Myelodysplastic syndrome with IgG4-related disease: A case report

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Abstract. At present, to the best of our knowledge, there are only a few case reports of IgG4-related disease (IgG4-RD) involving myelodysplastic syndrome (MDS), yet the incidence of MDS and IgG4-RD is increasing in middle-aged and elderly people. The present study presents a case of MDS combined with IgG4-RD admitted to Zhejiang Provincial Hospital of Chinese Medicine in September 2022. The (66-year-old; male) patient was admitted to the hospital due to hematopenia with an elevated IgG4 index. The diagnosis of MDS combined with IgG4-RD was confirmed after various exams, including pathological examination. The condition of the patient improved after 3 weeks of hormone therapy, with a significant increase in complete blood count compared with the pre-treatment period. MDS is a malignant hematological disorder with a high risk of conversion to leukemia, and IgG4-RD is a systemic immune-mediated disease with a poor prognosis often associated with malignancy. The present study presents and reviews the literature to better understand the coexistence of these two diseases.

Introduction

Myelodysplastic syndrome (MDS) is a category of malignant hematological clonal system disorders of hematopoietic stem cells with heterogenous etiologies, characterized by ineffective bone marrow hematopoiesis, significant morphological dysplasia in one or more hematopoietic lineages or cytogenetic abnormality (1). The etiology of this disease is unknown and may be related to genetic, infectious or immune factors (2). In individuals aged ≥60 years, the prevalence was 7-35 cases per 100,000 individuals over the last two decades (3). MDS can be categorized into subtypes that are associated with lower or higher risk for acute myeloid leukemia transformation, which assists with therapy selection. Management focuses on treating symptoms and reducing the number of required transfusions in patients with low-risk disease. For those with higher-risk MDS, hypomethylating agents such as azacitidine, or decitabine, are first-line therapy. Hematopoietic cell transplantation is considered for higher-risk patients and represents the only potential cure (3). IgG4-related disease (IgG4-RD) is an immune-mediated progressive inflammatory disease associated with fibrosis (4), a specific organ predisposition involving the submandibular glands, parotid glands, lymph nodes, liver, and biliary tract (5). The true prevalence of IgG4-RD is unknown, and it is likely that it is underrecognized and underreported due to its relatively recent discovery, lack of widespread recognition and frequently indolent presentation (6). The separate incidence rate of MDS and IgG4-RD is high in the elderly population, but the coexistence of the two diseases is rare (7), and effective treatment of the simultaneous comorbidity of both diseases is unclear (8,9).

Case report

Patient history. A 66-year-old male attended Zhejiang Provincial Hospital of Chinese Medicine (Hangzhou, China) in September 2022 with 'recurrent episodes of weakness and dizziness for 2 years'. The patient felt dizzy and weak, along with leukopenia, severe anemia and thrombocytopenia (Table I). Bone marrow aspirations performed at the First Hospital of Chun'an County (Chun'an Branch of Zhejiang Provincial People's Hospital; Zhejiang, China) in June 2020 showed strong hematopoietic function, with impaired maturation of leukocytes and megakaryocytes, and active erythropoiesis. The patient received oral folic acid (5 mg, 3 times a day) and methylcobalamin (0.5 mg, 3 times a day) to replenish hematopoietic raw materials and relieve dizziness. The patient was transfused with B-type platelets when severely lethargic. In September 2022, the patient came to Zhejiang

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Provincial Hospital of Chinese Medicine with worsening fatigue and acute pruritus of both legs. The general condition and the results of conventional investigations are detailed in Fig. 1, Fig. 2 and the following descriptive record.

Tests

Laboratory correlation examination. Immunoprogram results showed the following results: Immunoglobulin (Ig)A, 482 mg/dl (normal range, 82-453 mg/dl); IgG, 2,050 mg/dl (normal range, 751-1,560 mg/dl), IgG4 493 mg/dl (normal range, 3-201 mg/dl); and IgE, 12.43 IU/dl (normal level, <100 IU/dl). The patient's ferritin level was 3,917.5 ng/ml (normal range, 16.40-293.9 ng/ml) and the erythropoietin level was >7,500 mU/ml (normal range, 4.3-29.0 mU/ml). The normal indicators of IgM, C3, C4, thyroid function, folic acid and vitamin B12 ruled out some of the common diseases that cause peripheral hypoperfusion.

