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LETTER TO THE EDITOR

ImmunoglobulinG4-related disease mimicking lymphoma

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Dear Editor,

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a relatively newly recognized fibroinflammatory disease characterized by a dense lymphoplasmacytic infiltrate with increased IgG4-positive plasma cells, tumefactive lesions, and fibrosis, often accompanied by elevated serum IgG4 concentrations [1, 2]. IgG4-RD has been reported to develop in many organs, and comprehensive diagnostic criteria of IgG4-RD were suggested in 2011 comprising elevated serum IgG4 level (> 135 mg/dL), increased IgG4+ cells (> 10/high-power field (HPF)), and increased IgG4+/IgG+cell ratio of more than 40% [3]. Few cases with bone marrow (BM) involvement have been reported [4, 5]; this is possibly due to the overlapping features of many other hematologic conditions that need a differential diagnosis and due to the low recognition of the disease entity among hematologists [6]. Thus, we report a case of IgG4-RD with BM involvement. This study was approved by the institutional review board, and informed consent was obtained from the patient.

An 82-year-old man with a past medical history of colon cancer was consulted for cytopenia, increased globulin fraction, and multiple lymph node (LN) enlargements detected on imaging; he was suspected with lymphoma. Laboratory results at the time of diagnosis are shown in Table 1. Abdominal computed tomography (CT) was performed, which showed diffuse swelling of the pancreas and dilatation of the biliary tree with abrupt transition at the intrapancreatic common bile duct, suggesting autoimmune pancreatitis with increases in lipase and amylase levels. Whole-body positron emission tomography was performed showing hypermetabolic lesions in the lungs, multiple systemic LNs, spleen, pancreas, and BM, suggesting either lymphoma involvement or reactive changes in the spleen and BM with pancreatitis. Thus, LN and BM biopsies were obtained.

Inguinal LN biopsy showed atypical paracortical proliferation of small- to medium-sized CD4-positive T cells and increased IgG4-positive cells (> 100 cells/HPF) and IgG4/IgG ratio (> 0.9). The BM revealed normocellular marrow with 3.6% plasma cells, no abnormal lymphocytic infiltrations, and normal karyotype. IgG4-positive cells were increased (> 10/HPF) and IgG4/IgG ratio (> 0.4) (Fig. 1). Serum IgG level was elevated to 4996 mg/dL, and serum IgG4 level was 1317 mg/dL. Serum protein electrophoresis showed a diffuse increase in gamma fraction, suggesting polyclonal gammopathy.

The patient was administered oral prednisolone (1 mg/kg/day) with a gradual decrease in prednisolone dose; at 2 months after follow-up, the results of complete blood cell count were within the reference range, with normalization of the globulin fraction, lipase, and amylase (Table 1). IgG4 level also decreased to 580 mg/dL. The prednisolone dose was gradually decreased to 0.1 mg/kg/day, and the patient remains well.

As hematologists, IgG4-RD must be diagnosed with caution because the characteristic pathology of storiform fibrosis and obliterans phlebitis is rarely present in LNs and the BM [6], and IgG4-RD also mimics many other hematologic diseases, such as lymphoma, plasma cell neoplasms, and histiocytic disorders. However, this case showed typical imaging findings with diffuse pancreatic swelling suggesting autoimmune pancreatitis with a very high serum IgG4 level [7], increased IgG4+ plasma cells with IgG4/IgG ratio (> 0.4) in both LNs and the BM, and responsiveness to steroid treatment, suggesting the BM involvement of IgG4-RD. It is important to stain for IgG4 and IgG in suspected cases to identify IgG4-RD in the BM. Although organ-specific criteria do not

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Table 1 Laboratory findings at diagnosis and follow up

