Diffuse large B-cell lymphoma and monoclonal gammopathy secondary to immune thrombocytopenic purpura: A case report

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Received July 21, 2022; Accepted November 3, 2022

DOI: 10.3892/ol.2023.13823

Abstract. The present study reports the case of a patient with diffuse large B-cell lymphoma (DLBCL) and monoclonal gammopathy (MG) secondary to immune thrombocytopenia purpura (ITP). The clinical diagnoses and investigations of this case are reported. To the best of our knowledge, this is the first study to report DLBCL and MG secondary to ITP. The patient presented with a rare constellation of diseases, which made the diagnosis and treatment difficult for the physicians. The patient was followed up for 10 years using the morphological examination of bone marrow cells after chemotherapy, and currently continues with follow-up examinations. Treatments and prognoses for ITP, DLBCL and MG are common. However, treatments and prognoses are unclear for patients with all three conditions. The different clinical manifestations and disease processes of DLBCL and MG secondary to ITP cause difficulties for physicians in terms of treatment and prognosis. The present case report describes the comprehensive evaluation, diagnosis and treatment of a patient with DLBCL and MG secondary to, and concurrent with, ITP.

Introduction

Immune thrombocytopenia purpura (ITP) is an autoimmune disease that destroys platelets. In certain patients, ITP can be resolved after appropriate treatment in the early stages of the disease. However, some patients with ITP suffer relapse or have continuous progression even after treatment. ITP is a recognized complication in patients with non-Hodgkin's lymphoma (NHL) (1,2). The incidence of NHL after ITP is low, and in one previous study, only 76 out of 8,067 patients with ITP had NHL, so the increased risk of NHL could not be considered as very large (3). The incidence of immune platelet destruction in patients with NHL is ~5% (4-6); however, most cases occur in patients with chronic lymphoblastic leukemia. To the best of our knowledge, there have been no reported cases of secondary lymphoproliferative diseases in patients with primary ITP. Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL and accounts for 30-40% of NHL (7). DLBCL is characterized by a broad heterogeneity in its clinical manifestations and prognoses (8).

Monoclonal gammopathy (MG) is a disease in which the body produces a higher concentration of immunoglobulins due to the abnormal proliferation of monoclonal B cells, tending to result in tumor formation. The association between MG and well-differentiated B-cell NHL has been reported (7). MG has been reported in certain patients with DLBCL; however, the number of MG cases in patients with DLBCL is still insufficient for further statistical research (9). Little is known about the pathogenesis and prognosis of patients with DLBCL coinciding with MG (10). To the best of our knowledge, there have been no previous case reports describing DLBCL secondary to ITP. The current study presents the case of a patient diagnosed with DLBCL and MG secondary to ITP.

Case report

A 67-year-old man presented to the Department of Hematology, Gansu Provincial People's Hospital (Lanzhou, China) in August 2009 complaining of oral hematoma and gingival bleeding. A routine blood examination demonstrated a white blood cell count of $9.3x10^9$/l (reference range, 4.0-10.0x10^9/l), a platelet count of $6.0x10^9$/l (reference range, 100.0-300.0x10^9/l) and a hemoglobin level of 153 g/l (reference range, 120-165 g/l). Primary ITP was diagnosed after bone marrow cytomorphological examination of the anterior superior iliac spine, and ultrasound examination (used for finding any masses on the body surface) excluded other primary diseases. A treatment regime consisting of glucocorticoid, γ immune globulin and danazol was initiated, but the platelet count remained at $10.0x10^9$/l. Upon failure of this ITP treatment, splenic embolization was performed on the patient. The patient's platelet count increased to $120x10^9$/l after 1 month. Due to marked bleeding in both lower limbs, the patient was admitted to the 940th Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army (Lanzhou, China)

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Key words: immune thrombocytopenic purpura, diffuse large B-cell lymphoma, non-Hodgkin's lymphoma, monoclonal gammopathy

in November 2009, 100 days after the initial presentation. A routine blood examination demonstrated a white blood cell count of $7.9x10^9$/l, a platelet count of $1.0x10^9$/l and a hemoglobin level of 95 g/l. B-scan ultrasonography of the abdomen demonstrated normal splenic color blood flow, which indicated a failure of the splenic embolization. Maturation arrest of megakaryocytes was found upon morphological examination of the bone marrow cells, which indicated ITP (Fig. 1A and B).

