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Chronic eosinophilic leukemia with a *FIP1L1-PDGFRA* rearrangement: Two case reports and a review of Korean cases

TO THE EDITOR: According to the 2008 World Health Organization (WHO) guidelines, eosinophilia is associated with hematologic diseases such as chronic eosinophilic leukemia-not otherwise specified (CEL-NOS); idiopathic hypereosinophilic syndrome (HES) or idiopathic hypereosinophilia; and myeloid and lymphoid neoplasms with eosinophilia, and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1* [1]. CEL is diagnosed in cases with increased blasts or cytogenetic/clonal abnormalities. We report 2 cases of myeloid and lymphoid neoplasms (CEL) with the *FIP1L1-PDGFRA* rearrangement.

CASES

The first case, 27-year-old man was referred to our hospital for a dyspnea workup. The echocardiogram revealed severe tricuspid valve regurgitation and moderate mitral valve regurgitation. A valvuloplasty was performed and dizziness developed after the surgery. Brain magnetic resonance imaging revealed microbleeding in the right temporo-occipital lobe. He was referred to the hemato-oncology department for evaluation of eosinophilia. The laboratory findings were as follows: WBC count, 21.1×10^9/L (eosinophil count,

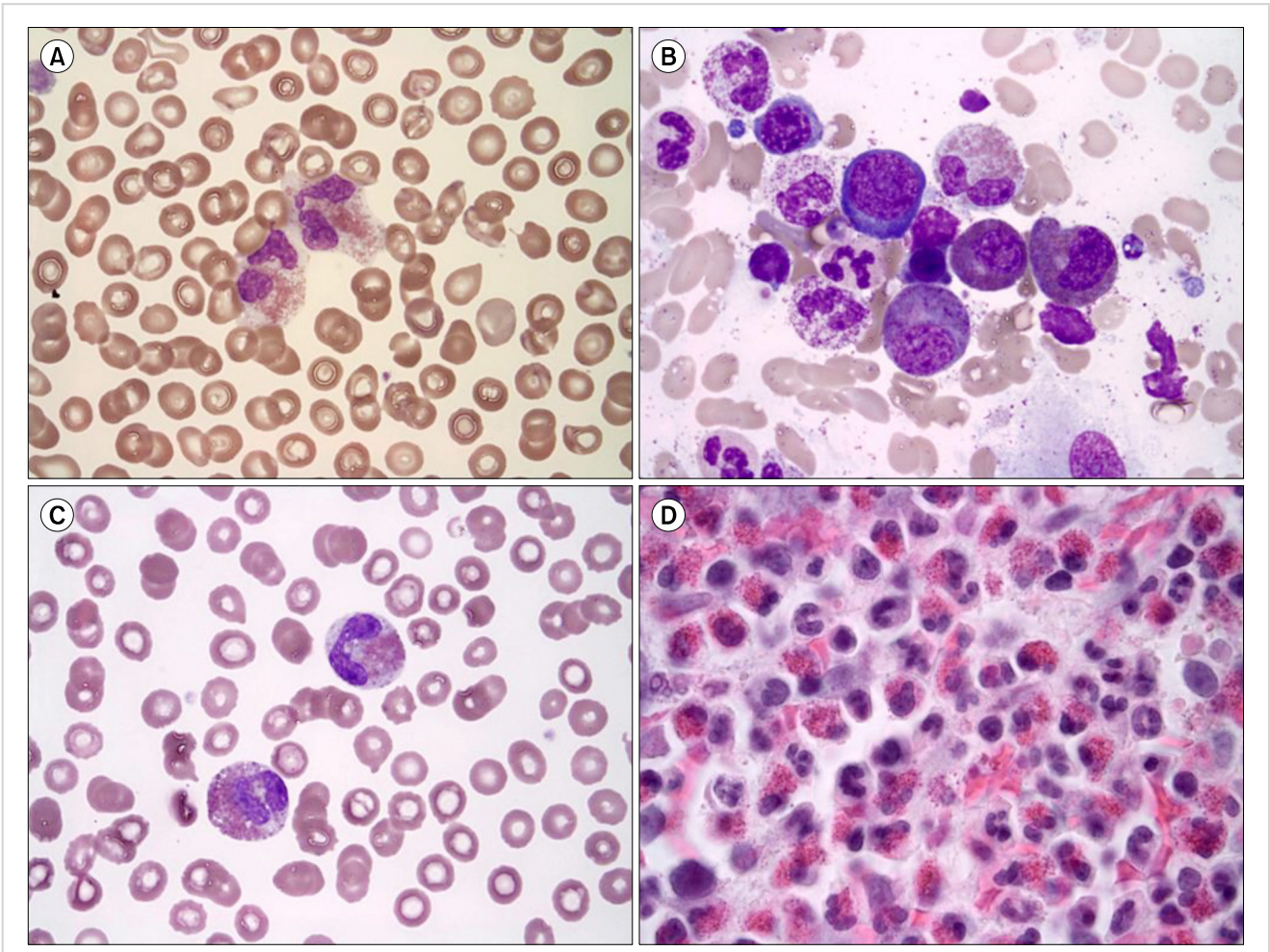

Fig. 1. Peripheral blood (PB) smear and bone marrow (BM) aspirate findings of first case **(A, B)** and second case **(C, D)**. **(A)** Eosinophilia (13.0×10^9/L) was observed in the PB (Wright-Giemsa, ×1,000). **(B)** Dysplastic eosinophils (sparse and mixed granules) were increased in the BM aspirate (Wright-Giemsa, ×1,000). **(C)** Eosinophilia (55.316×10^9/L) was observed in the PB (Wright-Giemsa, ×1,000). **(D)** The BM section was packed with eosinophils (hematoxylin-eosin, ×400).

