Acute Mast Cell Leukemia Preceded by Malignant Mediastinal Germ Cell Tumor: A Rare Case Report and Literature Review

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Case Report

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Abstract

Background: Mast cell leukemia (MCL) is a highly life-threatening and extremely rare subtype of systemic mastocytosis (SM). MCL, divided into de novo subtype and secondary to mastocytosis subtype, often genetically contains one or more somatic mutations, particularly the activating mutations of *KIT*. In this study, an acute MCL case was reported, who had rare phenotype and genetic mutants with a history of primary malignant mediastinal germ cell tumor (GCT).

Case presentation: A male patient aged 30, who underwent two rounds of surgery and chemotherapy with a history of malignant mediastinal GCT, was admitted to our hospital due to persistent chest pain and severe fatigue. The diagnosis of acute MCL was confirmed by morphology analysis and chemical staining of marrow aspirate and biopsy, with the addition of C-findings including splenomegaly and cytopenia. The atypical MCs phenotypically expressed CD9, but no CD2 and CD25. Next gene sequencing of marrow aspirate identified heterozygous mutations in *TP53* P301Qfs*44, *FLT3* R973X, *SETBP1* N272D, and *JAK3* I688F, whereas the mutations in *KIT* were not found. Although the initial therapy of corticosteroids and dasatinib-based regimen was effective, he died of acute respiratory distress syndrome after the first cycle of chemotherapy with cladribine and cytarabine. The survival time of the patient was 2.4 months after the initial presentation of MCL.

Conclusion: In this case, MCL preceded by malignant mediastinal GCT has similar clinical symptoms and morphological manifestations but distinctly different genetic profiles in contrast to primary MCL. The characteristic morphology of MCL provides the most pivotal evidence that led our diagnosis in the right direction. A hypothesis was speculated that there is a common embryonal cancer stem cell between primary malignant GCT and secondary de novo MCL, whereas the latter is gradually developed in the context of additional “driver mutations”.

Introduction

Mastocytosis is a malignant disease characterized by the clonal expansion and infiltration of mast cells (MCs) in the skin, marrow, and other organs. Due to its unique clinical and pathological features, mastocytosis has been excluded from the myeloproliferative neoplasm category and is regarded as a distinct disease category, according to the 2016 version WHO classification of myeloid neoplasms [1]. Mastocytosis is clinically subdivided into cutaneous mastocytosis, systemic mastocytosis (SM), and localized MC tumors, in which the first form usually appears in childhood with a favorable prognosis and the latter two forms frequently develop in adulthood [2]. SM is a rare subtype characterized by multifocal infiltration of high-grade MCs in the bone marrow and other various organs.

The diagnostic criteria of SM are categorized into major and minor criteria. The major criteria indicate multifocal dense infiltrates of MCs (≥15 MCs in aggregates) in BM biopsies and/or in other extracutaneous organ(s). The minor criteria include a). > 25% of atypical MCs are detected on BM smears or are spindle-shaped in MC infiltrates detected on other organs. b). An activating point mutation at

codon 816 of *KIT* in the marrow or another extra-cutaneous organ. c). MCs in the marrow, blood, or another extra-cutaneous organ exhibit CD2 and/or CD25. d). Baseline serum tryptase level is >.20 ng/mL (in case of an unrelated myeloid neoplasm, item d is not valid as an SM criterion). SM is confirmed with the major criteria and at least 1 minor criteria, or more than 3 minor criteria [2, 3]. SM is classified into indolent SM, smoldering SM, SM with an associated hematologic (non-MC lineage) neoplasm, aggressive SM (ASM), and mast cell leukemia (MCL) in the updated 2016 WHO classification document [4, 5].

MCL is a highly life-threatening and extremely rare subtype of SM, accounting for less than 0.5% of SM [6]. It can be divided into de novo or secondary to earlier mastocytosis, and the ratio of the two subtypes is approximately 3:1 [7]. MCL is fatal because of its systemic nature and resistance to current therapeutic agents [7]. The diagnostic criteria for MCL are as follows: 1) the establishment of SM diagnosis; 2) the neoplastic infiltration by atypical MCs in BM biopsy; 3) the presence of atypical MCs in marrow with or without other internal organs (more than 20% of BM nucleated cells) [5]. Traditionally, MCL includes an aleukemic variant (most cases) when the percentage of atypical MCs < 10% of peripheral blood mononuclear cells (PBMCs) and a classical/leukemic variant when the percentage ≥ 10% [8]. MCL can be further subdivided into *chronic* versus *acute* MCL, and the latter follows a more aggressive course, with the presence of ≥ 1 C findings (including cytopenia, hepatomegaly, splenomegaly, and gastrointestinal or skeletal involvement) [3]. Neoplastic MCs usually express proto-oncogene KIT (CD117), tryptase, and CD25, with or without co-expression of CD2. Genetically, they often contain one or more somatic mutations, represented by the activating mutations of *KIT*. In this study, a primary acute MCL case of a young male patient was reported herein, who had rare phenotype and genetic mutants with a history of primary malignant mediastinal germ cell tumor (GCT).

Case Presentation

This is a 30-year-old male patient, who had no family history of tumor and genetic disease, was first diagnosed with a primary malignant mixed GCT encompassing seminoma and immature teratoma in the mediastinum in 2010. At that time, he received the surgical tumorectomy and then was consolidated with radiation therapy concurrent with 4 cycles of cisplatin-based chemotherapy. At the end of 2014, however, he experienced the recurrence of GCT with a metastatic lesion located on the posterior basal segment of the lower lobe of the left lung, followed by undergoing pneumoresection and 6 cycles of consolidated chemotherapy including vindesine, ifosfamide, and cis-platinum again. The pathological result revealed a single immature teratoma. The patient afterward remained in a stable remission condition.

