CSF3R T618I mutant myelodysplastic/myeloproliferative neoplasm in the elderly: An age-related disease with unfavorable prognosis

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ABSTRACT

We reported two MDS/MPN-U and one CMML patients with CSF3R T618I mutation. There were two males and one female, with a median age of 84 years. Three patients presented with leukocytosis and anemia, two with thrombocytopenia, and one with monocytosis. In all the patients, bone marrow showed hypercellularity with myeloid or erythroid predominant trilineage hematopoiesis and dysplasia. Two cases carried -7/-7q abnormalities. In addition to CSF3R T618I mutation, each case carried 3–5 additional somatic mutations. The median survival was only 2 months. These rare patients were characterized by old age, high mutation rates, clonal hematopoiesis-associated mutations, clonal evolution, and unfavorable prognosis.

Abbreviations
BM, bone marrow;
CMML, chronic myelomonocytic leukemia;
FISH, Fluorescence in situ hybridization;
HBG, hemoglobin;
IHC, immunohistochemistry;
LDH, lactate dehydrogenase;
MCH, mean corpuscular hemoglobin;
MCV, mean corpuscular volume;
MDS/MPN-U, myelodysplastic/myeloproliferative neoplasm unclassifiable;
MG, myeloid granularity;
PB, peripheral blood;
WBC, white blood cell. # Baseline parameters, * Not available in our system

1. Introduction

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) were rare hematological neoplasms with myelodysplastic and myeloproliferative features. The 2016 World Health Organization (WHO) classification included five subtypes of MDS/MPN: chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia, MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T), and MDS/MPN-unclassifiable (MDS/MPN-U) [1]. Colony-stimulating factor 3 (CSF3) played an important role in the production, differentiation, and function of granulocytes [2]. Mutations in CSF3 receptor gene (CSF3R) have been identified in the majority of chronic neutrophilic leukemia (CNL) patients, most commonly T618I membrane proximal point mutation [3, 4]. Thus, the 2016 WHO classification has incorporated CSF3R T618I mutation or another activating mutation into the diagnostic criteria for CNL. Additionally, CSF3R mutations were reported in approximately 5 to 10% of aCML patients [5]. However, CSF3R mutations are very rare in other MDS/MPN subtypes, and these cases have not been well-characterized due to a low frequency [5]. Here, we reported three patients of CSF3R T618I mutant MDS/MPN, including two MDS/MPN-U and one CMML.

2. Results

2.1. Clinical findings

This study was approved by the Institutional Review Board of Northwell Health. Table 1 summarized the clinical and laboratory
findings of the three patients. Patient 1 was an 89-year-old woman who presented with MDS/MPN-U on bone marrow biopsy and treated with hydroxyurea (500 mg, Oral Daily). Her hematological parameters showed progressive improvement and the response lasted about 30 months in terms of leukocytosis. During this period, she had a median white blood cell (WBC) of $20.5 \times 10^9$/L, a median hemoglobin (Hb) of 10.3 g/dL, and a median platelet of $198 \times 10^9$/L. With disease progression, her platelet count has been gradually elevated while the WBC count was relatively stable. She eventually developed significant leukocytosis ($56.2 \times 10^9$/L at peak) and thrombocytosis ($752 \times 10^9$/L at peak) (Fig. 1G). During the entire clinical course, her WBC ranged from 13.2 to $75.0 \times 10^9$/L, Hb from 6.7 to 11.3 g/dL, mean corpuscular volume (MCV) from 96.7 to 122.1 fl, and platelet from 67 to $752 \times 10^9$/L, and she received ten RBC transfusions. She has been hospitalized twice for a total of 26 days, which occurred within the last two months of her life. She received palliative care and died 33 months after diagnosis. Patient 2 was an 84-year-old man with multiple comorbidities. He presented with severe shortness of breath, productive cough, and had marked thrombocytopenia. Complete blood count (CBC) showed WBC of $16.2 \times 10^9$/L, Hb of 9.2 g/dL, and platelet of $32 \times 10^9$/L. There was a possibility that acute febrile condition might partly contributed to his thrombocytopenia. During the hospitalization, he received two RBC transfusions and five platelet transfusions, and became refractory to platelet transfusion. He subsequently developed sepsis and was treated with vancomycin and Zosyn. Bone marrow biopsy findings were consistent with MDS/MPN. He received supportive care and died of multiorgan failure ten days after the admission. Patient 3 was an 81-year-old man with a history of hepatitis C and cirrhosis who was admitted for leukocytosis, worsening anemia, and marked thrombocytopenia. He was diagnosed with MDS/MPN-U on bone marrow biopsy and initially treated with a hypomethylating agent. After treatment, his leukocytosis significantly