The patient underwent a splenectomy in January 2010, 152 days after the initial presentation, and the platelet count increased to $140x10^9$/l. In May 2016, subsequent B-scan ultrasonography of the pelvis revealed multiple enlarged lymph nodes (3.0x2.5 cm) in the left inguinal region. The patient reported pain in the anterior tibial region due to the compression of the enlarged lymph nodes of the left leg, which limited its use. A biopsy of the lymph nodes demonstrated DLBCL in the left inguinal lymph node originating from the germinal center, based on assessment using the Hans algorithm (11). Immunohistochemical analysis of the tissue from the left inguinal lymph node demonstrated the presence of $CD20^+$, Bcl-6^+, interferon regulatory factor-1^-, $CD3^-$ and $CD10^+$ B cells. IgM was highly expressed in the cytoplasm of certain neoplastic cells, but the protein expression levels of IgG, CD38 and CD138 were below detection limits.

Ki-67^+ cells accounted for ~75% of the tumor cells. The cells were negative for BCL-6 rearrangement as assessed using fluorescence *in situ* hybridization (FISH). Dysregulation of BCL-2 and MYC was also negative.

Whole-body bone scintigraphy revealed lesions that indicated bone destruction. Abnormally high radioactivity was demonstrated in the bilateral scapula, bilateral humeri and femurs, bilateral anterior ribs, vertebral bodies, the left anterior iliac spine, the upper tibia, and the left knee and ankle joints (Fig. 2A and B). These lesions were considered metastatic foci. The patient received eight courses of an rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) regimen as follows: 375 mg/m^2 rituximab, intravenous (IV), on day 0; 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin and 1.4 mg/m^2 vincristine, IV, all on day 1; and 100 mg prednisone, *per os*, on days 1-5. After R-CHOP treatment, a positron emission tomography-computed tomography (PET-CT) scan found no further bone destruction.

The patient returned for a follow-up examination in May 2019, 3,555 days after the initial presentation. An investigation of bone marrow cell morphology demonstrated that a proportion of lymphocytes (19%) and plasmacyte (1.2%) were normal, and bone marrow hyperplasia was active (Fig. 1C and D). A total of ~8% of nucleated cells were lymphocytes, of which mature B lymphocytes accounted for 14.5%. No abnormal immune phenotype was observed in the proliferative B lymphocytes. Enlarged lymph nodes (1.5x0.5 cm) were found in the left neck upon superficial B-scan ultrasonography. Immunofixation electrophoresis, using a 1% agarose gel, demonstrated the presence of λ light chains and IgGs. Serum protein electrophoresis demonstrated a γ band (40.7%), a β band (6.1%), an α2 band (6.5%) and an albumin band (44.6%). PET-CT demonstrated an abnormal increase of F-18 fluorodeoxyglucose lymph node metabolism in numerous body regions (Fig. 3A-E), which was consistent with metabolic changes in the progressive disease stage after lymphoma treatment.

The malignant lymphoma showed a progressive increase in globulin and IgG levels (Fig. 4A and B), and the patient was diagnosed with DLBCL and MG secondary to ITP. The patient was administered one course of the R-CHOP regimen after the DLBCL diagnosis. The patient's levels of globulins (42 g/l; reference range, 20-40 g/l) and IgG (2,520 mg/dl; reference range, 700-1,660 mg/dl) decreased but remained higher than normal. Immunofixation electrophoresis testing demonstrated the presence of λ light chains. The patient remains under follow-up treatment using the R-CHOP regimen at the time of writing.