At the beginning of 2020, he was urgently admitted to our hospital with 1 day of persistent chest pain and severe fatigue. Clinical symptoms showed low-grade fever, skin flush, and splenomegaly. Complete blood cell count showed anemia (hemoglobin 8.2 g/dL) and thrombocytopenia (38*109/L). Coagulation tests presented a higher D-dimer value (2,340 ug/L) and a slightly prolonged activated partial thromboplastin time (37.4s). The routine chemical analysis detected a high level of LDH (878 U/L) in peripheral blood. The results of computed tomography scan and transabdominal ultrasound revealed hepatosplenomegaly and seroperitoneum. PET-CT detected a diffuse increase in systemic bone metabolism,

hepatosplenomegaly with slightly increased FDG metabolism, which was consistent with the manifestation of blood system diseases. There was no evidence pointing to the second recurrence of GCT.

Peripheral blood smear revealed the existence of 22% MC-like immature cells. BM aspiration showed the substantial infiltration (67% of all nucleated cells) from morphologically heterogeneous atypical circles to oblong cells, containing abundant cytoplasm with metachromatic coarse granules. Chemical staining results showed that atypical cells were NSE(-), POX(-), DCE(-) except for Toluidine Blue(+) (Figure 1). Analysis of BM aspirate by multi-parameter flow cytometry revealed that abnormal cells were positive for CD45, CD117, CD13, CD33, and CD9, but dimly positive for CD22 and negative for CD16, CD7, κ, λ, CD19, CD38, HLA-DR, CD35, CD65, CD15, CD11b, CD123, CD79a, CD10, CD25, CD2, CD34, and MPO (Figure 2). Chromosomal G banding analysis showed a normal karyotype. A total of 16 myeloid leukemia-associated fusion genes, such as *MLL-AF6*, *CBFB-MYH11*, *AML1-ETO*, *PML-RARa*, *BCR-ABL*, etc., were negative through reverse transcription-polymerase chain reaction (RT-PCR). Fluorescence in situ hybridization detected that *RARa* rearrangement was negative. Next gene sequencing (NGS) of BM aspirate identified stable mutations in *TP53* P301Qfs*44 (variant allele frequency [VAF] 13.2%), *FLT3* R973X (VAF 58.4%), *SETBP1* N272D (VAF 48.4%) and *JAK3* I688F (VAF 57.3%), whereas *KIT* mutations were not detected. Four mutated genes were sequenced again in Sanger sequencing (Figure 3). The PCR primers used are listed in Table 1. Bone marrow biopsy revealed atypical cells, mainly oval and short spindle cells distributed in clusters, which were eosinophil by hematoxylin-eosin (HE) staining, accounting for 80%. Immune-histochemical staining confirmed positive for CD117 and negative for MPO, CD25, and CD34 (Figure 4).

Table 1
Primers for Genomic PCR

genes	primer sequence (5' to 3')
TP53	F: cttaggctccagaaaggacaag
	R: agaggcaaggaaaggtgataaa
FLT3	F: gcgcataacatgtgcatctac
	R: GTGGAGGGATGAAGTCCTTAAA
SETBP1	F: tttctctctctgtctctctcc
	R: CCTTTGTACCTCCTCCATCTTG
JAK3	F: CTGTGTTAAGCCTGGAGAgtaag
	R: CCACTAAACACTTCCCAGACC

The patient was first treated with 2 weeks of dexamethasone (10mg/day for 1 week then 5mg/day for 1 week). Surprisingly, his anemia and thrombocytopenia had significant improvements. When the diagnosis of MCL was confirmed, the patient was transferred to another hospital for treatment. His

following prognosis was further tracked. He was diagnosed with MCL again and treated with the combination therapy of dasatinib (100mg/day), ruxolitinib (5mg/bid for the first week then 10mg/bid as maintenance), and dexamethasone (20mg/day for 1 week then 10mg/day for 4 days) in the First Affiliated Hospital of Zhejiang University. After two weeks of treatment, his condition had evident remission, particularly a notable decrease in the spleen size. Nevertheless, he then died of acute respiratory distress syndrome after undergoing the first cycle of combination chemotherapy with cladribine (9.5mg d1-5) and cytarabine (1930mg d1-5). The survival time of the patient was 2.4 months after the initial presentation of MCL.

Discussion

In this case, a male patient was first reported, who had acute MCL secondary to previous primary malignant mediastinal GCT. As a group of neoplasms commonly occurring in gonads, GCT is a model of curable cancer that often has a satisfactory outcome with cisplatin-based chemotherapy [9]. However, primary mediastinal non-seminomatous GCTs (PM-NSGCTs) tend to have a poor prognosis due to the evolution of neoplasms in other somatic types and resistance to cisplatin, particularly hematologic malignancies with a median survival time of fewer than 6 months [10]. Moreover, the second hematologic malignancies preceded by or concurrent with PM-NSGCTs are mostly acute myeloid leukemia (AML) (the largest proportion is acute megakaryoblastic leukemia), sharing more genetic similarities characterized by i (12p) and/or *TP53* mutations with PM-NSGCTs rather than primary AML. The most competing hypothesis is that a common cancer progenitor cell with the capacity of differentiation into germ cells and hematopoietic lineages may evolve into both tumors [11].

The diagnosis of acute MCL of this case was based on the implementation of SM with the major criteria (dense infiltration of over 15 aggregated MCs in marrow) and one minor criterion (>25% atypical MCs in the marrow aspirate and biopsy), with the addition of up to 22% atypical MCs in PBMCs and C-findings including splenomegaly and cytopenia. It was found that the typical morphology and positive results of chemical staining with Toluidine Blue played decisive roles in the differential diagnosis of MCs.