| Table 1 | Clinical and laboratory findings of CSF3 T618I mutant MDS/MPNs. |
|---------|-----------------------------|
| Variables | Patient 1 | Patient 2 | Patient 3 |
| Demographics | | | |
| Sex | Female | Male | Male |
| Age (years old) | 89 | 84 | 81 |
| Clinical findings# | | | |
| Clinical history | Persistent leukocytosis and weight loss | Prostate cancer, cardiovascular disease, diabetes, anemia | Hepatitis C, cirrhosis |
| Splenomegaly | - | + | + |
| Hepatomegaly | - | + | - |
| Lymphadenopathy | - | + | - |
| LDH (U/L) | 385 | 418 | 220 |
| Number of Transfusion | 10 | 7 | 19 |
| Duration of hospitalization | 26 | 10 | 43 |
| Laboratory findings# | | | |
| Albumin (g/dL) | 4.0 | 3.8 | 4.1 |
| C-reactive protein (mg/dL) | 3.1 | N/A* | N/A* |
| Ferritin (ng/dL) | 428 | 833.0 | 162 |
| C-reactive protein (mg/dL) | 3.1 | N/A* | N/A* |
| Transferrin saturation (%) | 31 | Unable to calculate | 33 |
| Peripheral blood | | | |
| WBC ($10^9$/L) | 58.5 | 16.2 | 14.6 |
| HBG (g/dL) | 10.6 | 9.2 | 7.3 |
| MCV (fL) | 99.7 | 85.5 | 100.4 |
| MCH (pg) | 32.3 | 28.9 | 31.6 |
| Platelet ($10^9$/L) | 216 | 32 | 27 |
| Band + Segment (%) | 90 | 85 | 90 |
| Immature gran (%) | 3 | 0 | 0 |
| Monocyte ($10^9$/L) | 1.2 | 1.8 | 0.9 |
| Monocyte (%) | 3 | 10 | 6 |
| Lymphocyte (%) | 4 | 1 | 4 |
| Blast (%) | 0 | 0 | 0 |
| Reticulocyte count (k/μL) | 65 | N/A | 63.8 |
| Bone marrow | | | |
| Cellularity (%) | 90 | 70–85 | 85–90 |
| M:E ratio | 10:1 | 1:1 | Myeloid predominance |
| Trilineage maturation | + | + | ↑Makeryocytes |
| Erythroid | + | + | |
| Myeloid | - | + | + |
| Megakaryocytic | <3 | 7 | <3 |
| Blasts (%) | Multiple lymphoid aggregates | Granulomas; increased macrophages | Fibrosis |
| Others | + >15% | + >15% | NA |
| Ring sideroblasts | <3% | 7% | <3% |
| IHC for CD34+ cells | | | |
| Flow cytometry | SLL/CLL monoclonal B cells in 0.6% PB and 1.6% of BM | 10% Myeloblasts + promonocytes, 13% monocytic cells; decreased MG | Mildly decreased MG |
| Cytogenetics | 46,XX(20) | 46,XY,del(7)(q22) | 45,XY,-7 |
| FISH MDS panel | Normal | Del 7q | Monosomy 7 |
| Diagnosis | MDS/MPN-U | Negative BCR-ABL | Negative for BCR-ABL |
| Treatment | Hydroxyurea | CMML | MDS/MPN-U |
| Outcomes | Died, 33 months | Died, 10 days | Died, 2 months |