Methods

Immunohistochemical analysis. Tissue from the left inguinal lymph node were fixed using 4% paraformaldehyde at room temperature for 24 h, paraffin embedded and sliced into 5 μm sections. Sections were dewaxed by heating to 65˚C for 5 min, washed with xylene three times for 10 min and rehydrated using a descending ethanol series. Antigen repair was performed by incubation with EDTA for 3 min. Sections were incubated with 5% bovine serum albumin (Shengshi Technology Co., Ltd.) for 10 min at 37˚C to block endogenous peroxidase activity and then washed three times with PBS for 3 min. Sections were incubated with primary antibodies against CD20 (L26) (1:100; cat. no. M0755; Dako; Agilent Technologies, Inc.) for 60 min at 25˚C. Sections were incubated with Goat Anti-Mouse IgG HRP Conjugate secondary antibodies (1:500; cat. no sc-2005; Santa Cruz Biotechnology, Inc.) for 30 min at 25˚C. Sections were imaged using a BX53 biological light microscope (magnification x20; Olympus Corporation).

FISH. Vysis LSI IGH/BCL2 Dual Color, Dual Fusion Translocation Probe Kit (Abbott Molecular Inc.) was used to perform FISH. Tissues were fresh frozen at -20˚C and cut into 5 μm sections. Sections were fixed using a methanol and glacial acetic acid mixture (30 and 10 ml, respectively) at 25˚C For 10 min. Colcemid (0.1%; MedChemExpress) was used to arrest the cells in metaphase. Cells were centrifuged at 447.2 x g for 10 min at room temperature, the supernatant was discarded and 5 ml fixative (3:1 mixture of methanol to glacial acetic acid) was added for 10 min at room temperature. The aforementioned process was repeated for secondary fixation. KCl (0.075 M) was used as the hypotonic solution with incubation for 25 min at 37˚C. The suspension was dropped on to dry glass slides.

The probe was thawed at room temperature, mixed manually, and centrifuged at 600 x g for 10 min at 25˚C. A total of 5 μl (10 ng/μl) probe working solution (50 ng DNA template, 0.3 μM primer and 1 unit Taq DNA polymerase were required, and the total reaction volume was 25 μl) with saline sodium citrate buffer (2X SSC; 0.3 M NaCl, 0.03 M sodium citrate dihydrate, distilled water, adjusted to pH 7.0 with hydrochloric acid or sodium hydroxide) was used per sample and covered with a coverslip, which spread out the probe. Liquid adhesive was used to seal the edges of the coverslip. Slides were heated to 75˚C for 2 min to denature the probe. Slides were incubated at 37˚C overnight for hybridization.

The coverslips were removed and slides were placed in 72˚C 0.4X SSC [60 mM NaCl, 20 mM Tris-HCl (pH 7.5), 0.5% SDS and 1 mM EDTA] solution for 2 min. Redundant probes were removed using buffer (0.05% Tween-20/2x SSC solution:

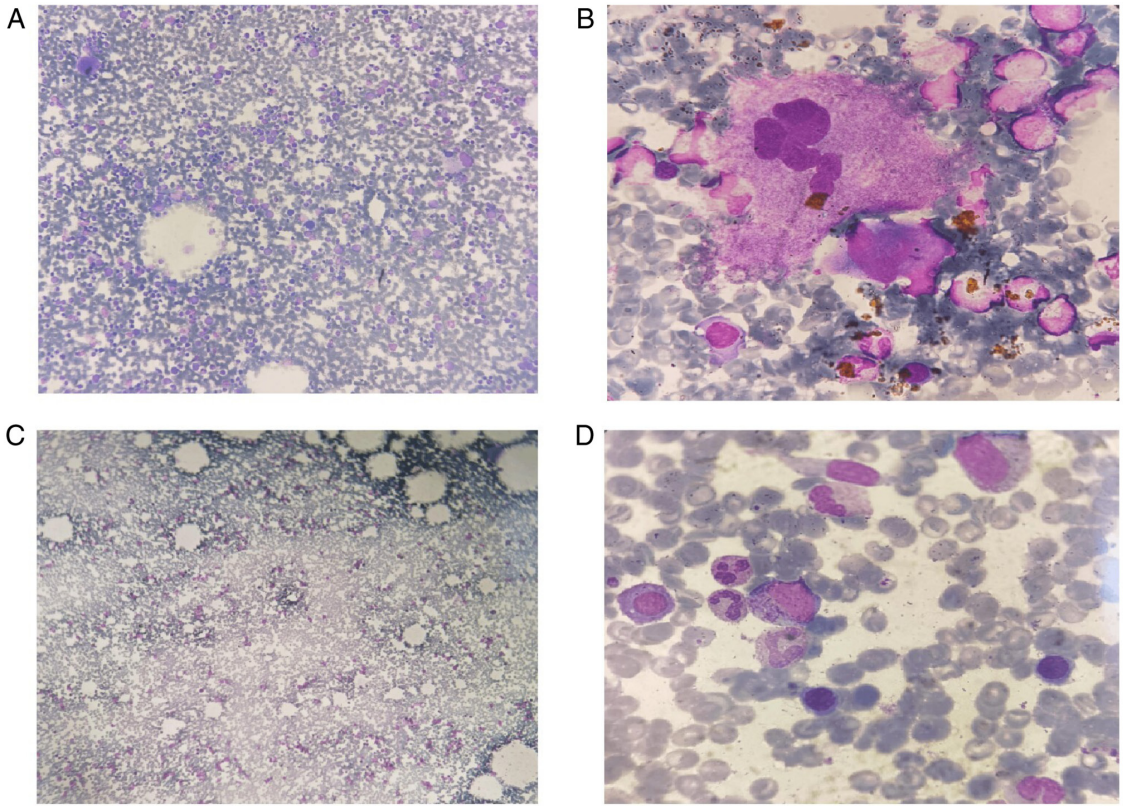

Figure 1. Hematoxylin and eosin staining of bone marrow cells. (A and B) A large number of scattered megakaryocytes were demonstrated in the bone marrow. November 2009, 102 days after the initial presentation. [(A) x10 magnification; (B), x100 magnification]. (C) Normal proportions of lymphocytes and plasmacytes (x10 magnification). (D) Hyperplasia of bone marrow cells (x100 magnification). January 2010, 163 days after the initial presentation.

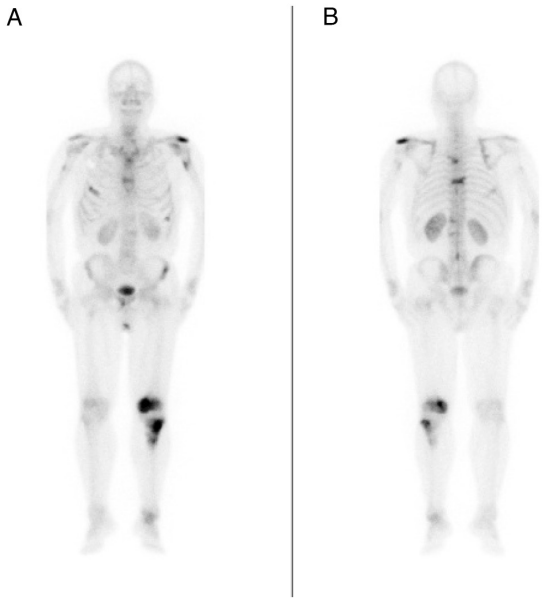

Figure 2. Whole-body bone scintigraphy. Whole-body bone scintigraphy [(A) anterior and (B) posterior view] demonstrated high radioactivity areas in numerous locations (bilateral scapula, bilateral humerus and femur, bilateral anterior ribs and vertebral bodies, left anterior iliac spine and upper tibia, and left knee and ankle joints), which were considered metastatic foci.

