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CASE REPORT

The first case of peripheral T cell lyphoma with a *CSF3R* variant resulted in relapsing febrile neutropenia and aplastic anemia

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Abstract

Colony-stimulating factor 3 receptor (*CSF3R*) gene mutations have been previously identified in chronic neutrophilic leukemia, atypical chronic myeloid leukemia, chronic myelomonocytic leukemia, de novo acute myeloid leukemia, and severe congenital neutropenia, although there is limited data regarding lymphoid malignancies. Here, we present the first case of peripheral T cell lymphoma with *CSF3R* variant that developed persistent neutropenia in the follow-up visit and aplastic anemia after autologous hematopoietic stem cell transplantation. Next-generation sequencing (NGS) was performed on bone marrow aspiration (Qiagen clinical insight-QCI™). *CSF3R* single nucleotide variant (transcript variant 4), 46.0% (of 1081 reads) of variant allele fraction on exon 16 (lying to intronic region), nucleotide NM_172313.3, g36932463A > g, c.2041-35 T > C was identified by NGS. The case study presented here is an example of use of NGS in diagnosis, classification, prognostic or response indicator of hematologic malignancies, and identification of targeted therapy options in clinical practice. Additional work is needed to understand the clinical significance of this mutation.

Keywords *CSF3R* · Peripheral T cell lymphoma · Febrile neutropenia · Aplastic anemia

Introduction

The peripheral T cell lymphoma (PTCL) corresponds to approximately 10% of non-Hodgkin lymphomas. PTCL originates from mature T-cells and has heterogeneous features resulting in various morphologic subtypes. The most common subtype is PTCL-not otherwise specified (NOS) (26%), followed by angioimmunoblastic T cell lymphoma, anaplastic large cell lymphoma, extranodal NK/T cell lymphoma (nasal type), and subcutaneous panniculitis-like T cell lymphoma [1]. In terms of genetic features, PTCL generally has T cell receptor gene rearrangements, immunoglobulin germline mutations, chromosomal gains (7q, 8q, 17q, 22q), and chromosomal losses (4q, 5q, 6q, 9p, 10q, 12q, 13q). Gene expression profiling (GEP) studies have introduced two molecular subgroups of PTCL-NOS. These subgroups are high expression of transcription factors TBX-21 and GATA-3, and they are associated with differentiation of CD4 + T cells into Th1 and 2 [2, 3].

Colony-stimulating factor 3 receptor (*CSF3R*) gene encodes the granulocyte colony-stimulating factor receptor (G-CSFR, CD114) which is fundamental for binding G-CSF and provides subsequently granulocyte proliferation, differentiation and survival. The localization of gene on chromosome 1 was established by hybridization and polymerase chain reaction methods. *CSF3R* consists of an Ig-like domain, a cytokine receptor homologous domain, 3 fibronectin type III domains, a transmembrane domain, and a cytoplasmic region and contains 17 exons [4].

Acquired nonsense and frameshift truncation variants in the cytoplasmic domain and activating missense variants in the membrane proximal region of *CSF3R* have been frequently observed in chronic neutrophilic leukemia (CNL) and rarely observed in atypical chronic myeloid leukemia (aCML), chronic myelomonocytic leukemia (CMML) and de novo acute myeloid leukemia (AML). Germline homozygous and compound heterozygous nonsense and frameshift truncating variants in the extracellular domain of *CSF3R* and acquired cytoplasmic truncating *CSF3R* variants have been observed in severe congenital neutropenia (SCN) [5–8]. Furthermore, B-cell acute

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lymphoblastic leukemia and multiple myeloma cases with *CSF3R* mutation or variants have been recently observed [9, 10]. Significance of heterozygous germ line variants is unknown [9]. The association of *CSF3R* mutations/variants and lymphoid malignancies is limited even in T cell lymphoid malignancies. We have seen one case that was diagnosed with cutaneous T-cell lymphoma a concomitant *CSF3R* germline variant [11]. Here, we report the first case with cytopenia and relapsing febrile neutropenia during lymphoma treatment that resulted in aplastic anemia after autologous hematopoietic stem cell transplantation co-occurrence peripheral T cell lymphoma and *CSF3R* variant in exon 16 at diagnosis.