13.0×10^9/L); Hb, 9.1 g/dL; and platelet count, 99.0×10^9/L. In addition, parasite antibodies for *Clonorchis sinensis*, *Paragonimus westermani*, *Cysticercus cellulosae*, and *Sparganosis* were negative. The number of eosinophils in the peripheral blood smear was increased (Fig. 1A). Analysis of the bone marrow aspirate showed that 1.95% of all nucleated cells were blasts and eosinophils were increased (Fig. 1B). Conventional cytogenetic analysis revealed a normal karyotype (46,XY). Fluorescence in situ hybridization (FISH) for *FIP1L1-PDGFRA* using the Vysis 4q12 Tri-Color probe (Abbott, Des Plaines, USA) was positive (Fig. 2A, B). We confirmed the *FIP1L1-PDGFRA* rearrangement by reverse transcription-polymerase chain reaction (RT-PCR) and sequencing analysis (Fig. 2D, E). The primers for RT-PCR and sequencing analysis were as follows: forward, 5'-TCAGACAAGTACTGCCTCCAGA-3' and reverse, 5'-AG GCTCCCAGCAAGTTTACA-3'. According to the 2008 WHO guidelines, a diagnosis of myeloid and lymphoid neoplasm (CEL) associated with *FIP1L1-PDGFRA* was established. Tyrosine kinase inhibitor treatment with imatinib mesylate was initiated and the eosinophil counts decreased.

The second case, 23-year-old man was referred to our hospital for a workup as eosinophilia had been detected in a routine health checkup. The laboratory findings were as follows: WBC count, 70.0×10^9/μL (eosinophil count, 55.3×10^9/L); Hb, 10.1 g/dL; and platelet count, 131.0×10^9/L. The number of eosinophils in the peripheral blood smear was increased (Fig. 1C). In the bone marrow aspirate, 90% of all nucleated cells were eosinophils. Infiltration by eosinophils was observed in the bone marrow section (Fig. 1D). Conventional cytogenetic analysis revealed a normal karyotype (46,XY) and FISH for *FIP1L1-PDGFRA* was positive (Fig. 2C). Tyrosine kinase inhibitor treatment with imatinib mesylate was initiated and the eosinophil counts decreased.

