



A Case of IgG4-related Disease With Bone Marrow Involvement: Bone Marrow Findings and Flow Cytometric Immunophenotyping of Plasma Cells

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Dear Editor,

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD), an immune-mediated fibro-inflammatory disorder, is diagnosed based on tissue biopsies [1-3]. The key features include dense lymphoplasmacytic infiltration rich in IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis, and mild-to-moderate eosinophil infiltration. IgG4 immunohistochemical (IHC) staining is needed to confirm the diagnosis in the presence of these features. IgG4-RD can invade almost all organs including the kidneys, lungs, and aorta and frequently form a tumefactive mass that destroys the involved organs. Comprehensive criteria for IgG4-RD diagnosis were suggested by a Japanese group in 2012: high serum IgG concentration (>1.35 g/L), increased numbers of IgG4-positive cells (>10 cells/high-power field [HPF]), and IgG4/IgG-positive cell ratio of $>40\%$ [4]. Blood plasmablasts have been reported as biomarkers for diagnosis and assessment of treatment response. IgG4-RD patients have elevated plasmablast concentrations in the peripheral blood (PB; median: 4,698 cells/mL, range: 610–79,524 cells/mL) [5]. Plasmablasts with CD19^{low}CD38⁺CD20⁺CD27⁺ have been measured by flow cytometric immunophenotyping [6].

Although IgG4-RD is well known for variable organ involvement, only three cases of bone marrow (BM) involvement have

been reported [7-9]. Hwang, *et al.* [9] reported a case in Korea in 2019; however, neither PB nor BM plasma cell flow cytometry was conducted. We present a case of IgG4-RD with BM involvement and demonstrate the usefulness of flow cytometric immunophenotyping of plasma cells in PB and BM aspirates in IgG4-RD diagnosis. The Institutional Review Board of Asan Medical Center, Seoul, Korea (S2020-1248-0001) approved this study and waived the need for informed consent from the patient.

A 63-year-old man with renal failure was diagnosed as having IgG4-RD a year ago, confirmed by a kidney biopsy (tubulointerstitial nephritis with increased interstitial lymphoplasmacytic infiltration and >30 IgG4-positive plasma cells/HPF). He had visited the outpatient clinic complaining of abdominal pain and a skin rash that had developed one month earlier. The computed tomography scan showed multiple lymphadenopathies, and the torso positron emission tomography images revealed hyperactive BM. Blood tests revealed leukocytosis, thrombocytopenia, marked eosinophilia (51% on white blood cell [WBC] differential count), and rare nucleated red blood cells (1/100 WBCs). Total serum IgG and IgG4 concentrations were increased (Table 1). PB smear showed poikilocytosis and rouleaux formation (Fig. 1A). Serum protein electrophoresis indicated polyclonal gam-

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Table 1. Laboratory findings

	Results	Reference range	Unit
WBC	16.5	4–10	10 ⁹ /L
Hb	122	130–160	g/L
Platelet	45	150–350	10 ⁹ /L
Total protein	74	60–80	g/L
Albumin	20	35–52	g/L
AST	1.5	0–0.7	μkat/L
ALT	1.05	0–0.7	μkat/L
Alkaline phosphatase	12.4	0.7–2.0	μkat/L
Total bilirubin	102.6	3.4–20.5	μmol/L
Direct bilirubin	99.2	0–8.6	μmol/L
Sodium	133	135–145	mmol/L
Potassium	4.1	3.5–5.1	mmol/L
Chloride	93	98–110	mmol/L
Creatinine	636.5	61.9–123.8	μmol/L
BUN	10.4	3.6–9.3	mmol/L
Amylase	1.4	0.5–1.8	μkat/L
Lipase	1.4	0.2–1.0	μkat/L
CK	1.2	0.8–4.2	μkat/L
LD	6.25	2.0–4.2	μkat/L
CRP	79.3	0–6	mg/L
IgG	33.9	7–16	g/L
IgG4	19.1	0.061–1.21	g/L

Abbreviations: WBC, white blood cell; Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; LD, lactate dehydrogenase; CPR, C-reactive protein; IgG, Immunoglobulin G; IgG4, Immunoglobulin G4.

mopathy.