Abbreviations: BM, bone marrow; CMML, chronic myelomonocytic leukemia; FISH, Fluorescence in situ hybridization; HBG, hemoglobin; IHC, immunohistochemistry; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; MDS/MPN-U, myelodysplastic/myeloproliferative neoplasm-unclassifiable; MG, myeloid granularity; PB, peripheral blood; WBC, white blood cell. # Baseline parameters, * Not available in our system.
improved, but anemia and thrombocytopenia persisted. During the clinical course, the WBC ranged from 2.6 to 14.6 × 10⁹/L, Hb from 6.6 to 9.2 g/dL, platelet from 6.0 to 27.0 × 10⁹/L. He became transfusion dependent after the diagnosis of MDS/MPN-U and received a total of nineteen RBC transfusions over the entire clinical course. He had multiple hospitalizations lasting for 43 days and the last admission was complicated by sepsis. He received palliative care and died two months after diagnosis. Splenomegaly was present only in patient 3 (19 cm in length by CT scan). Serum lactate dehydrogenase level was elevated in patient 1 and patient 2.

2.2. Peripheral blood findings

The CBC at presentation showed a median WBC count of 16.2 × 10⁹/L (range, 14.6–58.5), a median Hb level of 9.2 g/dL (range, 7.3–10.6), a median MCV of 99.7 fl (range, 85.5–100.4), a median corpuscular hemoglobin (MCH) of 31.6 pg (range, 28.9–32.3), and a median platelet count of 32.0 × 10⁹/L (range, 27.9–216.0). Differential cell count revealed greater than 80% neutrophils and less than 10% immature granulocytes in all the patients. There was no increase in peripheral blood blasts, lymphocytes, or eosinophils in any of the patients. The absolute reticulocyte counts were 65.0 k/ul and 63.8 k/ul in patient 1 and patient 3, respectively.

2.3. Bone marrow findings

Bone marrow biopsy showed marked hypercellularity in all the patients, including two patients with myeloid predominance and one

Fig. 1. Bone marrow findings in CSF3R mutant MDS/MPN cases. The bone marrow biopsy of case 1 shows hypercellularity with myeloid predominant trilineage hematopoiesis with maturation (×400 magnification) (A) and a lymphoid aggregate (×400 magnification) (B). The bone marrow aspirate smear of case 1 shows myeloid hyperplasia with maturation and decreased erythroid elements with mild dyserythropoiesis (×1000 magnification) (C). The bone marrow biopsy of case 2 shows hypercellularity with erythroid predominant trilineage hematopoiesis, dysplastic megakaryocytes, increased macrophages, and one small granuloma (×400 magnification) (D). The bone marrow aspirate smear of case 2 shows erythroid predominance, dyserythropoiesis, occasional macrophages with hemophagocytosis, and ring sideroblasts (inset) (×600 magnification) (E). The bone marrow biopsy of case 3 shows hypercellularity with myeloid predominant trilineage hematopoiesis with maturation, megakaryocytosis with dysplasia, and increased fibrosis (F). The trends of basic complete blood count parameters during the clinical course of patient 1 (G).
patient with erythroid predominance (patient 2). Myelopoiesis and erythropoiesis showed normal maturation in all the patients. Megakaryocytes were normal number in two patients and markedly increased in one patient (patient 3). Multilineage dysplasia was evident in two patients while only dyserythropoiesis was present in patient 1. Bone marrow aspirate smear iron stain showed >15% ring sideroblasts in two patients (patient 1, patient 2). Other bone marrow findings included multiple lymphoid aggregates (patient 1), presence of granulomas and increased macrophages with focal hemophagocytosis (patient 2), megakaryocytosis and fibrosis (patient 3). (Fig. 1A-1F)

Immunohistochemical studies revealed bone marrow involvement by 10% B cells with SLL/CLL phenotype (patient 1), 7% CD34-positive blasts (patient 2), and significantly increased megakaryocytes (patient 3). There was no increase in CD34-positive blasts in patient 1 and patient 3.