Laboratory tests	Diagnosis	Two months after diagnosis	Reference range
White blood cell count	2.8×10^9/L	11.2×10^9/L	$4.0–10.0 \times 10^9$/L
Absolute neutrophil count	1.3×10^9/L	6.4×10^9/L	$1.5–7.5 \times 10^9$/L
Hemoglobin	117 g/L	131 g/L	130–170 g/L
Platelet	54×10^9/L	192×10^9/L	$130–400 \times 10^9$/L
Total protein	92 g/L	77 g/L	60–80 g/L
Albumin	23 g/L	32 g/L	33–52 g/L
Total cholesterol	98 mg/dL		0–200 mg/dL
Blood urea nitrogen	17 mg/dL	16 mg/dL	10–26 mg/dL
Creatinine	1.20 mg/dL	0.72 mg/dL	0.7–1.4 mg/dL
Lactate dehydrogenase		226 IU/L	100–225 IU/L
Aspartate aminotransferase	206 IU/L	31 IU/L	0–40 IU/L
Alanine aminotransferase	186 IU/L	29 IU/L	0–40 IU/L
Amylase	696 U/L	94 U/L	30–100 U/L
Lipase	7943 U/L	103 U/L	23–300 U/L
Total bilirubin	1.28 mg/dL	0.79 mg/dL	0.2–1.20 mg/dL
Alkaline phosphatase	653 IU/L	125 IU/L	30–115 IU/L
C-reactive protein	3.51 mg/dL	1.15 mg/dL	0–0.5 mg/dL
Immunoglobulin (Ig) G	4996 mg/dL		700–1700 mg/dL
IgG4	1317 mg/dL	580 mg/dL	6.1–121.4 mg/dL
IgA	284 mg/dL		90–400 mg/dL
IgM	108 mg/dL		45–230 mg/dL
Serum protein electrophoresis	Polyclonal gammopathy		

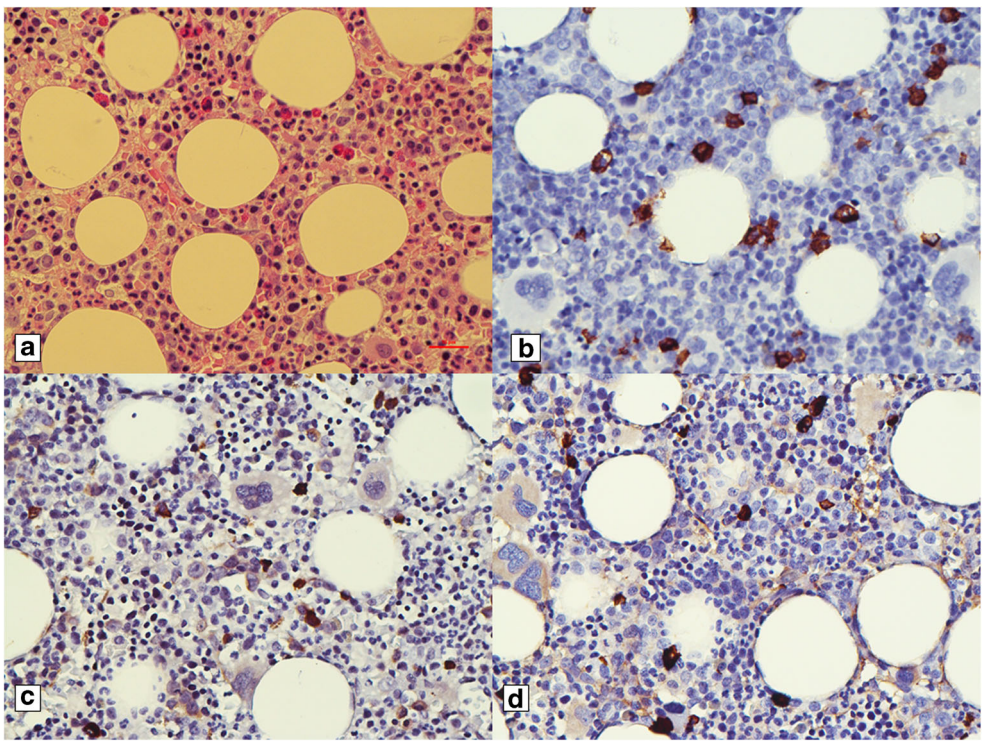

Fig. 1 Bone marrow section and immunohistochemical staining results. **a** Hematoxylin & eosin, **b** CD138 plasma cells, **c** IgG plasma cells, **d** IgG4 plasma cells. IgG, immunoglobulin G; IgG4, immunoglobulin G4

exist for the BM, applying the common criteria of IgG4 > 10/HPF and IgG4/IgG > 0.4 in the BM seems to be suitable [3, 4].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the institutional review board (B1902–520-701).

Informed consent Informed consent was obtained from the individual included in the study.

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