75 nM NaCl, 37.5 mM sodium citrate, 0.05% Tween-20, pH 7.0). Blocking was performed using 5% bovine serum albumin (Sangon Biotech Co., Ltd.) at room temperature for 1 h.

Slides were counterstained using 10 μl DAPI and immediately covered with a coverslip and placed in the dark at 4˚C for 5-10 min. The slides were assessed using a fluorescence microscope. First, the cell area was confirmed under a low-magnification objective lens, and then a 40X objective lens was used to select areas with better nuclear distribution (such as areas in which a single nucleus could be distinguished). In order to accurately observe and interpret the results of FISH, a representative area for observation that accurately reflected the distribution of the signals was selected. After selecting the observation area, the FISH results of the nucleus were accurately counted.

Immunofixation electrophoresis. The serum of the patient was centrifuged at 5,180 x g for 10 min at room temperature and the supernatant was collected. Total protein was extracted using 20% ammonium sulfate and separated by 2% agarose gel electrophoresis. The separated protein was fixed and immunoprecipitated using an Immunoprecipitation Kit, Protein A/G Plus Agarose (cat. no. GS4780; Beijing Biolab Technology Co., Ltd.). The unprecipitated protein was removed using absorbent paper and washed with distilled water. The protein was stained using Coomassie brilliant blue at 37˚C for 10 min and the locations of these immunoprecipitation bands were compared with the abnormal protein bands observed after electrophoresis.

Discussion

ITP is an autoimmune hemorrhagic disease characterized by increased platelet destruction and inhibition of platelet