Clinical history

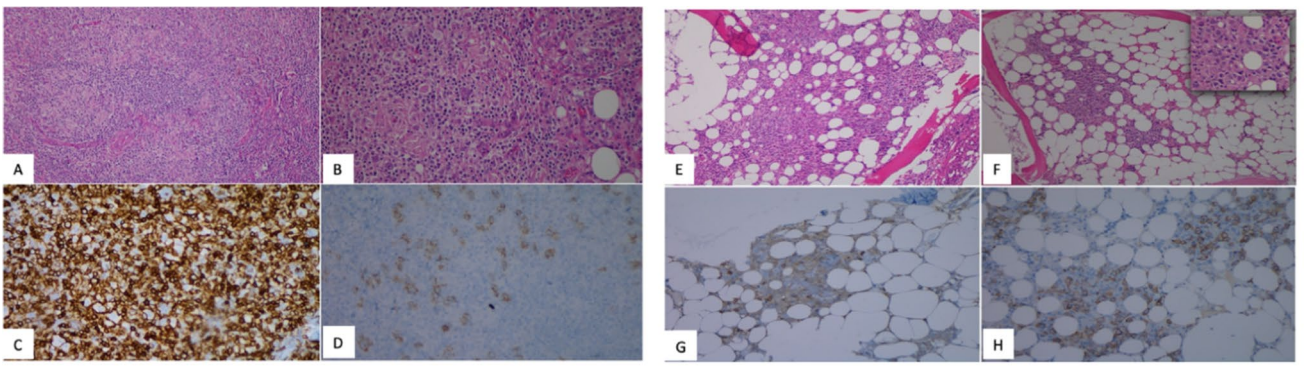
A 69-year-old woman arrived at the hospital with anemia, leukopenia, and cervical and abdominal lymphadenopathies. The patient had mild leukopenia, moderate anemia, and multiple lymphadenopathies, liver-spleen-diffuse bone involvements in PET/CT scans. The patient was diagnosed with CD30 (+) peripheral T cell lymphoma, NOS by axillary lymph node (Fig. 1A, B, C and D) and bone marrow biopsies via morphology and immunhistochemistry examination (Fig. 1E, F, G, and H). She had stage IV_{EB} disease and International Prognostic Index (IPI) was 4. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP protocol) and entecavir due to hepatitis serology was initiated to the patient. During the treatment in every cycle, she had grade 2/3 febrile neutropenia without any proven origin of infection and needed broad-spectrum antibiotics and granulocyte-colony stimulating factor (G-CSF) support. She was responsive to G-CSF administrations.

Material and methods

Next-generation sequencing (NGS) was performed on somatic panel which consists of ASXL1, CALR, CBL, CEBPA, CSF3R, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, RUNX1, SETBP1, SF3B1, SH2B3, SRSF2, TET2, TP53, U2AF1, and ZRSR2 from bone marrow aspiration sample (Qiagen clinical insight-QCI™). Clinical significance of variants were interpreted as tier 1A and 1B, strong significance; tier 2C and 2D, potential significance, and tier 3, uncertain significance based on guidelines.

Results

In the genetic analysis, *CSF3R* single nucleotide variant (transcript variant 4), 46.0% (of 1081 reads) of variant allele fraction on exon 16 (lying to intronic region), nucleotide NM_172313.3, g36932463A > g, and c.2041-35 T > C was identified by NGS from bone marrow aspiration sample and was interpreted as tier 3 uncertain significance according to database (Qiagen clinical insight-QCI™). After favorable interim assessment, 6 courses of CHOP was completed and remission was achieved. The patient had autologous hematopoietic stem cell transplant (ASCT) without any complications. Neutrophil and thrombocyte (> 20.000/mm^3) engraftment occurred in the fourth week after the transplant and eltrombopag treatment started. Initially the response to eltrombopag was favorable. However, in the follow-up, the patient's thrombocyte count started to drop. On the 100th day assessment, relapse was demonstrated with PET/CT scans and bone marrow biopsy. Afterwards, brentixumab and bendamustine treatment was initiated. The patient also had febrile



A) Axillary lymph node revealed polymorphic lymphoid infiltration admixed with many histocytes and rich in vascular structures (H&E x100).
B) Pleomorphic large cells, small sized hyperchromatic atypic lymphocytes with irregular contours and accompanying histiocytes (H&Ex200)
C) CD4 expression on the neoplastic cells (IHC x 200)
D) CD30 immunopositivity on the large neoplastic cells (IHC x 200).
E) Bone marrow biopsy showed %60 cellularity. Between bone marrow elements, nodular and interstitial atypic lymphoid infiltration consistent with bone marrow involvement by peripheral T cell lymphoma (H&E x100)
F) Last bone marrow biopsy showed marked myelosuppression and atypic lymphoid infiltration. Inset shows characteristic futures of the lymphoid infiltration (H&E x100)
G) CD4 immunopositivity on the neoplastic cells. Note the hypocellularity on the bone marrow biopsy (IHC x 200)
H) CD30 expression on the large sized atypic cells of the lymphoid infiltration (IHC x 200)

