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CASE REPORT

Monocytosis and Clonal Hematopoiesis in Peripheral Blood as Indicators of Myeloid Neoplasm in Erdheim-Chester Disease

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SUMMARY

Background: **Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytosis, with ~10% of cases showing myeloid neoplasms (MNs).**
Methods: **A 70-year-old woman with cardiac arrhythmia and right atrial mass was diagnosed with ECD by biopsy. Complete blood count showed persistent monocytosis. Targeted next-generation sequencing (NGS) of peripheral blood (PB) for evaluating clonal hematopoiesis (CH) was performed.**
Results: **The NGS revealed *ASXL1* Asn893Cysfs*12 (variant allele frequency [VAF]: 37.2%), *TET2* His1031 Glnfs*11 (VAF: 49.0%) and *TET2* Tyr1255* (VAF: 47.5%). Bone marrow examination confirmed concomitant chronic myelomonocytic leukemia.**
Conclusions: **NGS using PB needs to be considered in ECD for the detection of CH and for the diagnosis of coexisting MNs.**
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KEYWORDS

Erdheim-Chester disease, clonal hematopoiesis, chronic myelomonocytic leukemia, *TET2, ASXL1*

INTRODUCTION

Erdheim-Chester disease (ECD) is a rare clonal non-Langerhans cell histiocytosis, classified as a macrophage-dendritic cell neoplasm in the 5th edition of the World Health Organization (WHO) classification [1]. It is characterized by tissue infiltration of foamy histiocytes, along with fibrosis and inflammation, affecting multiple organs, including the bones, lungs, kidneys, lymph nodes, heart, and brain [1]. Although the etiology of ECD has remained unclear for decades, subsequent studies have revealed that more than 60% of ECD patients harbor somatic *BRAF* V600E variants [2], and that nearly all patients have a variant that activates the

RAS-RAF-MEK-ERK pathway [2]. Consequently, ECD is considered a clonal hematopoietic malignancy [2,3]. Several studies have reported a high frequency (approximately 10%) of concomitant myeloid neoplasms - including myeloproliferative neoplasms (MPNs), myelodysplastic neoplasms (MDS), and MDS/MPNs - in adult ECD patients, with chronic myelomonocytic leukemia (CMML) being the most common [4].

Several large-scale sequencing studies have revealed that clonal variants in genes associated with myeloid malignancies are not limited to individuals with myeloid neoplasms (MNs), but can also be detected in individuals without hematological malignancies [5]. This condition, termed clonal hematopoiesis (CH), is characterized by the presence of somatic variants in hematopoietic cells without overt hematological malignancy. When these variants occur in known driver genes with a variant allele frequency (VAF) of at least 2%, the condition is referred to as CH of indeterminate potential (CHIP) [5,6]. The prevalence of CHIP increases with age [5,6]. CHIP is associated with an increased risk of hematological malignancies, cardiovascular diseases, and death [7,8]. In the original definition of CHIP, 19 candidate genes were proposed, among which *DNMT3A*, *TET2*, and *ASXL1* account for the majority of observed variants [5]. Isolated CHIP variants may not directly lead to a myeloid malignancy, unless accompanied by an additional genomic "hit," such as variants in other myeloid neoplasm driver genes [5]. The acquisition of these additional variants may occur randomly or can be facilitated by the proinflammatory environment induced by preexisting CHIP variants, leading to clonal instability [9].

Herein, we describe a patient with ECD in whom somatic variants in peripheral blood (PB) were explored using targeted next-generation sequencing (NGS), and hematologic neoplasm was confirmed by bone marrow examination.

CASE PRESENTATION

A 70-year-old female was referred to Samsung Medical Center for further treatment after being diagnosed with atrial flutter at another hospital. She had a history of unstable angina for which she had undergone percutaneous coronary intervention three years ago, followed by coronary artery bypass grafting two years ago. One month later, the patient experienced syncope due to ventricular arrhythmia and was treated with temporary pacemaker placement and implantable cardiac defibrillator insertion. Despite these interventions, she continued to experience dyspnea and recurrent syncope, along with new-onset right upper quadrant abdominal pain. Chest computed tomography revealed a mass in the right atrium, and abdominal ultrasonography revealed gallbladder wall thickening and biliary tree dilatation. Biopsy of the right atrial mass confirmed the diagnosis of ECD. Biopsy revealed a *BRAF* V600E variant in the ECD lesion.