Bone marrow aspirate. At 1 day after admission, the bone marrow smear revealed pathological hematopoiesis and 3.5% primordial immature granulocytes. Proliferating leukocytes accounted for 72.5% of all cells, with a marked increase in eosinophils, accounting for 26% of leukocytes. The erythrocyte ratio was 16% and erythrocytes showed pathological hematopoiesis. Lymphocytes accounted for 7.5% of the total cell count and presented normal morphology. A total of 2 megakaryocytes could be found throughout the smear, the megakaryocyte lineage was inactive and small nucleated megakaryocytes were easily seen. Lobulated nuclei and multinucleated megakaryocytes were reduced (Fig. 3A and B). Bone marrow smear and cytochemical staining analysis were performed by Department of Hematology of Zhejiang Provincial Hospital of Chinese Medicine(Hangzhou, China). Wright-Giemsa stain was applied for 10 sec at room temperature, then the same amount (0.5-0.8 ml) of phosphoric acid buffer was added and mixed with the dye solution at room temperature for 25 min. Subsequently, the smear was washed with distilled water and the slides were air-dried. The mounted slides were then examined and photographed using a light microscope (magnification, x1,000).

Flow cytometry. Flow cytometry analysis of the bone marrow revealed 1.85% medullary primitive cells with abnormal immunophenotype. Elevated proportions of eosinophils were detected, with the overall proportion of nucleated cells at 20.7%. The differentiation of granulocytes was abnormal and the expression of nucleated red blood cell CD36/CD71 expression was diminished.

Bone marrow biopsy. Bone marrow biopsy showed the fat percentage at ~65%, with 35% active nucleated cell proliferation, significantly active granulocyte lineage proliferation and increased eosinophil levels. A less active red lineage proliferation was shown with 2-10 megaloblasts/high power field (HPF). Multinucleated megakaryocytes and small nucleated megakaryocytes with reduced fractionated nuclei were easily seen. Few mature lymphocytes and plasma cells were seen. Pathological biopsies of the bone marrow showed immunophenotypic abnormalities, exhibiting CD34 (individual +), CD117 (individual +), MPO, CD15, CD235a, E-cadherin (partial +), CD61 (megakaryocyte +), CD20 (individual +); CD3 (few +), CD138, κ and λ (few +). Histopathology was performed by the Department of Pathology of Zhejiang Provincial Hospital of Chinese Medicine. Bone marrow tissue was fixed in 10% neutral formalin for 30-50 min at room temperature and rinsed under running water. The tissues were dehydrated sequentially by ethanol gradient. An equal mixture of pure alcohol and xylene was added for 15 min and xylene I and II solutions were each infiltrated for 15 min. A mixture of equal amounts of xylene and paraffin was infiltrated for 15 min, and then put into paraffin I and paraffin II permeable wax for 50-60 min each. Samples were slice to a thickness of 5 μm. Hematoxylin and eosin (HE) staining was performed according to routine protocols. Briefly, after deparaffinization and rehydration, 5-μm-thick sections were stained with hematoxylin solution for 5 min at room temperature, followed by five washes in 1% acid ethanol and then rinsed in distilled water. Subsequently, the sections were stained with eosin solution for 3 min at room temperature, followed by dehydration in ethanol twice for 20 min each and clearing in xylene. The mounted slides were then examined and photographed using a light microscope (optical microscope; Leica; magnification, x50).

Special staining. Myelofibrosis grade 0 (reticular fiber). Perls (-) (Perls' Prussian blue Stain). Reticulated fiber staining was performed by the Department of Pathology of Zhejiang Provincial Hospital of Chinese Medicine. 5-μm-thick sections were deparaffinized and fixed, oxidized with potassium permanganate solution for 3 min and rinsed in running water. The sections were bleached with oxalic acid solution for 1-2 min and rinsed in running water. Sections were stained with ferric ammonium sulfate solution for 3 min and rinsed with deionized water for 10 sec. Staining with silver ammonia solution for 5 min, rinsing with deionized water for 5-10 sec. Formaldehyde solution reduction for 30 sec, rinse with running water. Gold chloride solution toning 1 min and rinse. Staining with sodium thiosulfate solution for 2 min, rinse with running water. Slices were dehydrated until transparent and sealed. Iron staining was performed by the Department of Pathology of Zhejiang Provincial Hospital of Chinese Medicine. Dried bone marrow smears were placed in acidic potassium ferricyanide solution and stained for 30 min at room temperature. Following rinsing with distilled water, nuclear solid red stain was restained for 10-15 min and rinsed with running water. Sections were dried and sealed. Finally, the mounted slides were examined and photographed using a light microscope (optical microscope; Leica; magnification, x50).