The patient underwent a BM study because of unexplained thrombocytopenia with reversed albumin to globulin ratio. The BM aspirates showed increased number of plasma cells, which included immature forms (16.8% of plasma cells among the BM nucleated cells; Fig. 1B), as well as moderate eosinophilic hyperplasia (20.4% of eosinophils among the BM nucleated cells; Fig. 1C and D). The cellularity varied with an average of 50%. IHC staining of the BM biopsy showed increased numbers of CD138-positive plasma cells with interstitial and clustered infiltration; however, clonal restriction for kappa or lambda light chains was not observed. IgG and IgG4 stains showed increased numbers of IgG- and IgG4-positive plasma cells; 31 IgG4-positive plasma cells/HPF and 35 IgG-positive plasma cells/HPF were observed (IgG4/IgG-positive plasma cell ratio=0.88; Fig. 1E and F). IgH gene rearrangement with BM aspirate was not found.

Flow cytometric immunophenotyping was performed using a FACSCanto II flow cytometer (BD Biosciences, San Jose, CA, USA) and a CD38/CD138/CD19/CD45/CD56 panel. Plasma cells in the PB comprised 0.376% of the WBCs (62,040 cells/mL); 58.3% of plasma cells were atypical plasma cells (low CD19 expression with CD38⁺/CD138^{dim}/CD56⁻/CD45⁺). The immunophenotype of the atypical plasma cells in the BM (64.3% of the total BM plasma cells) was CD38⁺/CD138⁺/CD56⁺/CD19^{low}/CD45^{low}, slightly different from that of the PB cells (Fig. 1G and H). The difference in CD56 expression between PB and BM plasma cells is likely due to the nature of plasma cells in IgG4-RD. Among the heterogeneous plasma cells, only a few CD56-negative cells might migrate to the circulating system, as CD56 acts as an adhesion molecule. The patient was treated with high-dose steroids and discharged as his symptoms improved.

As IgG4-RD tends to form tumefactive lesions, patients are easily suspected of having malignancies. Additionally, BM findings can mimic other hematologic diseases such as lymphomas, plasma cell neoplasms, and histiocytic disorders. However, IgG4-RD diagnosis is difficult based on BM studies because the core pathological features are rarely present in the BM. Therefore, if a patient suspected of having IgG4-RD has an abnormal complete blood count, a BM study with IHC staining for CD138, kappa and lambda light chains, IgG, and IgG4 and flow cytometric immunophenotyping of plasma cells in the PB and BM aspirates should be considered. Furthermore, when a patient undergoes a BM study for lymphoma workup and diagnosis of plasma cell neoplasms or histiocytic disorders, hematopathologists should consider the possibility of IgG4-RD with BM involvement, if elevated serum IgG and IgG4 concentrations or other laboratory abnormalities are present.

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AUTHOR CONTRIBUTIONS

All authors have accepted their responsibility for the entire content of this manuscript and approved submission.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this paper were reported.