Before ECD was diagnosed, she already had leukocytosis, and monocyte count was continuously higher than 1.0 x 10^9/L (Figure 1). To detect CH, targeted NGS was performed on genomic DNA extracted from the PB. The DNA panel was designed to test the following genes: *ABL1*, *ASXL1*, *BCOR*, *BRAF*, *CALR*, *CBL*, *CEBPA*, *CSF3R*, *DNMT3A*, *ETV6*, *EZH2*, *FLT3*, *GATA2*, *HRAS*, *IDH1*, *IDH2*, *IKZF1*, *JAK2*, *KIT*, *KRAS*, *MPL*, *MYD88*, *NF1*, *NPM1*, *NRAS*, *PHF6*, *PRPF8*, *PTPN11*, *RB1*, *RUNX1*, *SETBP1*, *SF3B1*, *SH2B3*, *SRSF2*, *STAG2*, *TET2*, *TP53*, *U2AF1L5*, *WT1*, and *ZRSR2*. Sequencing was performed using the Ion S5 XL Sequencer (Thermo Fisher Scientific, Waltham, MA, USA). The public databases used for variant annotation were the Exome Aggregation Consortium (http://exac.broadinstitute.org/), and the Catalog of Somatic Mutations in Cancer (http://cancer.sanger.ac.uk/cosmic/). Targeted NGS identified variants *ASXL1* c.2677_2686del, p.(Asn893Cysfs*12) (variant allele frequency [VAF]: 37.2%), *TET2* c.3093_3095delTCTinsA, p.(His1031Glnfs*11) (VAF: 49.0%), and *TET2* c.3764dup, p.(Tyr1255*) (VAF: 47.5%) (Supplementary Table). The *BRAF* V600E variant was not detected in this study. Three variants were identified from a public database. A bone marrow examination was performed two months later to diagnose the underlying hematologic malignancy. At that time, complete blood counts were: WBC 11.1 x 10^9/L, hemoglobin 99 g/L, and platelets 65 x 10^9/L. PB smear and bone marrow aspirate smear showed monocytosis, dysplastic hematopoiesis and hemophagocytic histiocytes (Figures 2A and 2B). Immunohistochemical studies showed that these histiocytes and monocytes were positive for CD68 and negative for CD1a (Figures 2C and 2D). Chromosome study and fluorescence in situ hybridization for *BCR*::*ABL1* translocation and *FGFR*, *PDGFRA*, and *PDGFRB* rearrangements revealed normal results. The patient with ECD was diagnosed with concomitant CMML based on clinical information, cytomorphology, and molecular genetic characteristics according to the revised 4th edition of the WHO classification [10], which was re-evaluated using the 5th edition criteria [1]. She was treated with subcutaneous peginterferon-α2A at a dose of 180 μg once weekly following the diagnosis of ECD. CMML was managed with supportive therapy alone, including darbepoetin administration for anemia.

DISCUSSION

In this report, we described a case of ECD with CMML as a concomitant myeloid neoplasm. BM study was prompted by detection of three CHIP variants in PB in the patient via multi-gene panel NGS. These included a frame-shift variant for *ASXL1* and two variants (frame-shift and nonsense) for *TET2*. The VAF of the three CHIP variants detected in the PB were 37.2%, 49.0%,

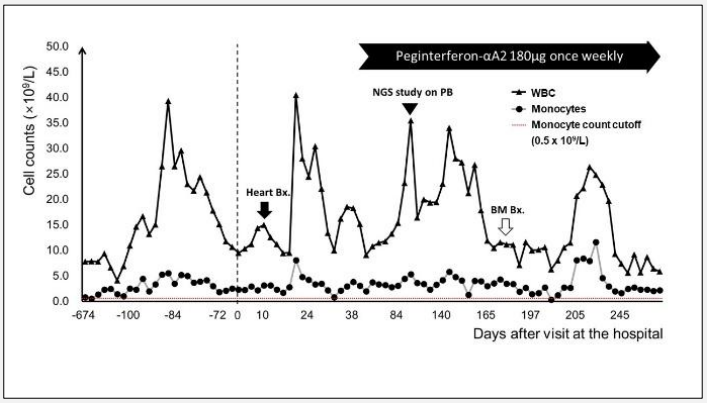

Figure 1. Clinical course of the patient.

The changes in white blood cell and monocyte counts during the hospital days, including the biopsies, next-generation sequencing study, treatment course, and follow-up, are shown. The horizontal dotted line indicates the monocyte count cutoff (0.5 x 10⁹/L), which is an essential diagnostic criterion for chronic myelomonocytic leukemia according to the 5th edition of the World Health Organization classification. The vertical dotted line represents the time point of the first hospital visit (Day 0). X-axis, course in days; Bx., biopsy; NGS, next-generation sequencing; PB, peripheral blood; BM, bone marrow; WBC, white blood cell.