The leukemic cells of the patient were heterogeneous in morphology, varying widely in size and shape with a very rare phenotype and genetic manifestations. The neoplasm cells phenotypically had CD9, neither CD2 nor CD25. Previous reports of SM revealed that the expression levels of two markers gradually decreased along with malignant progression [12–14]. It has been reported that 38% of MCL cases have a double-negative CD2/CD25 immuno-phenotype [7]. Besides, the positive co-expression of CD2 and CD25 has a significantly higher proportion in MCL patients with KIT D816V than those with no missense variant (66% vs 25%) [7].

MCL has typical genetic characteristics. The proportion of gain-of-function somatic mutations in *KIT*, including *KIT* D816V and other *KIT* mutants at exons 8, 9, 10, 11, 13, and 17, is approximately 90% [3]. *KIT* D816V in MCL can activate the PI3K pathway and oncogenic STAT5 molecule by JAK2 and MEK/ERK1/2 pathways, which can consistently contribute to persistent IL-6 induction. The level of IL6 is related to the

severity and prognosis of SM [15]. In addition, *KIT* D816V may be accompanied by other gene variants that jointly contribute to malignant expansion. The multivariable risk analysis of MCL patients indicated that the mutations of *SRSF2*, *ASXL1*, or *RUNX1* (S/A/R^{pos}) were the only dependent risk factor, which is adversely associated with phenotype, therapeutic response, progression, and OS [16]. However, the secondary MCL as the patient developed in the setting of primary mediastinal GCTs, appeared a classical genetic aberrance of *TP53* frameshift mutation, additionally with an *FLT3* nonsense mutation, a *SETBP1* missense mutation, and a *JAK3* missense mutation (approximately 50% high VAF for three genes), which may be genetic alterations related to chemotherapy or radiotherapy.

TP53 has been reported as an anti-oncogene to induce mutations in about 50% of human tumors [17], mainly located in the region of the DNA binding domain (DBD, codons 94-297). Both DBD and non-DBD mutations of *TP53* in AML are considered independent high-risk factors with a poor prognosis [18]. In this case, the mutation locus of *TP53* P301Qfs*44 is adjacent to the DBD. Consistent with our findings, *TP53* mutation is regarded as one of the typical genetic characteristics in secondary hematologic neoplasm preceded by mediastinal dysgerminoma [11]. Besides, it was previously reported that an ASM patient had a history of ovarian dysgerminoma, and *TP53* developed a somatic nonsense mutation in the dysgerminoma and bone marrow of an ASM period. Therefore, it is speculated that both above-mentioned tumors may derive from the common cancer stem cell, or that ASM is evolved from the residual cancer cells of dysgerminoma [19]. FLT3 is an oncogene of the receptor tyrosine kinase family that is involved in the proliferation and differentiation of hematopoiesis. The activating mutations represented by *FLT3-ITD* are closely related to tumorigenesis, especially AML. As previously reported for the exclusive relationship of *FLT3-ITD* and *TP53* mutations in AML [18], a rare nonsense mutation of *FLT3* R973X occurred in our case, corresponding to the inactivating mutation of *TP53*.

SETBP1 mutations, firstly identified in Chinzel-Giedion syndrome characterized by severe mental retardation, are considered as a biomarker of the myelodysplasia /myeloproliferative neoplasm overlap syndrome [20]. Additionally, *SETBP1* hotpot mutations within a conserved 11-nucleotide region (amino acids 868-871) are often detected in secondary AML and chronic myelomonocytic leukemia. It has been also reported that only hotpot mutations can induce the resistance and poor prognosis of myeloid neoplasm [21, 22]. The role of *SETBP1* non-hotpot mutations is currently elusive, such as *SETBP1* N272D in our case. Along with *SETBP1* mutations, a non-receptor tyrosine kinase *JAK3* mutation is identified as the secondary mutation in juvenile myelomonocytic leukemia (JMML), while the latter is involved not in the initiation but the progression of JMML, indicating a poor prognosis [23, 24]. *JAK3* mutation is regarded as a driver mutation that is frequently reported in T lineage acute lymphoblastic leukemia [25, 26]. Recurrent *JAK3* V722I is reported in malignant struma ovarii, a specific ovarian teratoma [27]. Consistent with *JAK3* V722I, the mutation site of *JAK3* I688F is located in the same protein domain, protein kinase 1, potentially harboring a similar function.

In this case, it was first considered as acute promyelocytic leukemia (APL) when blood and marrow smears showed a mass of coarse granules in the cytoplasm of abnormal cells, although the Auer body was not found. However, the subsequent laboratory results of marrow aspirate or biopsy were all negative

for MPO molecules, t (15; 17) (q22; q21), and *RARa* rearrangement, which were the classical diagnosis criteria for APL [28, 29], so that the disease was excluded. Myelomastocytic leukemia (MML) is another major differential diagnosis to MCL and is also considered an advance myeloid neoplasm with excess blasts accompanied by abnormal MCs morphologically, which fails to meet the criteria of SM to distinguish from MCL [14, 30].

Patients with MCL always have typical clinical symptoms. MC activation symptoms (MCAS, also known as mediator-related symptoms) include pruritus, flush, fever, malaise, diarrhea, etc., occurring more frequently among patients without KIT D816V mutations than positive mutations [7]. Besides, end-organ failure is another common clinical symptom of MCL patients. Similarly, our patient developed MCAS at the onset of MCL and died of respiratory failure in the end.