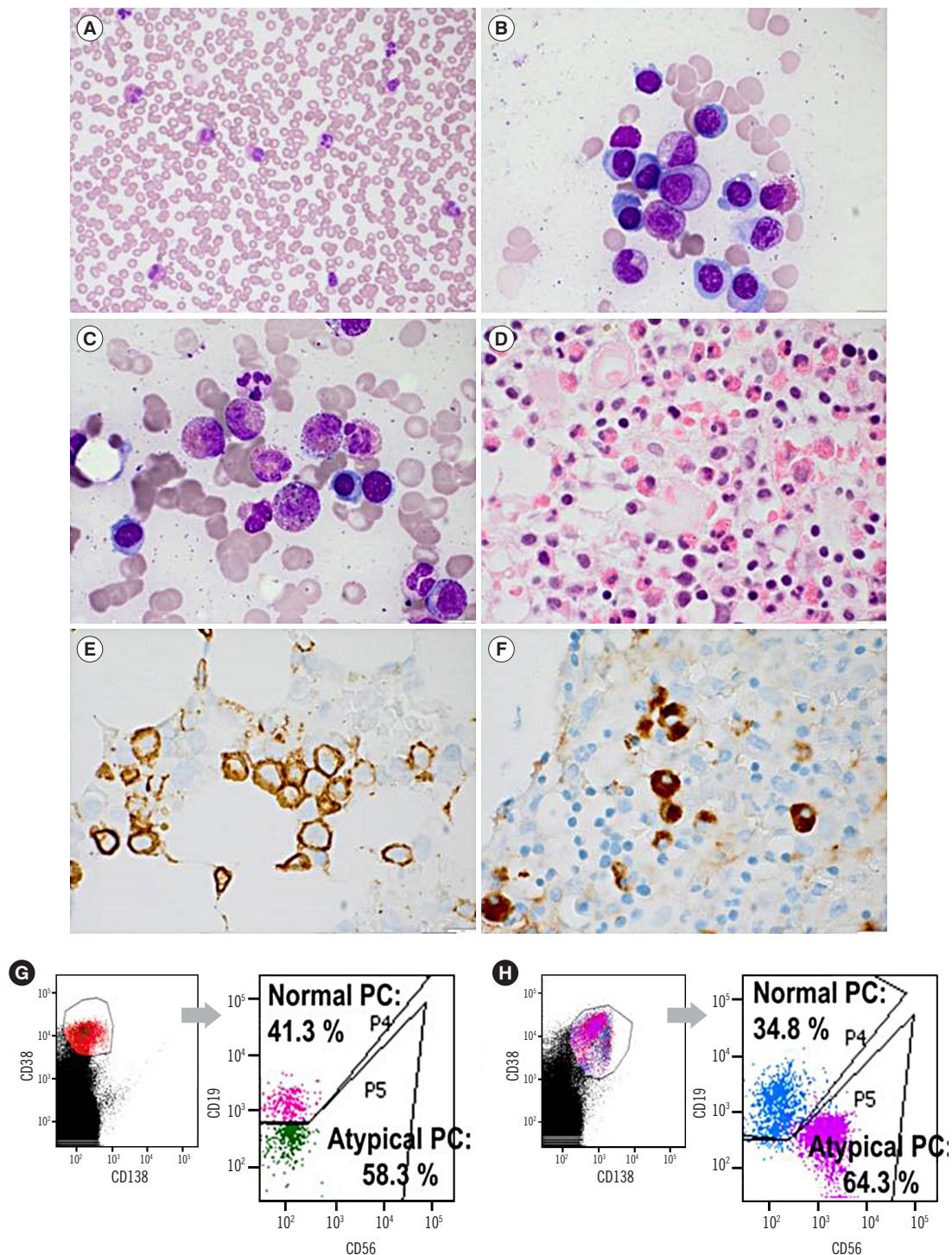


Fig. 1. Morphologic and IHC findings of PB and BM samples, and flow cytometric immunophenotyping of PC. (A) Eosinophilia, poikilocytosis (schistocytes and spherocytes), and rouleaux formation (PB, Wright stain, $\times 400$). (B) Increased numbers of PC including immature forms with slightly high NC ratio, nucleolus, and perinuclear halo (BM aspirate, Wright stain, $\times 1,000$). (C) Increased number of eosinophils (BM aspirate, Wright stain, $\times 1,000$). (D) Increased number of eosinophils and PC (BM biopsy, H & E stain, $\times 400$). (E) Increased number of PC (BM clot section, IHC stain for CD138, $\times 1,000$). (F) Increased numbers of IgG4+ PC (BM biopsy, IHC stain for IgG4, $\times 1,000$). (G, H) Presence of atypical PC with the immunophenotypes CD38⁺/CD138^{dim}/CD56⁻/CD19^{low}/CD45⁺ in PB and CD38⁺/CD138⁺/CD56⁺/CD19^{low}/CD45^{low} in BM aspirates.

Abbreviations: IHC, immunohistochemistry; PB, peripheral blood; BM, bone marrow; PC, plasma cells.

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