43 (majority +) and CD79α (partial +). Interestingly, next-generation sequencing of lymph node samples detected a TP53 mutation (NM_000546.5 on exon 6) with the nucleotide change of c.659a > G resulting in the amino acid change of p.Tyr220cys (dbSNP, rs121912666; mutation frequency, 3.85%). However, BRAF/V600E and MYD88L265P mutations were not detected. Analysis of bone marrow morphology showed active proliferation, normal proportion and morphology of mature lymphocytes, and visible lymphoid histiocytes. Bone

marrow biopsy showed focal or scattered distribution of lymphocytes and no morphologically abnormal lymphocytes (Figure4). Bone marrow immunophenotyping revealed abnormal B lymphocytes, accounting for 6.67% of nuclear cells, expressing CD19, CD20, Kappa, IgM and CD81; partially expressing FMC7; and not expressing CD103, CD10, CD43, CD11c, CD200, CD25, CD23, CD38, CD5, IgD, and Lambda (Figure 5).

FINAL DIAGNOSIS

By summarizing the features of the current case, the patient not only had generalized skin rashes and splenomegaly, but also showed extensive lymph node involvement; although WBC count was normal, we further assessed peripheral blood smear, bone marrow morphology, and flow cytometry to exclude leukemic change. Flow cytometry suggested abnormal B lymphocytes <20%. Combined with immunophenotypic data, diagnostic criteria for lymphoma leukemia were insufficient. Furthermore, based on pathological biopsy, next-generation sequencing and whole-body CT, the diagnosis of stage IVA MZL (high-risk group with an IPI score of 4) involving the spleen, bone marrow, bilateral neck, clavicular, axillary, mediastinal, retroperitoneal and inguinal lymph nodes with a TP53 mutation was made. Skin infiltration of lymphoma was excluded.

TREATMENT

Rituximab (375 mg/m^2 once every three weeks) plus zanubrutinib (160 mg twice daily) was given for 3 courses starting on November 13, 2021.Then,starting on April 8, 2022, patients received three courses of obinutuzumab (1000 mg/3 wk) in combination with zanubrutinib (160 mg twice daily), followed by a switch to maintenance zanubrutinib (160 mg twice daily) to date.

OUTCOME AND FOLLOW-UP

The course of treatment involved efficacy assessment after 3 courses of rituximab (375 mg/m^2 once every three weeks) plus zanubrutinib (160 mg twice daily) starting on November 13, 2021, which suggested stable disease (SD). The skin rashes did not improve significantly after 3 courses of treatment. CT of the neck, chest, abdomen and pelvis showed that lymph nodes in the neck, clavicular, axillar, retroperitoneal and inguinal regions were smaller than pre-treatment, with no significant spleen shrinkage (Figure 2E-H). Morphological and pathological examinations of the bone marrow showed no significant abnormalities but bone marrow immunophenotyping showed abnormal B lymphocytes accounting for 4.86% of nuclear cells in bone marrow samples, which expressed CD19, CD20 and Kappa, but not CD103, CD10, CD43, CD11c, FMC7, CD38, CD200, CD25, CD23, CD5, IgD, IgM, CD81 and Lambda. Treatment efficacy was close to complete remission (CR) after three courses of treatment with a switch to obinutuzumab (1000 mg/3 wk) combined with zanubrutinib (160 mg twice daily) starting on April 8, 2022 (Figure 1E-H). A repeat blood routine analysis showed a white blood cell count of 5.37×10^9/L, hemoglobin at 136 g/L, a lymphocyte count of 2.36×10^9/L, and a platelet count of 76×10^9/L. Further examination of bone marrow morphology and immunophenotyping showed no abnormal B lymphocytes, so thrombocytopenia was considered to indicate myelosuppression caused by BTK inhibitors. Contrast-enhanced CT of the neck, chest, abdomen and pelvis revealed significant retraction of lymph nodes on the neck, clavicular region, axilla, retroperitoneal region, inguinal region and spleen (Figure 2I-L). Subsequently, the patient was administered zanubrutinib (160 mg twice daily) as maintenance therapy, and the patient's condition has remained stable until now.

DISCUSSION

Marginal zone lymphoma is an indolent disease that tends to have an insidious onset, with MALT lymphoma showing the highest rate among the three subtypes. This subtype is further divided into gastric, cutaneous, and non-gastric/non-cutaneous MALT lymphomas. NMZL has the smallest proportion among all MZL cases,

representing about 10%, and less than 2% of all NHL cases[2]. About 10% of patients with NMZL show abnormal IgM protein elevation[3], which needs to be further distinguished from Waldenstrom macroglobulinemia (WM). Although NMZL mainly involves lymph nodes and occasionally the bone marrow and peripheral blood, a large proportion of patients have painless multiple lymphadenopathy. SMZL accounts for approximately 20% of MZL[2], and most patients are characterized by splenomegaly, lymphocytosis, and cytopenia, which may induce autoimmune disorders[4]. Although the patient had skin rashes and superficial lymphadenopathy, and bone marrow and spleen involvement was considered according to relevant examinations such as blood count, bone marrow count, and imaging, extranodal marginal zone lymphoma was considered in combination with different clinical manifestations and laboratory tests for the three MZL lymphoma subtypes.