The treatment of MCL is limited up to now, and there is no accepted standard first-line therapy. The application of corticosteroids can reduce the MC burden and improve clinical symptoms, but the effect is often transient [7]. Cladribine is considered an effective agent to induce a meaningful response in half of the patients with advanced SM, followed by a high percentage of resistance [31]. The effect of allogeneic hematopoietic stem cell transplantation has a fine result in non-transformed SM, but it is uncertain in overt MCL [32, 33]. Midostaurin is a targeted drug that blocks the kinase activity of wild-type KIT and its activation variants including *KIT* D816V, thus prolonging the median OS to 28.7 months [34]. Since 2017, the combination therapy of midostaurin with chemotherapy has been listed as the standard first-line therapy by FDA. Dasatinib as another selective KIT inhibitor may be the second choice because of its available application in China. The patient in this case was originally effective to corticosteroids and dasatinib-based treatment, with the identical knowledge that the KIT D816V mutant is more resistant to tyrosine kinase inhibitors [35]. The patient even became more optimistic about the progression of neoplasm, however, he died of complications from chemotherapy. Personalized therapy of MCL remains challenging.

There are some defects in this case. Due to clinical laboratory limitations, the concentration of serum tryptase was not examined to investigate the correlation between tryptase expression and leukemic development. In addition, the patient's relatives refused to perform gene sequencing, and specimens in the period of primary GCT were also not examined for genetic alterations. Thus, it is difficult to determine whether these gene mutations are germline or somatic.

Conclusion

In this case, the acute MCL preceded by malignant mediastinal GCT has similar clinical symptoms and morphological manifestations but distinctly different genetic profiles in contrast to primary MCL. The characteristic morphology of MCL provides the most pivotal evidence that led our diagnosis in the right direction. It is speculated that there is a common embryonal cancer stem cell between the primary malignant GCT and the secondary de novo MCL, whereas the latter is gradually developed in the setting of additional "driver mutations".

Abbreviations

Mast cell leukemia (MCL); Mast cells (MCs); Systemic mastocytosis (SM); Germ cell tumor (GCT); Acute myeloid leukemia (AML); Peripheral blood mononuclear cells (PBMCs); Polymerase chain reaction (PCR).

Declarations

Ethics approval and consent to participate

The ethical approval and documentation for a case report were waived by the Ethical Committee of the Zhejiang Provincial People's Hospital.

Consent for publication

Written informed consent for publication was obtained from the patient's parent and is available for review by the editors of this journal.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no conflict of interests.

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Authors' contributions

Huafang Wang analyzed the patient data and drafted the manuscript. Yuan Chen as the pathologist provided the pathological data. Huijun Lin as a laboratory technician provided the data of marrow smears. Jianping Lan provided the initial idea and writing skills of the manuscript. Lai Jin reviewed the literature and revised the manuscript. All of the authors read and approved the final manuscript.

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References

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391–405.
2. Peter Valent CA, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129:1420–7.
3. Leguit R, Hebeda K, Kremer M, van der Walt J, Gianelli U, Tzankov A, Orazi A. The Spectrum of Aggressive Mastocytosis: A Workshop Report and Literature Review. Pathobiology. 2020;87:2–19.
4. Polyatskin IL, Artemyeva AS, Krivolapov YA. [Revised WHO classification of tumors of hematopoietic and lymphoid tissues, 2017 (4th edition):lymphoid tumors]. Arkh Patol. 2019;81:59–65.
5. Pardanani A. Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. Am J Hematol. 2019;94:363–77.
6. Zheng Y, Nong L, Liang L, Wang W, Li T. De novo mast cell leukemia without CD25 expression and KIT mutations: a rare case report in a 13-year-old child. Diagn Pathol. 2018;13:14.
7. Georgin-Lavialle S, Lhermitte L, Dubreuil P, Chandesris MO, Hermine O, Damaj G. Mast cell leukemia. Blood. 2013;121:1285–95.
8. Preetesh Jain SW, Keyur P, Patel N, Sarwari J, Cortes. Hagop Kantarjian, Srdan Verstovsek: **Mast cell leukemia (MCL): Clinico-pathologic and molecular features and survival outcome**. Leuk Res. 2017;59:105–9.
9. Cheng L, Albers P, Berney D, Feldman D, Daugaard G, Gilligan T, Looijenga L. Testicular cancer. Nature reviews Disease primers. 2018;4:29.
10. Hartmann J, Nichols C, Droz J, Horwich A, Gerl A, Fossa S, Beyer J, Pont J, Fizazi K, Einhorn L, et al. Hematologic disorders associated with primary mediastinal nonseminomatous germ cell tumors. J Natl Cancer Inst. 2000;92:54–61.
11. Taylor J, Donoghue M, Ho C, Petrova-Drus K, Al-Ahmadie H, Funt S, Zhang Y, Aypar U, Rao P, Chavan S, et al. Germ cell tumors and associated hematologic malignancies evolve from a common shared precursor. J Clin Investig. 2020;130:6668–76.
12. Escribano L, Díaz-Agustín B, Bellas C, Navalón R, Nuñez R, Sperr WR, Schernthaner GH, Valent P, Orfao A. Utility of flow cytometric analysis of mast cells in the diagnosis and classification of adult mastocytosis. Leuk Res. 2001;25:563–70.
13. Escribano L, Orfao A, Díaz-Agustin B, Villarrubia J, Cerveró C, López A, Marcos MA, Bellas C, Fernández-Cañadas S, Cuevas M, et al. Indolent systemic mast cell disease in adults: immunophenotypic characterization of bone marrow mast cells and its diagnostic implications. Blood. 1998;91:2731–6.
14. Valent P, Sotlar K, Sperr WR, Escribano L, Yavuz S, Reiter A, George TI, Kluin-Nelemans HC, Hermine O, Butterfield JH, et al. Refined diagnostic criteria and classification of mast cell leukemia (MCL) and myelomastocytic leukemia (MML): a consensus proposal. Ann Oncol. 2014;25:1691–700.