Cytogenetic classification. The chromosomes were normal. Hematological oncogene mutation detection showed U2AF1:NM_006758.2:exon2:c.C101T:p.(S34F) 42.46%, ASXL 1:NM_015338.5:exon12:c.2422delC:p.(P808Lfs*10) 37.09%, ETV6:NM_015338.5:exon3:c.C313T:p.(R105X)(nonsense mutation) 33.97% and ETV6:NM_001987.4:exon6:c.G1106A:p.(R369Q) (missense mutation) 5.34%. Fusion genes ETV6-PDGFRA, FIP1L1-PDGFRA, TEL-PDGFRB, KIF5B-PDGFRA, STRN-PDGFRA, and PCM1-JAK2 were negative.

The patient had been leukopenic, anemic and thrombocytopenic for 2 years. The patient bone marrow smear shows morphologic dysplasia of erythrocytes and megakaryocytes. The 2016 WHO classification system was used to diagnose the patient with MDS with multilineage dysplasia (10). Three scoring methods were used to assess the MSD risk in accordance

Table I. Partial laboratory findings.

Date	Absolute leukocytes, 10^9/l	Absolute neutrophils, 10^9/l	Proportion of eosinophil, %	Hemoglobin, g/l	Platelet, 10^9/l	IgG4, mg/dl
The First Hospital of Chun'an County in 2020	1.5	/	/	52	33	/
First treatment in September 2022	1.8	0.7	26.3	40	41	493
Definite diagnosis in October 2022	1.4	0.4	27.2	44	42	510
After treatment in November 2022	1.4	1.1	0.0	56	49	398

Ig, immunoglobulin.