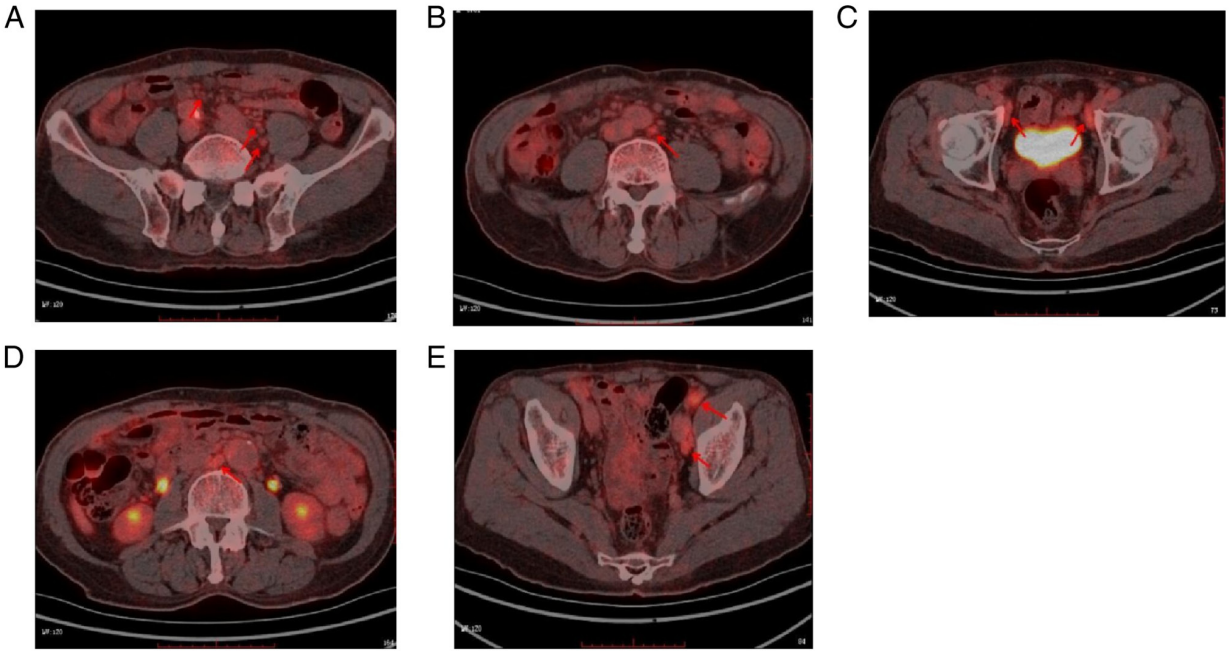

Figure 3. Whole body PET-CT. (A-E) PET-CT demonstrated abnormally increased 18F-fluorodeoxyglucose metabolism in lymph nodes in numerous regions of the body, which was consistent with the metabolic changes in progressive disease stage after lymphoma treatment. PET-CT, positron emission tomography-computed tomography. (A) Pelvic plane (S2). (B) Abdominal plane (L1-L2). (C) Pelvic plane (S5). (D) Abdominal plane (L2-L3). (E) Pelvic plane (S4).

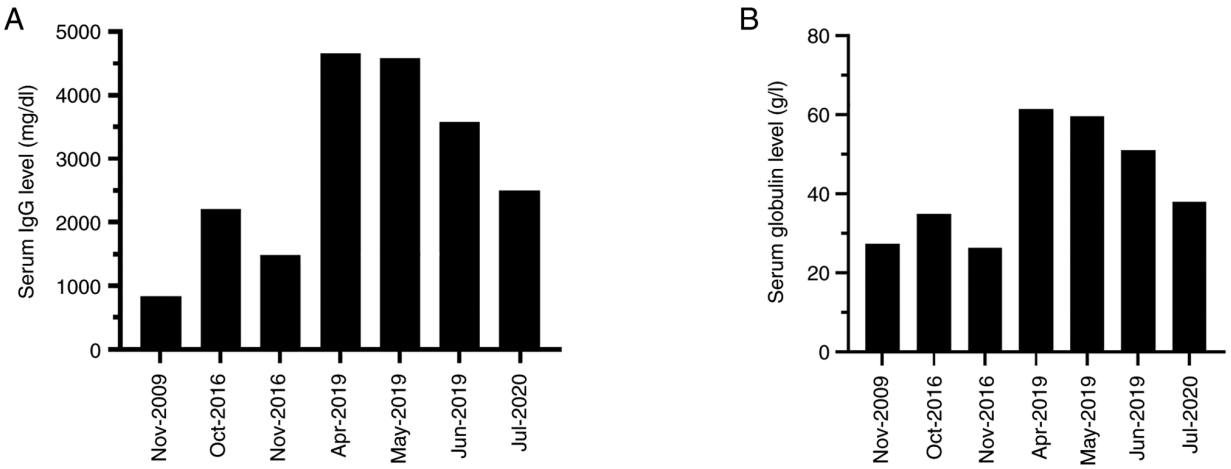

Figure 4. Serum IgG and globulin levels. Serum (A) IgG and (B) globulin levels.

production (12,13). Patients display purpura in regions of the body. B-cell production is increased in the spleen of patients with ITP (14). Chen *et al* (15) reported increased antibody levels, and increased B-cell regulator and B-cell activating factor levels in the plasma of patients with ITP. Another study reported that the function of $CD19^{+}$, $CD41^{hi}$ and $CD38^{hi}$ regulatory B cells (Bregs), which promoted peripheral immune tolerance in patients with ITP, were impaired (16). In a previous study, the levels of $CD19^{+}$, $CD24^{+}$ and $FOXP3^{+}$ Breg subsets in the spleen of patients with ITP were increased (17). Impairment of Bregs and B cells in patients with ITP was reported to lead to the production of pathogenic antibodies, which triggered platelet destruction and megakaryocyte-formation defects in the spleen and liver (18).