Fig. 1 The pathological specimens of axillary lymph node and bone marrow biopsy at diagnosis

neutropenia periods during the chemotherapy protocols which were responsive to antibiotherapy and G-CSF. She was admitted to hospital with febrile neutropenia after the third chemotherapy protocol, at which point pneumonia, pyelonephritis and pancytopenia were observed and broad-spectrum antibiotics and G-CSF treatments started. Cytopenia was attributed to primary disease infiltration, peripheral destruction and bone marrow suppression due to severe infection status. However, the patient did not respond to the antibiotic treatment, G-CSF, and blood transfusion support and deceased in the intensive care unit (Fig. 2).

Discussion

In recent years, use of NGS has been spreading. NGS has been especially useful in classification, diagnosis, prognostic indicator, and assessment of minimal residual disease of hematologic malignancies and targeted therapy options in clinical practice. However, these results may be confusing and may possess uncertain clinical significance in certain cases.

CSF3 and CSF3R are fundamental for production and proliferation of neutrophils. *CSF3R* mutations were observed in CNL, SCN, SCN-AML, de novo or secondary AML and limited B lymphoid malignancies such as B-ALL and multiple myeloma. As far as a germline mutation of *CSF3R* is concerned, we have encountered only one cutaneous T-cell lymphoma case in the literature [11]. There was no peripheral T-cell lymphoma report with this mutation/variant and consequently we initiated CHOP protocol for peripheral T-cell lymphoma. However, during the CHOP treatment, the patient (who had not have history of neutropenia or cytopenia and family history regarding cytopenia) had febrile neutropenia and needed broad-spectrum antibiotics and G-CSF support. The patient's recovery from ASCT procedure occurred unexpectedly, and neutrophil and thrombocyte levels stayed under the targeted levels and continued in the follow up visits, similarly. After relapse, we tried to treat infection and cytopenia with the salvage chemotherapy. Ultimately, she deceased due to infection and cytopenia in the status of dependence of blood transfusion and G-CSF support.

At the beginning, *CSF3R* variant was not considered to be of importance due to mentioned tier 3 uncertain significance who was diagnosed with PTCL. However, we reevaluated the patient's clinical history again due to the poor patient outcome. The patient's family was questioned about the patient's medical history and family history, especially her children's medical status due to possibility of having germline (46% of variant allelic fraction) of this variant which can develop neutropenia. There was no finding of neutropenia in the patient and patient's family. Because of no family history especially in her children and the possibility of being recessive, we did not analyze her children regarding this variant. We also could not obtain a sample from patient for verification of germline possibility due to death. We observed the ever-increasing rate of lipocytes and decreasing the cellularity in the bone marrow. Lipocyte/cellularity rate was 40/60, 60/40, and 90/10, at the diagnosis, before the transplant and first relapse, respectively. When lipocyte/cellularity rate was 90/10 in the bone marrow biopsy, WBC count was 2600/mm^3, neutrophil count was 700/mm^3, hemoglobin level was 9.6 g/dL, platelet count was 16.000/mm^3 and corrected reticulocyte count was 0.9%. These results were indicative of severe aplastic anemia.