DISCUSSION

The *FIP1L1-PDGFRA* rearrangement caused by a cryptic deletion of 800-kb on chromosome 4q12, which contains the *CHIC2* gene [2], cannot be detected in conventional chromosomal studies; FISH or RT-PCR must be used. The prevalence of *PDGFRA*, *PDGFRB* or *FGFR1* rearrangements is generally low. The *FIP1L1-PDGFRA* rearrangement is the most commonly found with an incidence of approximately 23%, but this varies (range, 3–56%) depending on the HES patient population [3], and is predominantly found in males. In a Korean study [4], only 1 case with a *PDGFRA*

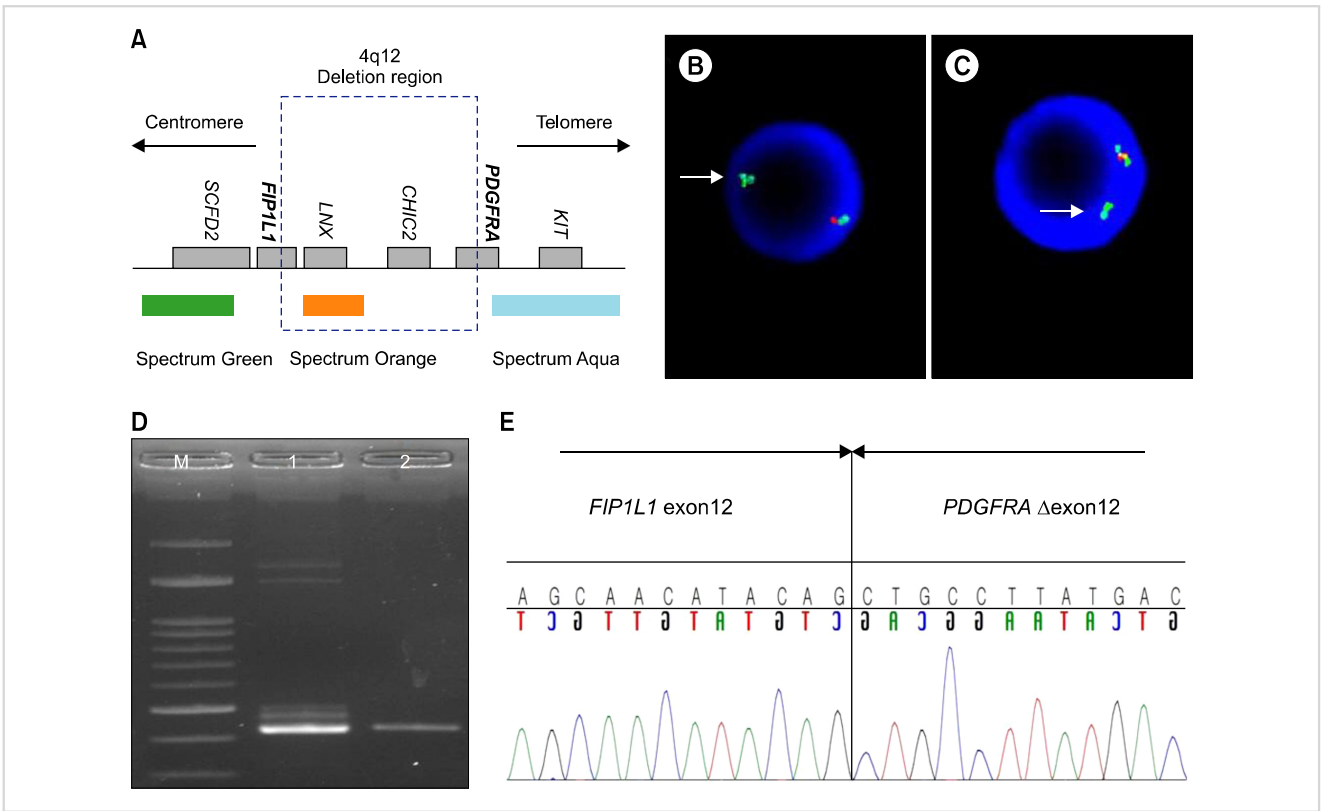

Fig. 2. Fluorescence in situ hybridization (FISH) for the *FIP1L1-PDGFRA* rearrangement, and reverse transcription – polymerase chain reaction (RT-PCR) and sequencing analysis. **(A)** Schematic representation of the 4q12 region and FISH probe. **(B)** Loss of the orange signal indicates deletion of the 4q12 region (white arrow) in first case. **(C)** FISH results for second case. **(D)** RT-PCR was performed using RNA extracted from the patient's (first case) white blood cells (lane 1). EOL-1 cells were used as a positive control (lane 2). Size marker (M). **(E)** Sequencing analysis of the RT-PCR products revealed the fusion of *FIP1L1*, exon 12 and truncated *PDGFRA*, exon 12 (breakpoint is between the 84th and 85th nucleotides of exon 12). *FIP1L1*, Ensemble Gene ID ENSG00000145216; PDGFRA, Ensemble Gene ID, ENSG00000134853.

Table 1. Summary of Korean cases with PDGFRA/PDGRB or FGFR1 abnormalities.

Case No.	Age/ Gender	Eosinophils ($\times 10^9$/L)	Clinical symptoms/ signs	Hematologic features	Karyotype	Gene	Treatment	Ref.
1	27/M	13.000	Dyspnea, valve regurgitation	CEL	46,XY	*PDGFRA*	Imatinib mesylate	Present study
2	23/M	55.316	No	CEL	46,XY	*PDGFRA*	Imatinib mesylate	Present study
3	49/F	2.820	Proteinuria, edema	CEL, MM	46,XX	*PDGRFA*	Imatinib mesylate with combination chemotherapy	[4]
