Chronic eosinophilic leukemia with a FIP1L1-PDGFRα 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 hyper-eosinophilic syndrome (HES) or idiopathic hyper-eosinophilia; 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-PDGFRα 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).
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.

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...
Table 1. Summary of Korean cases with PDGFRα/PDGFRβ or FGFR1 abnormalities.

| Case No. | Age/Gender | Eosinophils (×10⁹/L) | Clinical symptoms/signs | Hematologic features | Karyotype | Gene | Treatment | Ref. |
|----------|------------|----------------------|-------------------------|----------------------|-----------|------|-----------|------|
| 1        | 27/M       | 13,000               | Dyspnea, valve regurgitation | CEL                  | 46,XY     | PDGFRα | Imatinib mesylate | Present study |
| 2        | 23/M       | 55.316               | No                      | CEL                  | 46,XY     | PDGFRα | Imatinib mesylate | Present study |
| 3        | 49/F       | 2.820                | Proteinuria, edema       | CEL, MM              | 46,XX     | PDGFRα | Imatinib mesylate with combination chemotherapy | [4] |
| 4        | 30/M       | 8.036                | Hematuria, valve regurgitation | CEL                  | 46,XY     | PDGFRα | 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;q31) | PDGFRB | FGFR1 | Imatinib mesylate | [8] |
| 7        | 36/M       | 64.800               | Nasopharyngeal mass      | Precursor T-cell lymphoma | 45,XY-7,t(8;13)(p11.2;q12) | FGFR1 | FGFR1 | Combination chemotherapy | [5] |
| 8        | 29/M       | NA                   | Sore throat              | AML with MD          | 45,XY-7,t(8;13)(p11.2;q12) | FGFR1 | FGFR1 | Combination chemotherapy | [7] |
| 9        | 50/M       | NA                   | Inguinal lymphadenopathy | AMML                | 48,XY,t(6;9)(p11.2; q33),+19,+21 | FGFR1 | FGFR1 | Combination chemotherapy | [7] |
| 10       | 61/F       | NA                   | Easy bruising            | AML with MD          | 46,XX,add(8)(p11.2) | FGFR1 | 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.

rarrangement was detected among 34 hypereosinophilia patients who were suspected of having clonal eosinophilia. Until now, few cases of PDGFRα, PDGFRβ, 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 PDGFRα, PDGFRβ, 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-PDGFRα rearrangement. Eosinophilia with PDGFRα, PDGFRβ, 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 PDGFRα, PDGFRβ or FGFR1 rearrangements in patients with eosinophilia presenting with these symptoms and perform FISH or RT-PCR.

Sang-Yong Shin1, Chul-Won Jung2, Dong-Chull Choi2, Byung-Jae Lee2, Hee-Jin Kim1, Sun-Hee Kim1

Departments of Laboratory Medicine & Genetics, Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Correspondence to: Hee-Jin Kim, Sun-Hee Kim Department of Laboratory Medicine & Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 135-710, Korea E-mail: heejinkim@skku.edu, and sunnyhk@skku.edu

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REFERENCES
1. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC Press, 2008.
2. Pardanani A, Ketterling RP, Brockman SR, et al. CHIC2 deletion, a surrogate for F1P1L1-PDGFRα fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy. Blood 2003;102:3093-6.
3. Gotlib J, Cools J. Five years since the discovery of F1P1L1-PDGFRα: what we have learned about the fusion and other molecularly defined eosinophilias. Leukemia 2008;22:1999-2010.
4. Kim DW, Shin MG, Yun HK, et al. Incidence and causes of hyper-eosinophilia (corrected) in the patients of a university hospital. Korean J Lab Med 2009;29:185-93.
5. Park TS, Song J, Kim JS, et al. 8p11 myeloproliferative syndrome preceded by t(8;9)(p11;q33). CEP110/FGFR1 fusion transcript: morphologic, molecular, and cytogenetic characterization of myeloid neoplasms associated with eosinophilia and FGFR1 abnormality. Cancer Genet Cytogenet 2008;181:93-9.

6. Kim M, Lim J, Lee A, et al. A case of chronic myelomonocytic leukemia with severe eosinophilia having t(5;12)(q13;p13) with t(1;7)(q10;p10). Acta Haematol 2005;114:104-7.

7. Lee H, Kim M, Lim J, et al. Acute myeloid leukemia associated with FGFR1 abnormalities. Int J Hematol 2013;97:808-12.

8. Jang SE, Kang HJ, Chang YH, et al. A case of myeloid neoplasm with the PDGFRB rearrangement and eosinophilia. Korean J Med 2010;78:386-90.

9. Lim KS, Ko J, Lee SS, Shin B, Choi DC, Lee BJ. A case of idiopathic hypereosinophilic syndrome presenting with acute respiratory distress syndrome. Allergy Asthma Immunol Res 2014;6:98-101.

10. Ogbogu PU, Bochner BS, Butterfield JH, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. J Allergy Clin Immunol 2009;124:1319-25.

**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-2, 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.

Manavi Dang, Smeeta Gajendra, Shalini Goel, Bhawna Jha, Tushar Sahni, Ritesh Sachdev

Department of Pathology and Laboratory Medicine, Medanta-The Medicity, Gurgaon, India