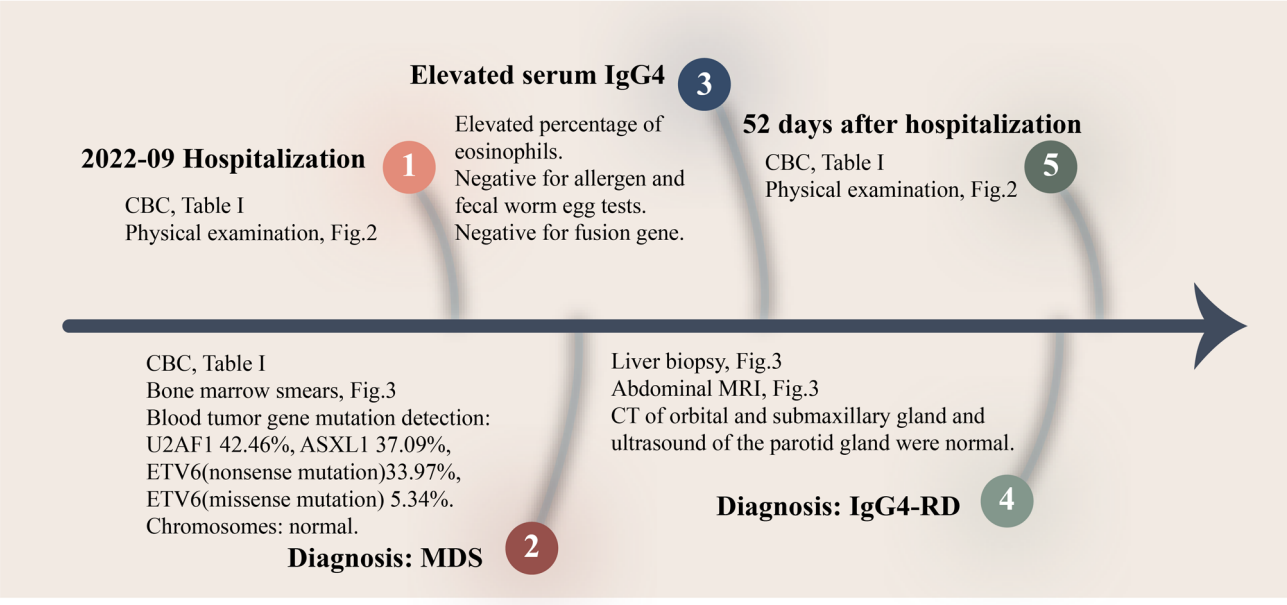

Figure 1. Flow chart of treatment. CBC, complete blood count; MRI, magnetic resonance imaging; CT, computerized tomography; Ig, immunoglobulin; IgG4-RD, IgG4-related disease; MDS, myelodysplastic syndrome; U2AF1, U2AF1:NM_006758.2:exon2:c.C101T:p.(S34F); ASXL1, ASXL1:NM_015338.5:exon12:c.2422delC:p.(P808Lfs*10); ETV6(nonsense mutation), ETV6:NM_015338.5:exon3:c.C313T:p.(R105X)(nonsense mutation); ETV6(missense mutation), ETV6:NM_001987.4:exon6:c.G1106A:p.(R369Q)(missense mutation).

with the '2019 Update on Diagnosis, Risk-stratification, and Management': The International Prognostic Scoring System (IPSS), the WHO classification-based Prognostic Scoring System (WPSS) and the Revised International Prognostic Scoring System (IPSS-R), where the patient scored, 0.5 (intermediate risk), 2 (intermediate risk) and 5 (high risk) respectively (11). However, the patient's eosinophil ratio (26.3% of leukocytes) and IgG4 (493 mg/dl) level were persistently abnormally elevated, which were inconsistent with the symptoms of MDS. The patient and his relatives requested for the MDS-related treatment to be withheld and only be provided with symptomatic treatment, including blood transfusion and granulocyte colony-stimulating factor leukostimulation.

Tests at days 2-7 post-admission

Refinement of diagnostic IgG4-RD-related auxiliary tests. Up to 6 days post-admission, the patient tested negative on allergen and fecal worm egg tests, thus allergies and parasitic diseases were ruled out. The parotid, orbital and submandibular glands of the patient, in addition to the pancreas and kidney of the patient showed no significant abnormalities, ruling out pathology.

Abdominal ultrasound. At day 2 after admission, the ultrasound showed regular liver morphology, the left lobe of the liver was enlarged, with an upper and lower diameter of 11.1 cm and the anterior and posterior diameters were 6.8 cm, while the right liver volume was also normal, with a smooth surface. The echogenicity of the liver area was dense and evenly distributed with well-defined blood vessels. The spleen was full in shape, 4.6 cm thick, with uniform echogenicity and a hyperechoic nodule of ~0.6 cm by 0.4 cm in size, with a clear border and regular shape.

Magnetic resonance imaging (MRI) of the upper abdomen. MRI results showed hepatic macrosomia, ferrous deposits and decreased T2W1 signal in the liver parenchyma and a large spleen. However, normal pancreatic morphology, no obvious abnormal kidney morphology and no clear posterior peritoneal structures were seen (Fig. 3C). From the imaging results,