15. Araceli Tobío GB, Denise A. Morris,1 D-K, Kim MP, O'Connell HD, Komarow MC, Carter, Daniel Smrz,, Olivera DDMaA: **Oncogenic D816V-KIT signaling in mast cells causes persistent IL-6 production**. *Haematologica* 2020, **105**:124-135.
16. Jawhar M, Schwaab J, Meggendorfer M, Naumann N, Horny HP, Sotlar K, Haferlach T, Schmitt K, Fabarius A, Valent P, et al. The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm. Haematologica. 2017;102:1035–43.
17. Muller P, Vousden K. Mutant p53 in cancer: new functions and therapeutic opportunities. Cancer cell. 2014;25:304–17.
18. Terada K, Yamaguchi H, Ueki T, Usuki K, Kobayashi Y, Tajika K, Gomi S, Kurosawa S, Miyadera K, Tokura T, et al. Full-length mutation search of the TP53 gene in acute myeloid leukemia has increased significance as a prognostic factor. Annals of hematology. 2018;97:51–61.
19. Tsutsumi M, Miura H, Inagaki H, Shinkai Y, Kato A, Kato T, Hamada-Tsutsumi S, Tanaka M, Kudo K, Yoshikawa T, Kurahashi H. An aggressive systemic mastocytosis preceded by ovarian dysgerminoma. BMC Cancer. 2020;20:1162.
20. Linder K, Iragavarapu C, Liu D. SETBP1 mutations as a biomarker for myelodysplasia /myeloproliferative neoplasm overlap syndrome. Biomark Res. 2017;5:33.
21. Winkelmann N, Schäfer V, Rinke J, Kaiser A, Ernst P, Scholl S, Hochhaus A, Ernst T. Only SETBP1 hotspot mutations are associated with refractory disease in myeloid malignancies. J Cancer Res Clin Oncol. 2017;143:2511–9.
22. Makishima H. Somatic SETBP1 mutations in myeloid neoplasms. Int J Hematol. 2017;105:732–42.
23. Sakaguchi H, Okuno Y, Muramatsu H, Yoshida K, Shiraishi Y, Takahashi M, Kon A, Sanada M, Chiba K, Tanaka H, et al. Exome sequencing identifies secondary mutations of SETBP1 and JAK3 in juvenile myelomonocytic leukemia. Nat Genet. 2013;45:937–41.
24. Wakamatsu M, Okuno Y, Murakami N, Miwata S, Kitazawa H, Narita K, Kataoka S, Ichikawa D, Hamada M, Taniguchi R, et al. Detection of subclonal SETBP1 and JAK3 mutations in juvenile myelomonocytic leukemia using droplet digital PCR. Leukemia. 2021;35:259–63.
25. Liu Y, Easton J, Shao Y, Maciaszek J, Wang Z, Wilkinson MR, McCastlain K, Edmonson M, Pounds SB, Shi L, et al. The genomic landscape of pediatric and young adult T-lineage acute lymphoblastic leukemia. Nat Genet. 2017;49:1211–8.
26. de Bock CE, Cools J. JAK3 mutations and HOXA9 expression are important cooperating events in T-cell acute lymphoblastic leukemia. Mol Cell Oncol. 2018;5:e1458014.
27. Poli R, Scatolini M, Grosso E, Maletta F, Gallo M, Liscia D, Nelva A, Cesario F, Forte G, Metovic J, et al. Malignant struma ovarii: next-generation sequencing of six cases revealed Nras, Braf, and Jak3 mutations. Endocrine. 2021;71:216–24.
28. Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood. 2008;111:2505–15.
29. Tran VT, Phan TT, Mac HP, Tran TT, Ho TT, Pho SP, Nguyen VN, Vo TM, Nguyen HT, Le TT, et al. The diagnostic power of CD117, CD13, CD56, CD64, and MPO in rapid screening acute promyelocytic

leukemia. BMC Res Notes. 2020;13:394.

30. Arredondo AR, Gotlib J, Shier L, Medeiros B, Wong K, Cherry A, Corless C, Arber DA, Valent P, George TI. Myelomastocytic leukemia versus mast cell leukemia versus systemic mastocytosis associated with acute myeloid leukemia: a diagnostic challenge. Am J Hematol. 2010;85:600–6.
31. Barete S, Lortholary O, Damaj G, Hirsch I, Chandesris MO, Elie C, Hamidou M, Durieu I, Suarez F, Grosbois B, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. Blood. 2015;126:1009–16. quiz 1050.
32. Ustun C, Reiter A, Scott BL, Nakamura R, Damaj G, Kreil S, Shanley R, Hogan WJ, Perales MA, Shore T, et al. Hematopoietic stem-cell transplantation for advanced systemic mastocytosis. J Clin Oncol. 2014;32:3264–74.
33. Ustun C, Gotlib J, Popat U, Artz A, Litzow M, Reiter A, Nakamura R, Kluin-Nelemans HC, Verstovsek S, Gajewski J, et al. Consensus Opinion on Allogeneic Hematopoietic Cell Transplantation in Advanced Systemic Mastocytosis. Biol Blood Marrow Transplant. 2016;22:1348–56.
34. Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, Awan FT, Hexner E, Mauro MJ, Sternberg DW, et al. Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. N Engl J Med. 2016;374:2530–41.
35. Zermati Y, De Sepulveda P, Féger F, Létard S, Kersual J, Castéran N, Gorochov G, Dy M, Ribadeau Dumas A, Dorgham K, et al. Effect of tyrosine kinase inhibitor STI571 on the kinase activity of wild-type and various mutated c-kit receptors found in mast cell neoplasms. Oncogene. 2003;22:660–4.