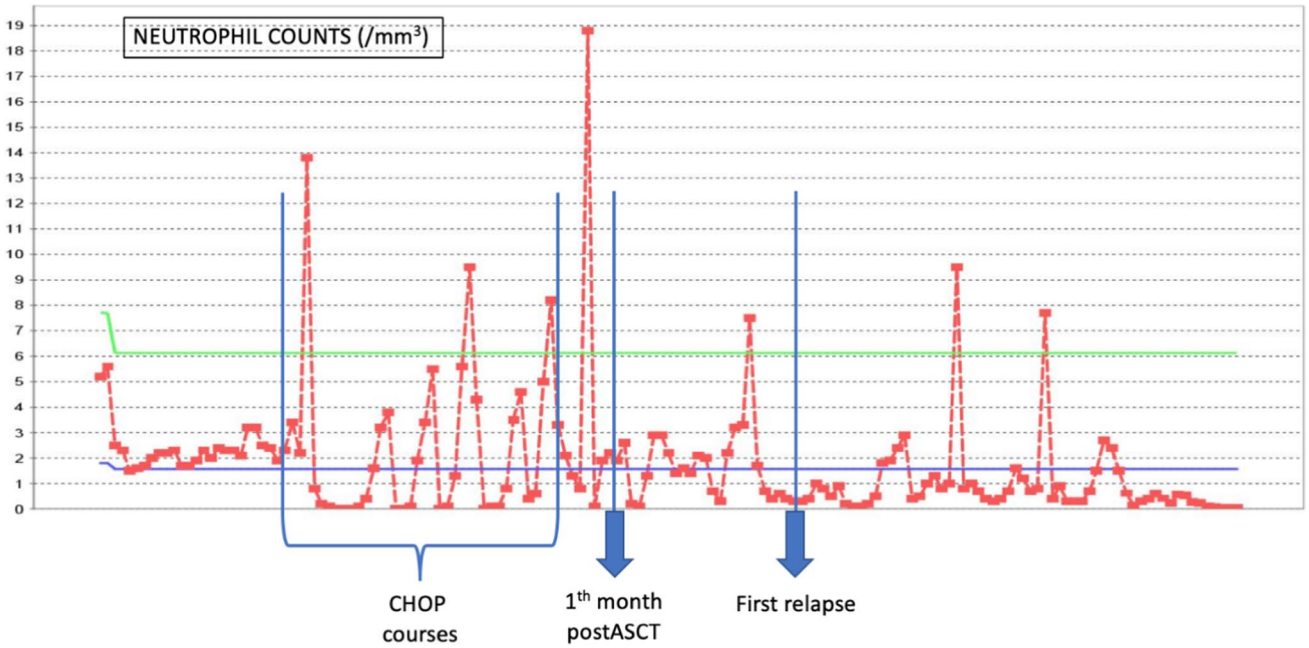


Fig. 2 The timeline of patient's neutrophil counts

As a summary, we encountered a patient who was diagnosed with PTCL concomitant *CSF3R* variant and developed severe neutropenia and aplasia compatible with aplastic anemia. Aplastic anemia (AA) is a disease of bone marrow failure associated with hypoplasia or aplasia due to inherited/genetic disorders or acquired factors such as immune disorders, drugs, toxic chemicals, viral infections [12]. AA has a high morbidity and mortality rate, with severe form of the disease having approximately 70% mortality risk in 2 years if the disease was not treated optimally. Somatic mutation rate is between 5 and 70% in the studies while germline mutations are establishing more frequent recently. In AA DNMT3A, BCOR, BCORL1, and ASXL1 can be detected in the molecular analysis [13–15].

We reviewed the literature regarding nucleotide NM_172313.3 mutation/variant and co-morbidity peripheral T cell lymphoma, neutropenia, and/or aplastic anemia. We have not found any work concerning the identical circumstance due to identified NM_172313.3:g36932463A > g, c.2041-35 T > C, and non-protein coding. We also searched the databases such as ClinVar (www.ncbi.nlm.nih.gov/clinvar), refSeq (www.ncbi.nlm.nih.gov/RefSeq), dbSNP (www.ncbi.nlm.nih.gov/dbSNP), MedGen (www.ncbi.nlm.nih.gov/MedGen), and OMIM (www.omim.org) and have found no identical case. Hence, this is the first patient who is presented with *CSF3R* variant with NM_172313.3:g36932463A > g, c.2041-35 T > C up to date.

In this case, the first challenge is where to locate this variant in the clinical range. There are also unanswered questions, e.g., this mutation could be associated with aplastic anemia or peripheral T cell lymphoma or isolated neutropenia, could *CSF3R* mutation be an indicator of aplastic anemia, did intensive and conditioning chemotherapies and ASCT accelerate this aplasia process, should we approach to such cases more nonintensive or use prophylaxis due to susceptible to be neutropenic and severe infections during chemotherapy, could *CSF3R* be a targeted therapy option in the future. Literature needs to be clarified regarding NGS and challenges of interpretations. We think additional studies and reports are needed to reach a more accurate conclusion.

Author contribution All authors have contributed significantly. All authors are in agreement with the content of the manuscript.

Declarations

Ethical approval Not applicable.

Consent to participate/informed consent Obtained from patient legal representative.

Consent for publication Obtained from patient legal representative.

Conflict of interest The authors declare no competing interests.

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