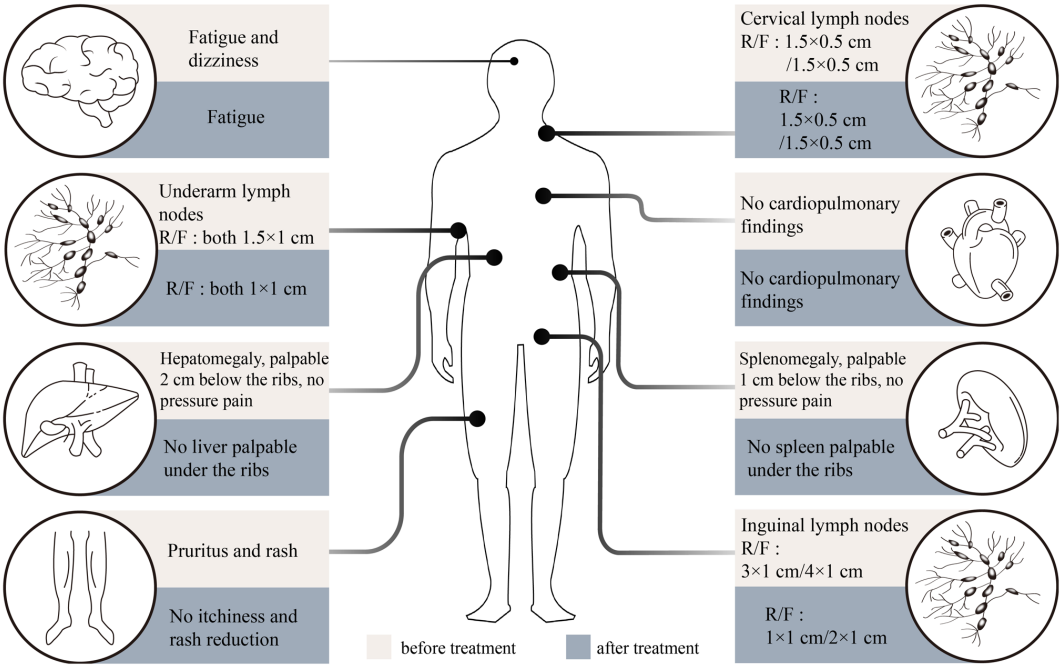

Figure 2. Physical examination before and after treatment. R, right; F, left.