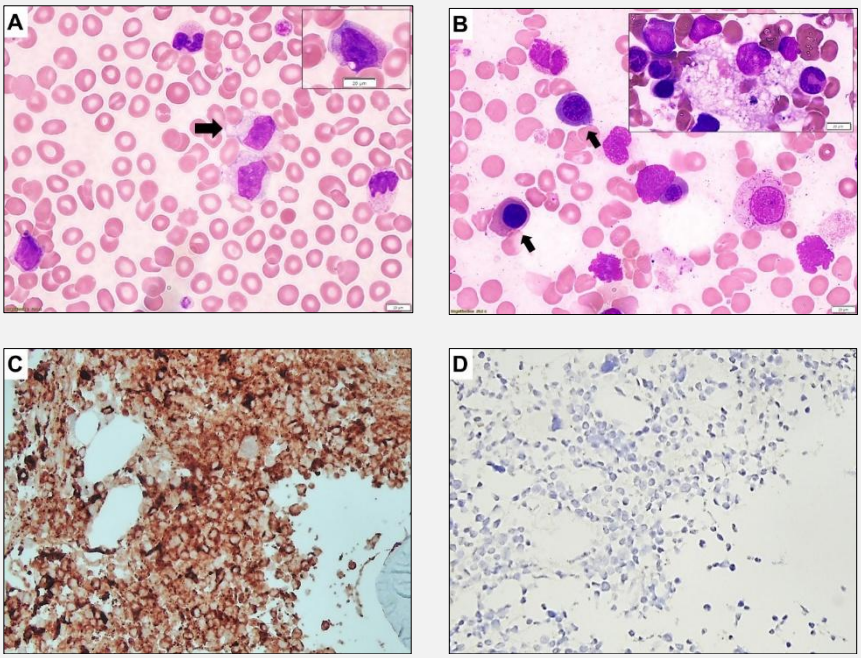

Figure 2. Peripheral blood and bone marrow cytomorphology in the patient with Erdheim–Chester disease and clonal hematopoiesis.

(A) Peripheral blood smear showing red blood cells with anisocytosis and poikilocytosis (elliptocytes, burr cells, and spherocytes), increased monocytes (arrow), left-shifted neutrophils (upper right box), and thrombocytopenia (Wright-Giemsa stain, oil immersion). (B) Bone marrow aspirate smear showing dysplastic hematopoiesis (arrows) and hemophagocytic histiocytes (upper right box) (Wright-Giemsa stain, oil immersion). Immunohistochemistry (x 400) of bone tissue sections revealed that the infiltrating cells were positive for CD68 (C) but negative for CD1a (D).

and 47.5%, respectively. A prospective cohort of patients with unexplained cytopenia demonstrated that the presence of a somatic variant with a VAF ≥ 10%, or the presence of two or more variants, had a high positive predictive value for the eventual diagnosis of a myeloid neoplasm [7]. Another study reported that the mean VAF at the time of blood sampling was significantly higher in individuals who subsequently developed hematologic malignancies than in those who did not (25.2% vs. 12.0%, p = 0.002) [11]. These findings suggest the possibility of concomitant hematologic neoplasms with ECD, and the BM examination that was subsequently performed revealed cytomorphological findings of CMML. The development of MNs in patients with ECD is reportedly fatal [4,9]. In addition to its association with MNs, CHIP is significantly associated with an increased risk of cardiovascular disease [11]. For these reasons, NGS of PB of patients with ECD is useful for the early detection of CHIP, and we herein highlight that CHIP in PB and persistent monocytosis were the key features of CMML in the previously described case of ECD [12].

TET2 protein plays a crucial role in the epigenetic regulation of hematopoietic stem cells by mediating DNA demethylation. Loss-of-function variants of *TET2* are associated with DNA hypermethylation and an increased risk of hematological neoplasms [6,9]. However, isolated CHIP variants may not be sufficient to cause myeloid malignancy unless they are accompanied by an additional genomic "hit," such as variants in other myeloid neoplasm driver genes [5,7]. The acquisition of such additional variants may occur randomly or may be facilitated by the proinflammatory effects of existing CHIP variants, which can induce clonal instability. In this case, the VAF of the *TET2* variant was higher than that of the *AXSL1* variant. Considering these findings, variants of *TET2* may represent ancestral events, followed by the acquisition of other variants through chronic inflammation or pressure from the microenvironment.

In this study, CMML was re-evaluated using the 5th edition of the WHO classification. Under updated guidelines, gene variants can lead to reclassification. For example, Yun et al. [13] found that 1.4% of MDS cases were reclassified as acute myeloid leukemia, and Kim et al. [14] showed that detecting multi-hit *TP53* variants led to the classification of MDS with biallelic *TP53* inactivation. However, no relevant variants were found in the present case; therefore, the diagnosis remained unchanged.

This study had some limitations. First, targeted NGS for myeloid neoplasm-related genes could not be performed on the cardiac ECD tissue due to the lack of specimen. Second, we could not determine whether the two *TET2* variants were cis or trans because we were unable to perform additional studies on non-hematopoietic tissues (e.g., skin or buccal swabs) or follow-up PB testing. However, according to Cohen et al. [15], the presence of the *TET2* variant is associated with the *BRAF* V600E variant in tissues with ECD lesions. Although myeloid NGS was not performed on tissues with ECD lesions, progenitor cells may present *TET2* variants, followed by the acquisition of *BRAF* V600E variants.

In conclusion, we detected CHIP variants in the PB of patients with ECD using NGS. This is useful for the diagnosis of MNs.

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Ethics Approval Statement:
The study was conducted according to the Declaration of Helsinki and approved by the Institutional Review Board of the Samsung Medical Center, Seoul, Republic of Korea (SMC 2025-06-091).

Data Availability Statement:
The data presented in this study are available upon request from the corresponding author. The data are not publicly available owing to patient privacy restrictions. The data were stored in a private database at Samsung Medical Center, Seoul, Republic of Korea.

Declaration of Interest:
The authors have no competing interests.

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Additional material can be found online at:
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