4	30/M	8.036	Hematuria, valve regurgitation	CEL	46,XY	*PDGFRA*	Imatinib mesylate	[9]
5	50/M	84.088	Dyspnea, hemothorax, cerebral infarct	CMML	46,XY,+1,der(1;7)(q10;p10), t(5; 12)(q31;p13)	*PDGFRB*	Hydroxyurea	[6]
6	82/F	12.240	General weakness	CEL	46,XX,ins(1;5)(q22;q33q13.3)	*PDGFRB*	Imatinib mesylate	[8]
7	36/M	64.800	Nasopharyngeal mass	Precursor T-cell lymphoma	45,XY,-7,t(8;13)(p11.2;q12)	*FGFR1*	Combination chemotherapy	[5]
8	29/M	NA	Sore throat	AML with MD	45,XY,-7,t(8;13)(p11.2;q12)	*FGFR1*	Combination chemotherapy	[7]
9	50/M	NA	Inguinal lymphadenopathy	AMML	48,XY,t(8;9)(p11.2; q33),+19,+21	*FGFR1*	Combination chemotherapy	[7]
10	61/F	NA	Easy bruising	AML with MD	46,XX,add(8)(p11.2)	*FGFR1*	Combination chemotherapy	[7]

Abbreviations: AMML, acute myelomonocytic leukemia; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; MD, minimal differentiation; MM, multiple myeloma; NA, not available.

rearrangement was detected among 34 hypereosinophilia patients who were suspected of having clonal eosinophilia. Until now, few cases of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangements have been reported in Korea [4-9], and these are summarized in Table 1.

The initial clinical manifestation of HES involves dermatologic, pulmonary, and gastrointestinal symptoms [10]. However, the presence of neurologic or cardiac signs and symptoms increases with disease progression or delayed diagnosis [10]. Severe cardiac complications include endomyocardial fibrosis, valve scarring, and embolism. Our patients also showed dyspnea, cardiac signs (valve regurgitation), and renal involvement (Case 1). Therefore, clinicians need to be alert for the presence *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangements in eosinophilia patients with systemic symptoms, especially those associated with the cardiopulmonary or renal systems.