Figures

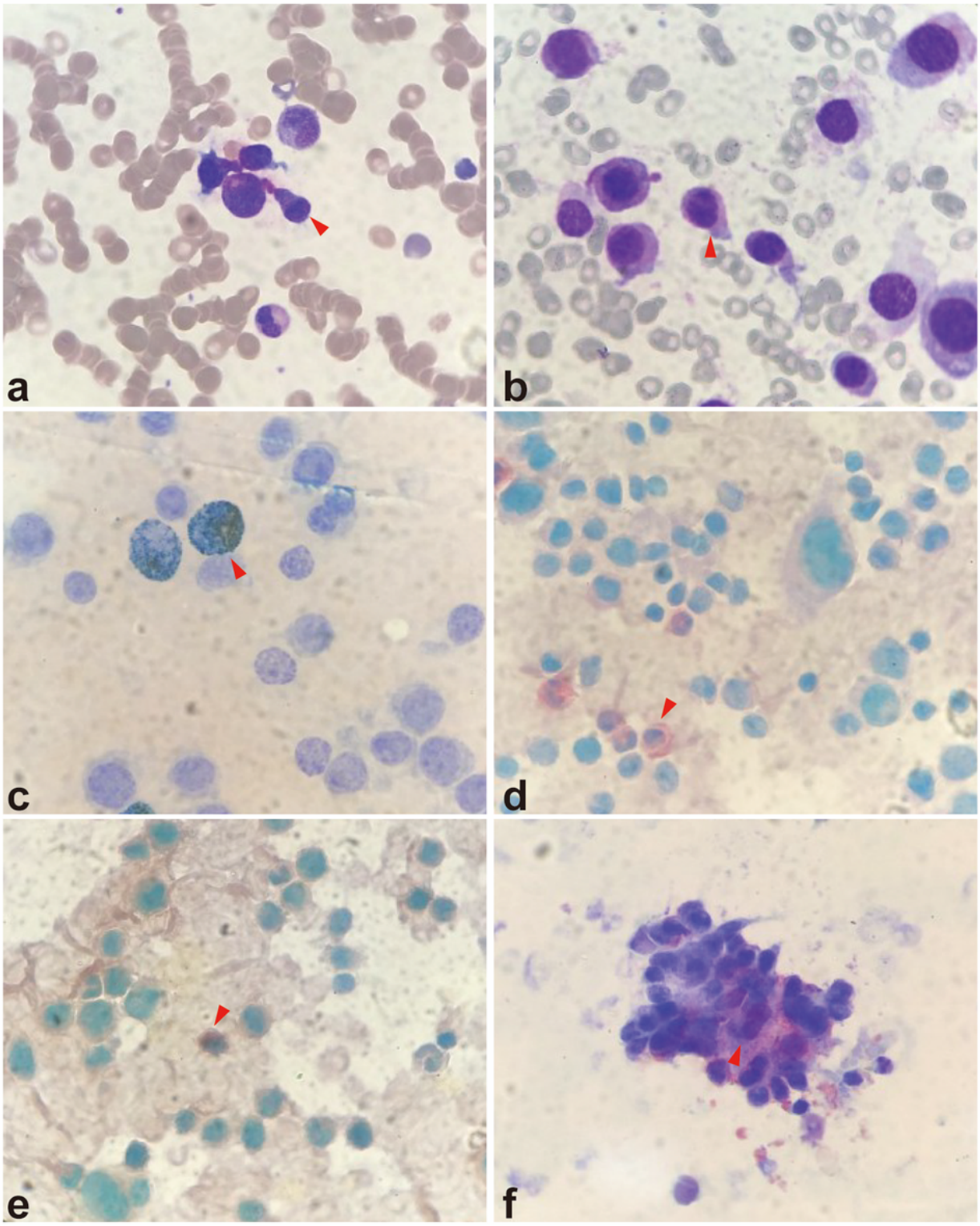

Figure 1

The features of morphology and chemical staining in the case. The morphology of Wright-Giemsa-stained peripheral blood smear (a) and marrow smear (b) were shown, 1000×, and the red triangle pointed to atypical mast cells. The results of chemical staining were negative for MPO (c), DCE (d), and NSE (e), and was positive for Toluidine Blue (f), 1000×. The red triangles pointed to the positive cells in the corresponding staining.