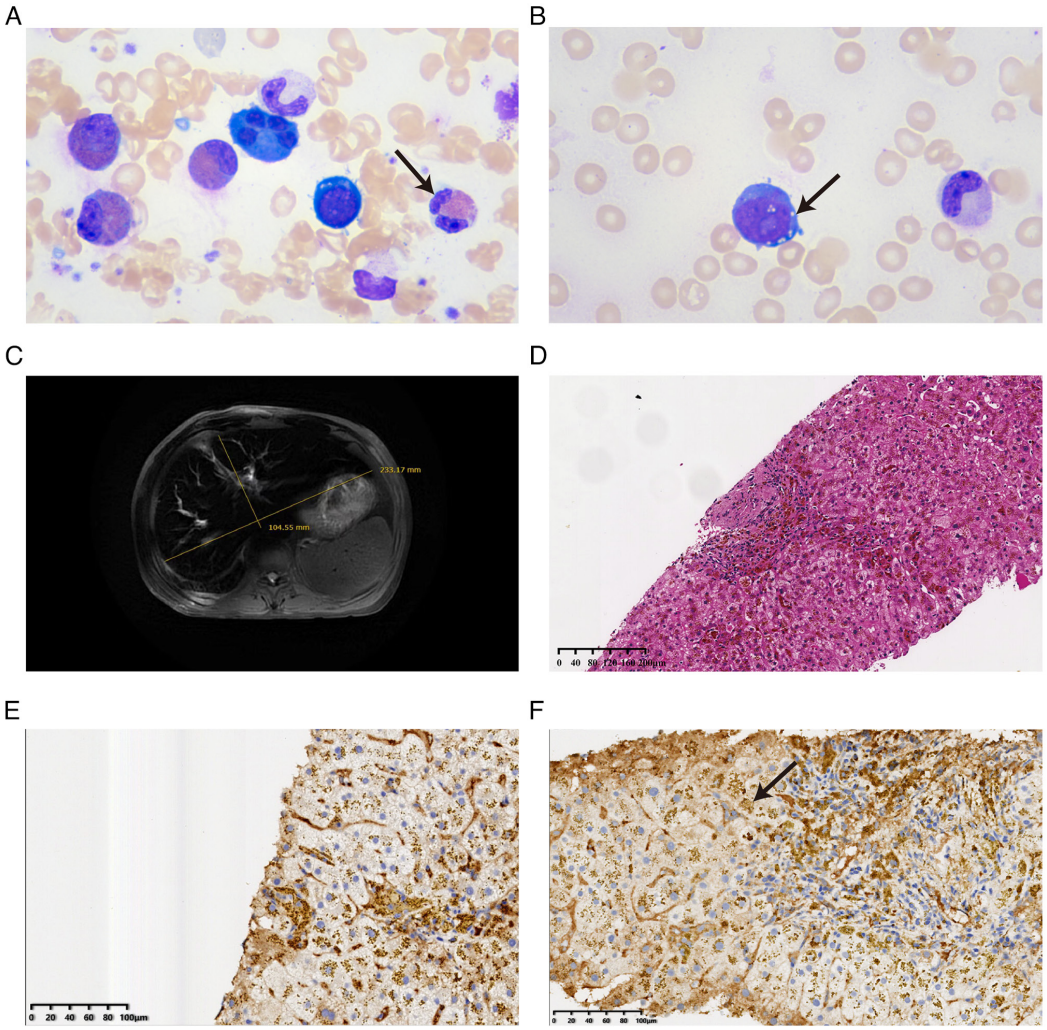

Figure 3. Wright-Giemsa staining of bone marrow smear from posterior superior iliac spine; arrows denote (A) eosinophils and (B) primordial cells (magnification, x1,000). (C) CT scan of the liver. (D) Hematoxylin and eosin staining of the portal area (magnification, x50). (E) IgG staining of the portal area (magnification, x100). (F) IgG4 staining of the portal area (magnification, x100); arrow indicates IgG4(+) cells.

liver lesions were considered, and a liver tissue biopsy was completed 10 days post admission. Hepatic puncture pathology (Fig. 3D-F) revealed cell swelling, metachromatic deposition of iron-containing heme and moderate chronic inflammatory cell infiltration in the confluent area. Pathological biopsies of the liver showed immunophenotypic abnormalities, exhibiting Ki-67 (<3% +), CK8 (+), CD10 (+), CD34 (vascular + in the confluent area), HBsAg (-), HBcAg (-), Hep (+), IgG (partial +), IgG4 (+ >10/HPF), CD20 (-), CD3 (lymphocytes +) and CD138 (+). The immunohistochemical staining for IgG and IgG4 was performed by Department of Pathology of Zhejiang Provincial Hospital of Chinese Medicine. Sections 5-μm-thick were placed in 10% neutral formalin and then stained with 12.5% IgG (ZA-0448, Amresco) or IgG4 (ZA-0576, Amresco) fluorescent antibody stained for 60 min at room temperature. Excess fluorescent antibody was poured off, and the sections were washed twice in phosphate buffered saline(PBS) at pH 7.2-7.4 with agitation for 5 min each time, and then washed with distilled water for 1 min to remove salt crystals. It was buffered with 50% buffer (0.5 mol/L carbonate buffer pH 9.0-9.5) and blocked with glycerol. The mounts were then examined and photographed using a light microscope (magnification, x100).

From these results IgG4-RD diagnosis was confirmed, and the patient was prescribed 20 mg prednisone twice daily for 3 weeks. Skin pruritus of both lower extremities improved dramatically, rashes were reduced, sizes of the liver and spleen were decreased, the lymph node sizes in the groin were reduced, blood cell counts were elevated compared with previous levels and IgG4 was reduced to 398 mg/dl (Fig. 2; Table I). After 52 days of hospitalization, the patient refused to continue treatment and requested to be discharged. In the first telephone follow-up on in March 2023 the patient reported a stable blood count, improved skin pruritus and no other significant discomfort. However, in the second follow up in September 2023 the patient reported low platelets and hemoglobin and was transfusion-dependent due to the lack of standardized treatment.

Discussion

MDS is a heterogeneous myeloid clonal disorder of hematopoietic stem cell origin that presents with abnormal myeloid cell development, ineffective hematopoiesis, refractory hematocrit and if left untreated, possible progression to acute myeloid leukemia (AML) (12). The life expectancy of patients with MDS and their treatment outcomes are highly disparate, therefore individualized treatment and prognostic goals should be curated according to the patient's disease risk classification, and current recommended guidelines. Thus, focusing on hematopoietic improvement in the lower-risk group and delaying disease progression, prolonging survival and avoiding transformation to AML in the higher-risk group (13).

IgG4-RD, as a rare multiorgan immune-mediated fibrotic inflammatory disease undefined until 2001 (14), is typically characterized by the presence of a dense IgG4-positive plasma cell infiltrate, the presence of mild to moderate eosinophilic infiltrate, extracellular matrix fibrosis and occlusive phlebitis (15). Organs considered typical for IgG4-RD infiltration are the lacrimal glands, major salivary glands, orbits, lungs, paravertebral soft tissue, pancreas, biliary tree, kidneys, retroperitoneum, aorta, meninges and thyroid gland (6). Since IgG4-RD is highly heterogeneous and has similar clinical manifestations, serological and pathological findings with isolated single organ diseases such as autoimmune pancreatitis, Mikulic disease, retroperitoneal fibrosis, autoimmune cell syndrome (AICy) and autoimmune disease (AID) (16), Diagnoses of these diseases are difficult to ascertain over a long period of time (17). Currently, hormonal shock therapy is recommended for undiagnosed patients presenting these symptoms, which provides good prognosis in most patients if treatment is commenced quickly (6).