In conclusion, we report 2 cases of CEL with the *FIP1L1-PDGFRA* rearrangement. Eosinophilia with *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangements is rare in the general population. However, its prevalence is high in HES patients (range, 3–56%) [3], and FISH or RT-PCR must be used for its detection. Unusual cardiopulmonary or gastrointestinal symptoms with severe complications may be observed initially. Therefore, clinicians must consider *PDGFRA*, *PDGFRB* or *FGFR1* rearrangements in patients with eosinophilia presenting with these symptoms and perform FISH or RT-PCR.

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

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Diffuse large B cell lymphoma with high M protein: an unusual finding

TO THE EDITOR: Paraprotein is an abnormal immunoglobulin (Ig) or part of an Ig in the blood or urine that is produced by a clonal population of B cells and plasma cells. Production of a monoclonal Ig paraprotein is associated with various types of B-cell non-Hodgkin's lymphomas (NHLs). Paraproteinemia is associated with about 20% of patients with indolent types of NHL, whereas it appears to be rare in aggressive lymphomas [1]. Immunofixation (IFX) and conventional serum protein electrophoresis (SPEP) are useful tools to detect even low levels of monoclonal Igs. Herein, we report a case of diffuse large B cell lymphoma with a very high level of IgG kappa monoclonal gammopathy, which was rarely reported in the literature [2].

CASE

A 68-year-old man with a known case of rheumatoid arthritis presented with upper gastrointestinal bleeding. On examination, he was found to have axillary lymphadenopathy with splenomegaly. F-18 fluoro-D-glucose (FDG) positron emission tomography showed FDG avid bilateral axillary, external iliac, and inguinal lymph nodes and splenomegaly with diffusely increased FDG uptake. Hematological analysis showed hemoglobin to be 7.7 g/L; total leucocyte count, 8.9×10^9/L; and platelets, 80×10^9/L. Axillary lymph node biopsy showed sheets of large atypical lymphoid cells with irregular contours, brisk mitoses, and prominent nucleoli as well as perinodal spread. According to immunohistochemical analysis, these cells were positive for CD20 and MUM-1 and negative for CD3, CD10, Bcl-6, CD5, and cyclin D1. The Ki-67 index was found to be 70% (Fig. 1). A final diagnosis of diffuse large B cell lymphoma (DLBCL) was made, and bone marrow examination was performed for staging. Bone marrow preparation showed approximately 25% lymphoid cells including few abnormal forms, suggestive of lymphoma infiltration; this was confirmed on bone marrow biopsy by the presence of CD20 positive lymphoid cells in a diffuse and nodular pattern. Furthermore, plasma cell percentage was not increased and no monoclonal population was noted on biopsy, which was confirmed by immunohistochemistry for kappa and lambda light chains. SPEP revealed a monoclonal M band of 4.66 g/dL (Fig. 1), IFX identified this monoclonal protein to be IgG, kappa. A serum-free light chain assay showed the kappa level to be 325.98 mg/L, lambda 161.56 mg/L, and the ratio of kappa to lambda 2.0. A final diagnosis of stage IV DLBCL with paraproteinemia was made and the patient was started on R-CHOP therapy.

DISCUSSION

Paraproteinemia, or monoclonal gammopathy, is the presence of excessive amounts of paraprotein or a single monoclonal gammaglobulin in the blood. It usually occurs as a part of an underlying immunoproliferative disorder, such as leukemia, lymphoma, or plasma cell dyscrasia. Serum paraprotein levels in lymphoma patients are usually low and commonly associated with low grade lymphomas. Detection of monoclonal paraprotein using SPEP with quantitation of Igs and IFX should be included in the staging of lymphoma patients, as the presence of monoclonal gammopathy may influence prognostic stratification of these patients. Serum-free light chain assay is also a useful technique and may represent a significant prognostic marker for the detection of bulk and residual disease, both before and after treatment [3]. Further studies should be conducted to correlate the survival of these patients with the quantity and type of paraproteins and any requirement of a specific chemotherapeutic drug combination for improving overall survival. High M protein sometimes can lead to mislabeling of a case as plasma cell dyscrasia, delaying appropriate investigation. High paraprotein levels must not dissuade one from suspecting an underlying lymphoma, especially when relevant investigation for plasma cell dyscrasia is non-contributory

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