### 2.4. Flow cytometry findings

In patient 1, flow cytometry analysis detected a minute population of monoclonal B-cells (positive for kappa, CD19, dim CD20, CD23, CD5; negative FMC-7, CD10, CD38) with SLL/CLL phenotype in both peripheral blood and bone marrow specimens. There was no increase in myeloblast or monocyte, and myeloid granularity was normal in bone marrow. In patient 2, flow cytometry of bone marrow showed increased myeloblasts (positive for partial HLA-DR, partial CD5, CD7, CD11b, partial CD13, CD33, partial CD34, partial CD117 and negative for CD2, CD3, CD4, CD56), increased monocytic cells (positive for partial HLA-DR, CD4, CD11b, heterogeneous CD13, partial CD14, CD15, CD33, CD64 and negative for CD2, CD34, CD56, CD117), and decreased myeloid granularity. The monocytic cells demonstrated an aberrant immunophenotype including partial expression of HLA-DR and heterogeneous expression of CD13. In patient 3, flow cytometry of bone marrow revealed mildly decreased myeloid granularity with no increase in blast.

### 2.5. Cytogenetics, fluorescent in situ hybridization (FISH), and next generation sequencing (NGS) findings

Conventional cytogenetic analysis revealed a normal karyotype in patient 1 and -7/-7q abnormalities in patient 2, patient 3. FISH studies using probes for MDS panel confirmed the cytogenetic findings and showed no additional abnormalities. **BCR-ABL** fusion was not detected in any of the patients.

NGS studies (OnkoSight Myeloid panel comprising 37 genes, Bioreference laboratories) identified four to six somatic mutations in each of the patients (Table 2). **CSF3R T618I** mutation was present in all the patients with a variant allele frequency (VAF) ranging from 27% to 49%. In addition, patient 1 harbored **TET2, SF3B1 and CSF3R S810Qfs** mutations; patient 2 harbored **ASXL1, U2AF1, SETBP1, KRAS, and RUNX1** mutations; patient 3 harbored **TET2, U2AF1, SETBP1, PTPN11**, and **ZRSR2** mutations. **CSF3R S810Qfs**, KRAS, and **PTPN11** mutations were present as subclones. NGS study was also performed in patient 1 when her CBC indices showed response to the treatment. The NGS revealed a disappearance of the **CSF3R S810Qfs** mutation, significantly decreased **CSF3R T618I VAF**, and a stable **SF3B1** mutation.

### 3. Discussion

**CSF3R** consisted of an N-terminal extracellular domain, a transmembrane domain, and a C-terminal cytoplasmic tail. It signaled downstream through JAK/STAT and SRC family kinases. **CSF3R** mutations were divided into two groups: activating mutations and truncation mutations. The former resulted in ligand-independent activation of **CSF3R** and JAK/STAT signaling pathway. The latter led to premature truncation of the cytoplasmic tail and a loss of negative regulatory motifs, which resulted in enhanced cell proliferation through activation of SRC kinase signaling. Activating mutations were sensitive to JAK kinase inhibitors while truncation mutations were sensitive to SRC kinase inhibitors [2].