The specificity of this case is that it was accompanied by a large area of rashes on the whole body in the early stage of onset, and further clinical symptoms were rare. Because the patient refused a second biopsy, the current evidence of lymphoma on skin biopsy was insufficient, but combined with his medical history, symptoms and treatment, the causes of rashes were considered to involve two aspects. On the one hand, the rashes may be non-specific skin manifestations caused by MZL; on the other hand, the pathological analysis may be unsuccessful and fail to provide evidence of lymphoma infiltrating skin lesions. Even if the rashes are lymphoma infiltrating the skin, they still could not be diagnosed as primary cutaneous marginal zone lymphoma (PCMZL), which belongs to extranodal non-Hodgkin lymphoma, accounting for about 25% of all cutaneous lymphomas[5]. The 2016 World Health Organization (WHO) classified PCMZL as a MALT lymphoma manifesting in the skin, which is currently considered of post–germinal center marginal zone B-cell origin, and the neoplastic infiltrates are composed of a varying admixture of small lymphocytes, plasma cells, and lymphoplasmacytoids[6]. By definition, essentially no evidence of extracutaneous disease is found at the time of presentation with symptoms, and relevant studies have also revealed bone marrow involvement in less than 1% of patients[7]. PCMZL cases

present with solitary or multifocal nodules, plaques, or papules that are generally localized to the arms or trunk[6, 8]. In terms of treatment, hormonal smearing and local radiotherapy may be considered for focal lesions, and rituximab may be administered to individuals with systemic lesions or recurrence[9]. Given the unique clinicopathologic features of primary cutaneous marginal zone lymphoma, it was included as a separate entity in the 5th Edition WHO classification of lymphoid neoplasms[10]. The current patient had extensive lesions, not only involving multiple lymph nodes but also affecting the spleen and bone marrow. Because hormonal treatment and first-line rituximab combination regimens were ineffective, extranodal marginal zone lymphoma was still considered for this case with a diagnosis other than PCMZL.

Due to extensive involvement, the disease was at an advanced stage, and rituximab-based regimens were preferred according to current guidelines. Next-generation sequencing of the pathological tissue revealed a TP53 mutation, which accounts for about 5.8% of MZL lymphomas[11]. As in chronic lymphocytic leukemia (CLL), this mutation not only shortens the time from diagnosis to first treatment but also impairs progression-free survival (PFS) and overall survival (OS), suggesting an association with worse prognosis[12]. Therefore, addition of targeted agents that may overcome TP53 mutations in combination with rituximab is recommended. A phase II clinical trial[13] of newly diagnosed CLL cases with del17p and/or TP53 mutations suggested that first-line ibrutinib therapy could lead to long-term remission. The present study suggests that BTK inhibitors (BTKi) can partially overcome P53 abnormalities.

Although no clinical studies have confirmed the use of BTKi for first-line treatment of advanced high-risk MZL, the NCCN and CSCO guidelines only included BTKi (ibrutinib and zanubrutinib) as second-line treatment options for stage III/IV MZL lymphoma. In the early disease stage, the patient is generally in poor condition and could not tolerate chemotherapy, so we selected the chemotherapy-free modality of BTKi in combination with rituximab for the first time. Compared with ibrutinib that exerts off-target effects, zanubrutinib, a potent, irreversible next-generation BTK

inhibitor, is more selective and has less adverse events due to off-target effects[14]. The superiority of zanubrutinib was further confirmed in the phase III ALPINE trial[15]. Besides, the MAGNOLIA Phase II clinical trial[16] demonstrated that zanubrutinib monotherapy has high overall response rate (ORR) and CR with durable disease control and safety in R/R MZL. Considering the efficacy and safety of zanubrutinib, the patient was administered zanubrutinib plus rituximab as the initial therapy.

After 3 treatment courses, lymph nodes and spleen in the patient had some regression, but the skin rashes did not significantly improve. Abnormal lymphocytes were still detected by bone marrow immunophenotyping, resulting in a stable disease (SD). Based on the treatment principle of indolent lymphoma, the original regimen could be considered. However, since the patient's skin symptoms persisted, the treatment regimen was adjusted to control the clinical symptoms as soon as possible. Obinutuzumab, a glycoengineered, type II anti-CD20 monoclonal antibody (mAb), exerts antitumor effects mostly *via* antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP) and direct cell death (DCD). ADCC and DCD are significantly enhanced by obinutuzumab compared with the type I anti-CD20 mAb rituximab[17]. In the CLL11 (NCT01010061) phase 3 trial, obinutuzumab plus chlorambucil showed a benefit in progression-free survival (PFS) compared with rituximab plus chlorambucil, extending follow-up by about 2 years. The trial also demonstrated a significant increase in OS[18-20]. Similarly, in the phase 3 GALLIUM trial (NCT01332968), obinutuzumab and rituximab were combined with CHOP, CVP or bendamustine, respectively, for the treatment of indolent non-Hodgkin lymphoma (iNHLL). The latter trial as a head-to-head clinical analysis also showed the superiority of obinutuzumab in the treatment of follicular lymphoma[21, 22]. Although current studies have reported no significant differences in PFS and adverse events (AEs) between obinutuzumab plus chemotherapy and rituximab plus chemotherapy in newly diagnosed MZL[23], no head-to-head study has compared the combination of two anti-

CD20 mabs and BTK inhibitors. In this case, the patient was switched to obinutuzumab instead of rituximab combined with zanubrutinib, and a CR was achieved after 3 cycles.

CONCLUSION

MZL diagnosis requires a comprehensive examination. When the involved site is used for disease staging, especially the skin, it is recommended to further complete a pathological biopsy to exclude lymphoma infiltration. This case of severe MZL with massive rashes is rare in clinical practice, and the individualized treatment regimen with BTK inhibitor combined with obinutuzumab was timely applied after failed first-line treatment. Although this combination has not been previously examined, it conferred benefits to the current patient, and it is suggested to expand the sample size to provide better treatment options for severe MZL.

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