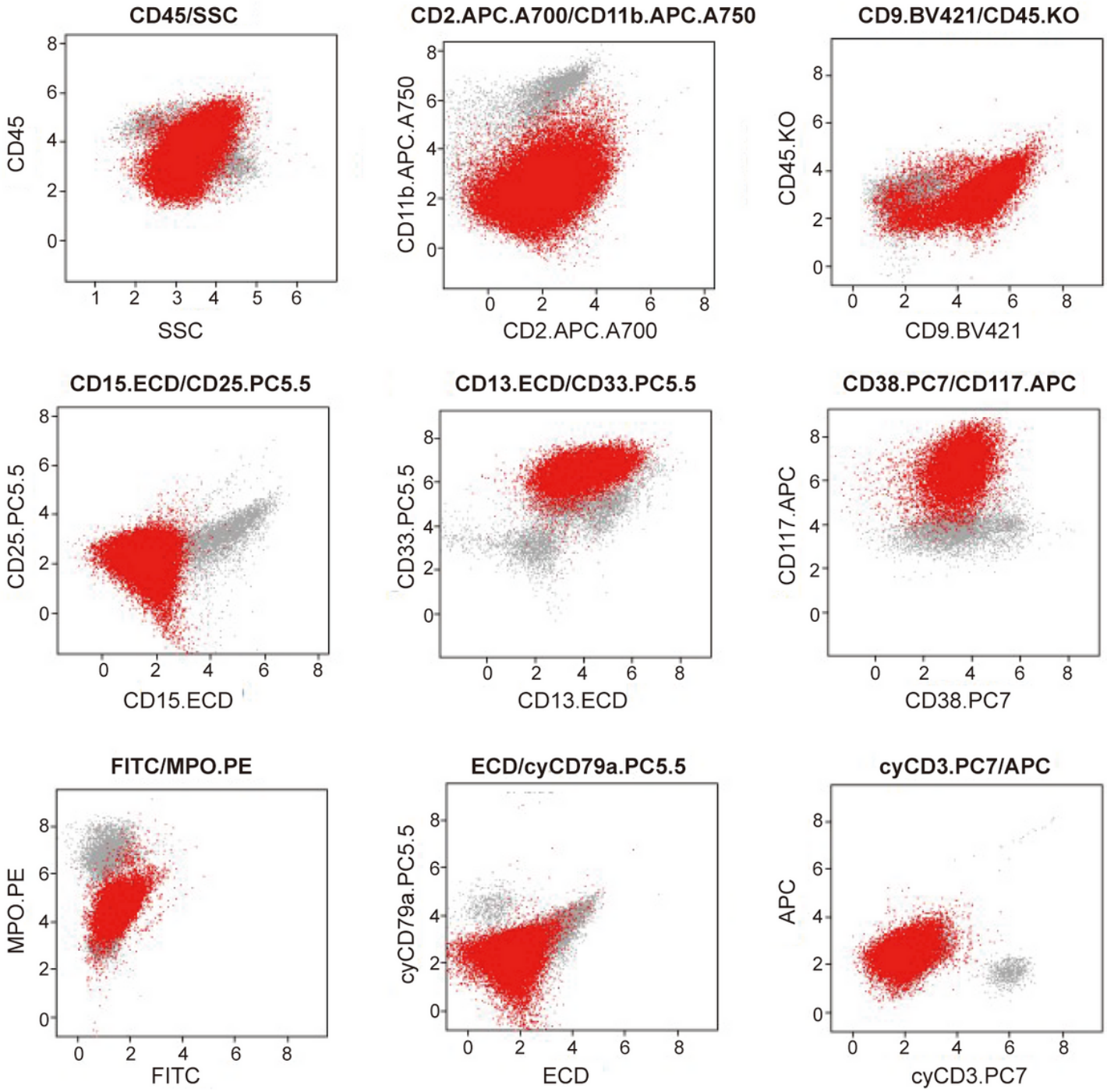

Figure 2

Multi-color flow cytometry analysis of cell surface markers of marrow mononuclear cells. Partial markers of the detected were presented. The cluster of cells colored in red indicated the leukemic cells.