One previous study reported a significant correlation between platelet count and the number of megakaryocytes in the bone marrow (13). The decrease in megakaryocyte levels was reported to be the main reason for the reduction in platelet count in patients with ITP (19). Anti-platelet antibodies have been reported in patients with chronic lymphoblastic leukemia, hairy cell leukemia, lymphoma, Hodgkin's disease and Waldenstrom macroglobulinemia, and indicated that an immune regulation mechanism is involved in the development of thrombocytopenia in lymphocyte proliferative diseases (20-24).

A previous study reported that platelet antibody IgG (PA-IgG) levels were elevated in 46% of patients with lymphoproliferative disorders (25). There was a certain correlation between thrombocytopenia and the increase of PA-IgG levels in patients with ITP after resection (26). The high incidence of elevated

anti-platelet antibodies in patients undergoing splenectomy indicated that other organs could produce autoantibodies (27).

DLBCL is the most common malignant tumor of the lymphatic system in adults (7); it is one in a group of malignant tumors that demonstrate heterogeneity in terms of clinical manifestations and prognosis. Studies showed that the response and survival rates of patients with DLBCL were greatly improved after treatment with CD20 monoclonal antibodies; however, up to 40% of patients relapsed and 10% of the entire cohort of treated patients progressed to refractory diseases (28,29).

An increased level of free light chains in serum is a factor for a poor prognosis in DLBCL (30). MG is common in well-differentiated indolent lymphoma and is usually characterized by increased immunoglobulin levels (31). However, the frequency and prognostic significance of MG in patients with DLBCL remains unclear.

A previous study reported that of all patients with lymphocytic lymphoma, ~44% had elevated serum immunoglobulin levels and ~20% had MG, usually of the IgM type (32). However, another study reported that MG was present in 14.6% of patients with DLBCL (33). IgM was the most commonly reported immunoglobulin in numerous MG cases (32). However, Kim *et al* (34) and Li *et al* (35) reported that patients with DLBCL were susceptible to IgG-type MG. Furthermore, Zhang *et al* (36) reported that the presence of MG was unrelated to the adverse effects on overall survival and progression-free survival. However, Li *et al* (35) and Cox *et al* (37) reported that non-IgM MG was a negative prognostic factor for both overall and progression-free survival.

In the present case study, DLBCL concurrent with MG secondary to ITP was reported. Different clinical manifestations of MG and lymphoma have previously confused diagnoses and presented dilemmas in treatment. In the present case report, IgG was observed in the patient's serum and it was hypothesized that the excessive production of immunoglobulin could have promoted MG. Immunohistochemical analysis was used for differential diagnosis and classification; however, the diagnosis of DLBCL was confirmed using biopsy. To the best of our knowledge, no previous study has reported that ITP could cause DLBCL. Although the probability of ITP patients with DLBCL is minimal, the diagnosis and treatment of the three diseases in this patient is still worth discussing. Different clinical manifestations of MG and lymphoma have caused confusion in diagnoses and dilemmas in treatment. The present study highlights the unusual source of immunoglobulin, and suggests that the excessive production of immunoglobulin may promote MG. Although the prognosis of patients with subsequent monoclonal immunoglobulin disease due to lack of renal biopsy remains unclear, it reminds us that a comprehensive and detailed assessment of the patient's condition is necessary.

The present case demonstrated the importance of a complete clinical assessment and examination of patients with lymphoproliferative diseases. This information assists in making a comprehensive assessment and helps direct effective treatment protocols.

Acknowledgements

Not applicable.

Funding

The present study was supported by a grant from the Gansu Province Innovation Base and Talent Plan (Gansu Province Leukemia Clinical Research Center; grant no. 21JR7RA015).

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

LR analyzed the data and wrote the manuscript. WL, FX and DM collected and provided data on the treatment of the case presented. LY, WL, FX and DM acquired the data and participated in critical revision of the manuscript. TW and HB analyzed the data, compiled diagnostic data and contributed to the writing of the manuscript. All authors read and approved the final manuscript. LY, TW and HB confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient to publish this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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