Patients with a poor survival prognosis of IgG4-RD tend to suffer from malignancy, especially pancreatic cancer and lymphoma, which may be associated with chronic inflammatory stimulation and immune system dysfunction (7,18). Immunization and biologic treatment of patients with IgG4-RD can perturb normal immune system function and increase the possible incidence of tumor or paraneoplastic syndromes (19), while the abnormal immune system state of the tumor and the local inflammatory factor microenvironment can lead to abnormal activation of immune-mediated pathways associated with IgG4-RD (20). It has been demonstrated that $CD4^+$ cytotoxic T lymphocytes (CTLs) in patients with IgG4-RD promote excessive replication of cytosine deaminase and induce DNA mutations, while abnormal antigen replication in the local tumor microenvironment can promote an autoimmune cascade that ultimately leads to illnesses such as IgG4-RD and scleroderma (21,22).

The association of IgG4-RD with malignancy has been demonstrated in previous clinical studies, and an active IgG4-RD state has been demonstrated to be a risk factor for the development of malignant tumors (23,24). Patients with IgG4-RD have significantly higher standardized incidence ratios (SIRs) (SIR, 2.57; 95% CI, 1.72-3.84) compared with the standard population of the same sex and age, with increased overall cancer risk and a significant decrease in patient quality of life (18). The specific SIRs for pancreatic cancer and lymphoma were higher than those of the general population in IgG4-RD patients (SIR, 4.07; 95% CI, 1.04-15.92; and SIR, 69.17; 95% CI, 3.91-1223.04, respectively) (18). This correlation has been demonstrated in a number of neoplasms, such as head and neck neoplasms (25), pulmonary carcinomas (26), breast carcinomas (27), gastrointestinal (28), hepatic carcinomas and cervical carcinomas (29).

IgG4-RD also enhances the morbidity of hematological malignancies, decreases overall survival and accelerates disease progression (30,31). AICy induces and complicates myeloid malignancies such as AML and lymphoma and patients with MDS with low- or intermediate-risk IPSS and timely diagnosis of AID or late onset have an improved quality of survival (32). The transformation of MDS as a premalignant stage of the hematological disease to AML is also closely related to immune system-related diseases, but its association with IgG4-RD has not been elucidated (33). Asano *et al* (34) observed a total of 34 malignancies, including two lymphomas and one MDS, in a 12-year follow-up of 158 patients with IgG4-RD (34). This study also confirmed that cases of IgG4-RD combined with

MDS exist but are extremely rare. Regarding treatment, AID associated with MDS could benefit from demethylating treatments for MDS, such as azathioprine, to reduce relapse rates and avoid hormone dependence, as confirmed by Roupie *et al* (35). Current evidence demonstrates an association between MDS and different systemic autoimmune diseases, but the exact underlying mechanisms remain unclear (36). Therefore, the present study suggests that there is an association between the development of these diseases.

The present case report presents a patient with a concurrent diagnosis of IgG4-RD and MDS who had a prolonged onset of the diseases, and the sequence of concurrent or predisposing events of the two diseases remained unclear. The present patient was at substantial risk of becoming leukemic, and IgG4-RD increased the malignancy risk. Therefore, the data suggests that the concurrent IgG4-RD and MDS of this patient was more than a simple coincidence, demonstrating a clinical need to raise awareness of the development of MDS combined with IgG4-RD, as early treatment is essential to prevent damage to multiple organs, enhance survival quality and prolong survival time of patients.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SL, BY and ZHu contributed to the conception and design of the study. CZ performed histopathological evaluation of the bone marrow specimens. LW, XP and ZHo made significant contributions to the acquisition, analysis and interpretation of the data, wrote the manuscript, prepared the figures and revised the article for critically important intellectual content. LW and XP confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written consent for publication has been obtained from both the patient and their daughter. All identifying information has been removed or anonymized to ensure confidentiality.

Competing interests

The authors declare that they have no competing interests.

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