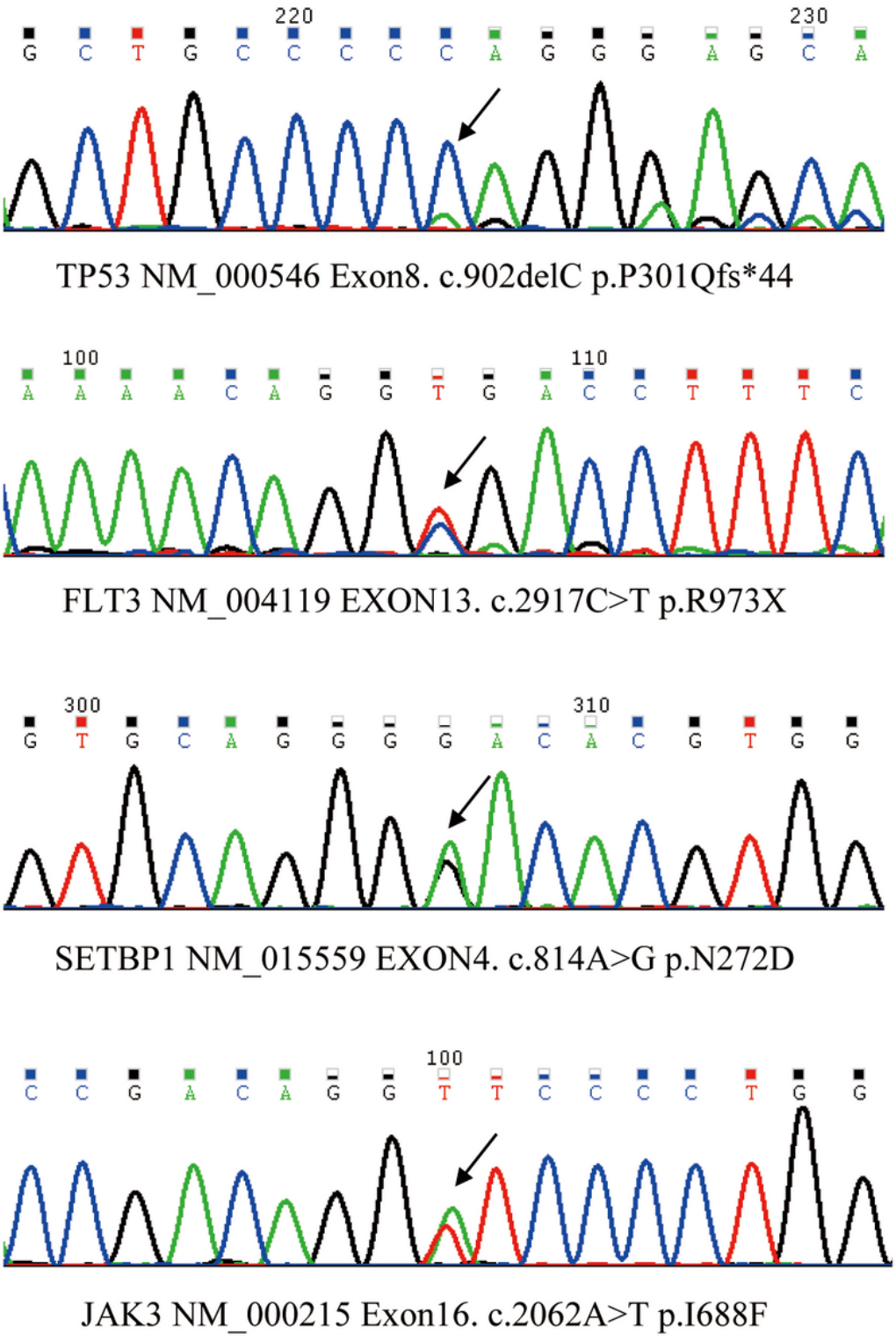

Figure 3

Sanger sequencing of genomic PCR products of bone marrow mononuclear cells. The detailed information of 4 genetic mutations was written below the corresponding peak diagram, respectively. The black arrow pointed to the mutant base. PCR, polymerase chain reaction.

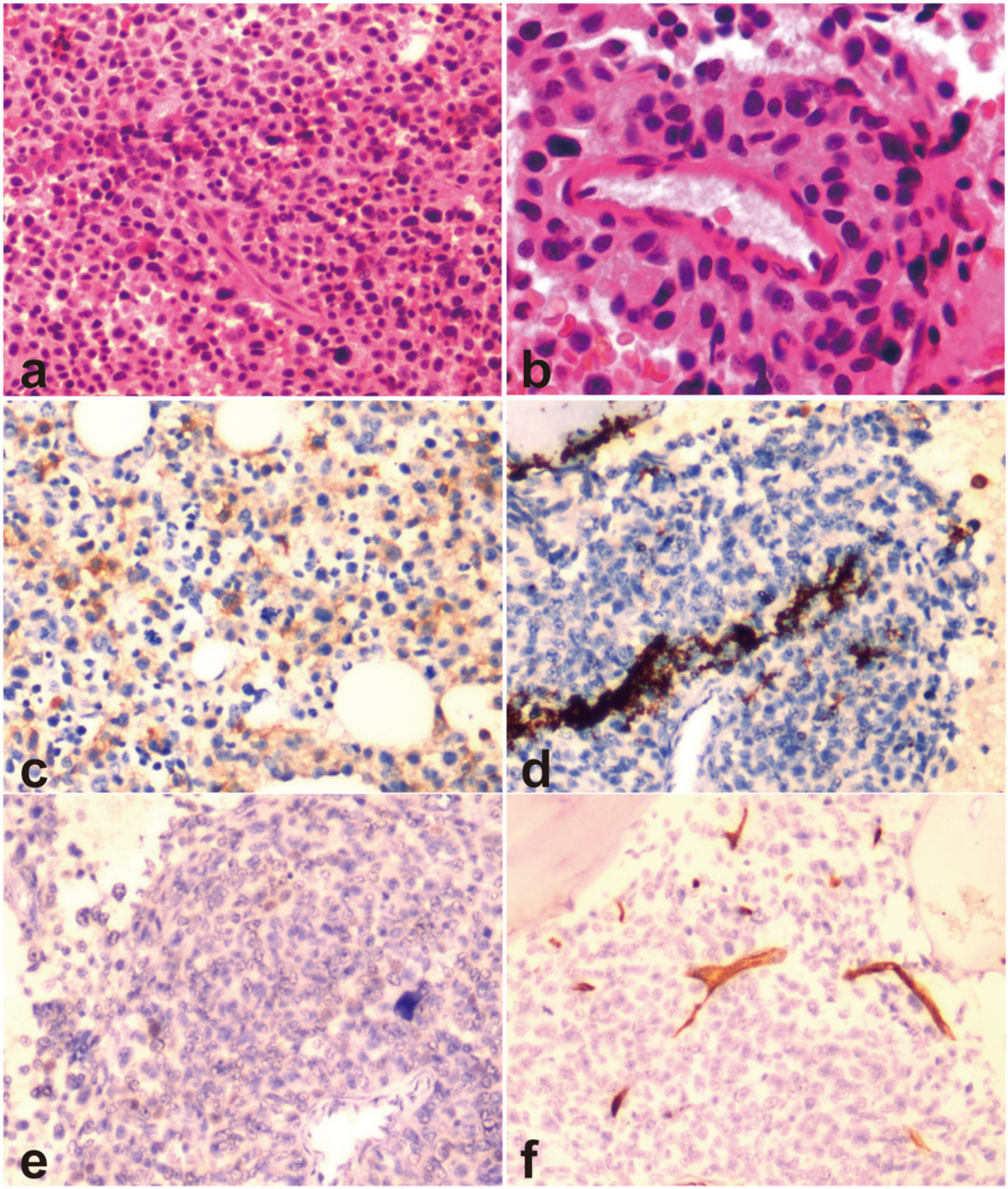

Figure 4

Morphologic and immune-histochemical features of the case. Marrow biopsy showed the architecture was diffusely infiltration by clusters of oval and short spindle cells (a-b), 200× and 400×. The neoplastic cells were positive for CD117 (c), but almost all negative for MPO (d), CD25 (e), and CD34 (f), 200×.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CAREchecklist.docx