The patients in this case series had negative **BCR-ABL** fusion, less than 20% blasts, and less than 10% immature granulocytes in peripheral

### Table 2

**Targeted next-generation sequencing data.**

| Targeted NGS | Case 1 VAF(%) | Case 2 VAF (%) | Case 3 VAF(%) |
|--------------|--------------|----------------|--------------|
|              | Initial      | Post-Tx        | Initial      | Initial      |
| **CSF3R T618I** | 39.3%       | 27.9%          | 44.4%       | 27.0%        |
| **CSF3R S810Qfs** | 0.0%        | 0.0%           | 43.4%       | 43.4%        |
| **TET2**     | 37.1%       | 30.1%          | 49.0%       | 49.0%        |
| **SF3B1**    | 46.9%       | 43.4%          |             |              |
| **RUNX1**    | 44.3%       |                | 45.2%       |              |
| **ASXL1**    | 45.2%       |                | 52.1%       |              |
| **SETBP1**   | 52.1%       |                | 48.7%       |              |
| **U2AF1**    | 52.1%       |                | 46.0%       |              |
| **KRAS**     | 20.5%       |                | 4.0%        |              |
| **PTPN11**   | 52.1%       |                | 50.0%       |              |
| **ZRSR2**    | 94.0%       |                | 94.0%       |              |

Abbreviations: NGS: next generation sequencing; Tx: treatment; VAF: variant allele frequency.
blood, which ruled out chronic myeloid leukemia, acute myeloid leukemia and aCML. Patient 1 met most of the diagnostic criteria for CNL except for the presence of dyserythropoiesis and $>1 \times 10^9$/L monocytes. However, the monocyte percentage was less than 10% which excluded CMML. Although there was increase in ring sideroblasts with SF3B1 mutation, a diagnosis of MDS/MPN-RS-T could not be rendered in the absence of thrombocytosis. Hence, it is classified as MDS/MPN-U. Interestingly, patient 1 also had bone marrow involvement by B cells with SLL/CLL phenotype meeting the criteria of monoclonal B-cell lymphocytosis. Patient 2 exhibited peripheral monocytosis (>1 $\times 10^9$/L and 10%), increased bone marrow monocytes with aberrant phenotype, and multilineage dysplasia, which supported a diagnosis of CMML. Patient 3 showed a hypercellular bone marrow with myeloid predominance, marked megakaryocytic proliferation with dysplasia, and increased fibrosis, consistent with MDS/MPN-U after CMML and aCML have been ruled out.

Clonal hematopoiesis (CH) was an age-related process that was frequently associated with mutations in genes that regulated epigenetic and/or splicing processes. It was associated with an increased risk of developing hematological malignancies. The estimated rate of progression to hematological malignancies was 0.5 to 1% per year [6–8]. In this series, all the patients were over 80 years of age and harbored multiple mutations including the CH associated mutations, such as TET2, ASXL1, SF3B1. In addition to CSF3R T618I mutation, each patient carried one additional signaling mutation as a subclone, suggesting clonal evolution. Review of the available CBC information showed that the patients had anemia, macrocytosis or a history of anemia before developing leukocytosis. Patient 1 developed macrocytosis with MCV of 101 fl and MCH 33.1 pg one and half years before the manifestation of leukocytosis. Patient 2 had a long history of anemia. Patient 3 developed mild macrocytic anemia with MCV of 109.8 fl and MCH of 34.6 pg three years before the manifestation of leukocytosis. In patient 1, after response to treatment, the CSF3R S110Q/*6 mutation disappeared and the VAF of CSF3RT618I was significantly decreased while the SF3B1 mutation was stable. This suggested that SF3B1 was a driver event and the CSF3R mutations represented secondary events that were responsible for the granulocytic phenotype. In patient 2, the KRAS mutation acted as a secondary mutation that contributed to the CMML phenotype. Study has shown that oncogenic RAS pathway mutations were typically associated with proliferative CMML phenotype, aggressive disease features and transformation to secondary AML. Clonal NRAS/KRAS activation drives a proliferative CMML phenotype [9]. Patient 2 had a history of prostate cancer status post brachytherapy but did not receive any myelotoxic type of treatment. The clinical history raised a possibility of therapy-related myeloid neoplasms. However, a recent population-based study showed that there was no increased risk of developing secondary MDS/AML in patients with prostate cancer who received brachytherapy [10]. Thus, the myeloid neoplasms was less likely to be related to his prostate cancer treatment. In patient 3, CSF3R T618I and PTPN11 acted as secondary/subclonal mutations. All the above findings supported the concept that CH was likely asymptomatic at the onset, possibly exhibiting features of myelodysplasia, but acquisition of a signaling mutation gave the clonal hematopoietic population a distinctive cell lineage phenotype [2]. Thus, these cases might represent an age-related disease driven by secondary acquired signaling mutations.

CMML with CSF3R T618I mutation was extremely rare with only six reported cases [11]. Its estimated frequency in CMML patients was 0.62%. These cases were characterized by a frequent association with ASXL1 mutation and proliferative disease, younger age, and an unfavorable prognosis [11]. Patient 2 exhibited similar features except for an old age. ASXL1, RUNX1, and SETBP1 mutations have been shown to be associated with decreased overall survival and poor prognosis in CMML [12]. U2AF1 mutation was a negative prognostic predictor for MDS/MPN. PTPN11 mutations were associated with poor outcomes in myeloid malignancies [13]. The presence of adverse risk cytogenetics was associated with inferior overall survival in MDS/MPN patients. The genetic and cytogenetic alterations may have contributed to the poor prognosis in patients 2 and 3. In a recent study, MDS/MPN-U was subdivided into five groups based on molecular profiles: “CMML-like”, “aCML-like”, “MDS/MPN-RS-T-like”, “TP53”, and “Other” [12]. Among the five molecular groups, MDS/MPN-RS-T-like group had a better clinical outcome than the other subgroups. SF3B1 mutations were frequently associated with myeloid neoplasms with ring sideroblasts [14,15]. In MDS/MPN-RS-T and MDS/MPN-U, SF3B1 mutations often co-occurred with JAK2 or other MPN mutations. However, concomitant SF3B1 and CSF3R mutations have rarely been reported in myeloid neoplasms. Overall, patient 1 had similar features to MDS/MPN-RS-T-like group.

There has been a vigorous debate whether CNL was truly a MPN or should be classified as MDS/MPN as it might share some clinical, hematological and cytogenetic features with MDS or MDS/MPN [16]. In the literature, there were rare reported CNL cases with evidence of significant dysplasia. However, when strict WHO criteria were applied, these cases were reclassified as either evolution from MDS or MDS/MPN [17,18]. Therefore, the WHO classification defined CNL as a MPN and included diagnostic criteria to exclude these mimickers [1]. CSF3RT618I mutation has been shown to be a sensitive and specific molecular marker for CNL, which led to its inclusion in the 2016 WHO diagnostic criteria for CNL. However, CSF3RT618I mutation was also found in aCML and to a much less extent in CMML and MDS/MPN-U. Sometimes, it became challenging to definitively classify these cases. Due to the overlapping mutational and expression profile of CNL and aCML, and to a lesser extent MDS and MDS/MPN-U, and their association with clonal hematopoiesis, it has recently been suggested that these entities might represent a continuum of closely related hematological disorders rather than discrete entities [19,20]. The findings in our patients supported this model, which suggested that it might be appropriate to collectively classify these cases as CSF3R positive myeloid neoplasm.

In summary, CSF3RT618I mutant MDS/MPN was rare and characterized, in this series, by old age, high mutation rates, presence of CH-associated mutations, evidence of clonal evolution, and overall unfavorable prognosis. This may represent a disease associated with advanced age and cellular senescence. Further study with a larger cohort was needed to confirm these findings.

Informed consent

This study was approved by the Institutional Review Board of Northwell Health.

CRediT authorship contribution statement

Xinmin Zhang: Conceptualization, Writing – original draft. Cristina Ghiuzeli: Visualization, Investigation. Erin Jou: Writing – review & editing. Peihong Hsu: Writing – review & editing. Jonathan Kolitz: Conceptualization, Writing – review & editing. Judith P Brody: Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors report no conflict of interest.

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