Case Reports

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Development of a myelodysplastic/myeloproliferative neoplasm-unclassifiable in a patient with acute myeloid leukemia: a case report and literature review

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Abstract

Myelodysplastic/myeloproliferative neoplasms (MDS/MPNs) are a heterogeneous group of hematologic malignancies characterized by dysplastic and myeloproliferative overlapping features in the bone marrow and blood. The occurrence of the disease is related to age, prior history of MPN or MDS, and recent cytotoxic or growth factor therapy, but it rarely develops after acute myeloid leukemia (AML). We report a rare case of a patient diagnosed with AML with t(8; 21)(q22; q22) who received systematic chemotherapy. After 4 years of follow-up, MDS/MPN-unclassifiable occurred without signs of primary AML recurrence.

Keywords

Myelodysplastic/myeloproliferative neoplasm-unclassifiable, acute myeloid leukemia, myeloid malignancy, Runt-related transcription factor 1/RUNX1 partner transcriptional co-repressor 1 mutation, BCR/ABL1 negative, case report

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Introduction

Myelodysplastic and myeloproliferative neoplasms (MDS/MPNs) are a rare and distinct group of myeloid neoplasms with overlapping MDS and MPN features that represent approximately 2% to 5% of all myeloid malignancies.[1] The MDS/MPN category is an integral part of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia, and it includes chronic myelomonocytic leukemia (CMML), atypical chronic myelogenous leukemia (aCML), juvenile myelomonocytic leukemia, MDS/MPN with ringed sideroblasts and thrombocytosis, and MDS/MPN-unclassifiable (MDS/MPN-U).[2] The MDS/MPN-U category is the least defined entity in this group and is a diagnosis of exclusion. Careful examination of blood smears and bone marrow samples is essential to exclude MDS, MPN, and MDS/MPN. Our understanding of the natural history and therapy of MDS/MPN-U overlap syndromes is limited. Historically, MDS/MPN-U has a high risk of converting into acute myeloid leukemia (AML). However, reports of patients who develop MDS/MPN after being diagnosed with AML are rare. We report a patient with AML who achieved deep molecular remission following regular chemotherapy, but transformation into MDS/MPN-U occurred after 4 years.

Case report

A 54-year-old male patient suffering from gum swelling, pain, and fever was admitted to The First Hospital of Jilin University in November 2013. His medical history was unremarkable. Complete blood count (CBC) analysis revealed a white blood cell count of 4.97×10^9/L, a hemoglobin concentration of 95 g/L, and a platelet count of 26×10^9/L. Peripheral blood smear analysis revealed 22% myeloid blasts with visible Auer bodies. Bone marrow biopsy showed a hypercellular marrow with hyperplasia, and bone marrow smears showed 76.5% myeloid blasts with visible Auer bodies (Figure 1a, b). Cytochemical staining was positive for peroxidase (Figure 1c) and esterase, and CD34, CD117, CD56, CD19, CD33, CD13, human leukocyte antigen-DR isotope (HLA-DR), and CD123 expression on the cell surface of leukemic blasts was detected by flow cytometry. An abnormal karyotype with 45, X, -Y, t(8; 21)(q22; q22)[4]/46, XY[7] (Figure 1d) and mutation in Runt-related transcription factor 1 (*RUNX1*)/RUNX1 partner transcriptional co-repressor 1 (*RUNX1T1*) were observed. FMS-like tyrosine kinase 3-internal tandem duplication, nucleophosmin 1, *C-KIT*, CCAAT/enhancer-binding protein alpha, isocitrate dehydrogenase (*IDH)1*/*IDH2*, and DNA (cytosine-5)-methyltransferase 3A (*DNMT3A*) mutations were negative. The patient was diagnosed as AML with t(8; 21)(q22; q22), with a superior prognosis. Induction chemotherapy with idarubicin (10 mg/m^2) for 3 days plus cytarabine (100 mg/m^2) for 7 days was initiated, and complete hematological remission was achieved. Deep molecular remission was achieved after two-cycle consolidation chemotherapy, including one cycle with daunorubicin (45 mg/m^2) for 3 days plus cytarabine (100 mg/m^2) for 5 days and another cycle with high-dose cytarabine (2.0 g/m^2 every 12 hours, intravenous injection on days 1, 3, and 5). Three courses of consolidation therapy with high-dose cytarabine were administered, and continued complete remission was maintained until the fourth year of follow-up.

At the beginning of March 2018, the patient was admitted to our hospital for fever, with temperature fluctuating between 37.0 and 37.7°C. Before coming to the hospital, 8-day cefuroxime and 6-day sulfamethoxazole were used, and there was no sign of improvement in body temperature.

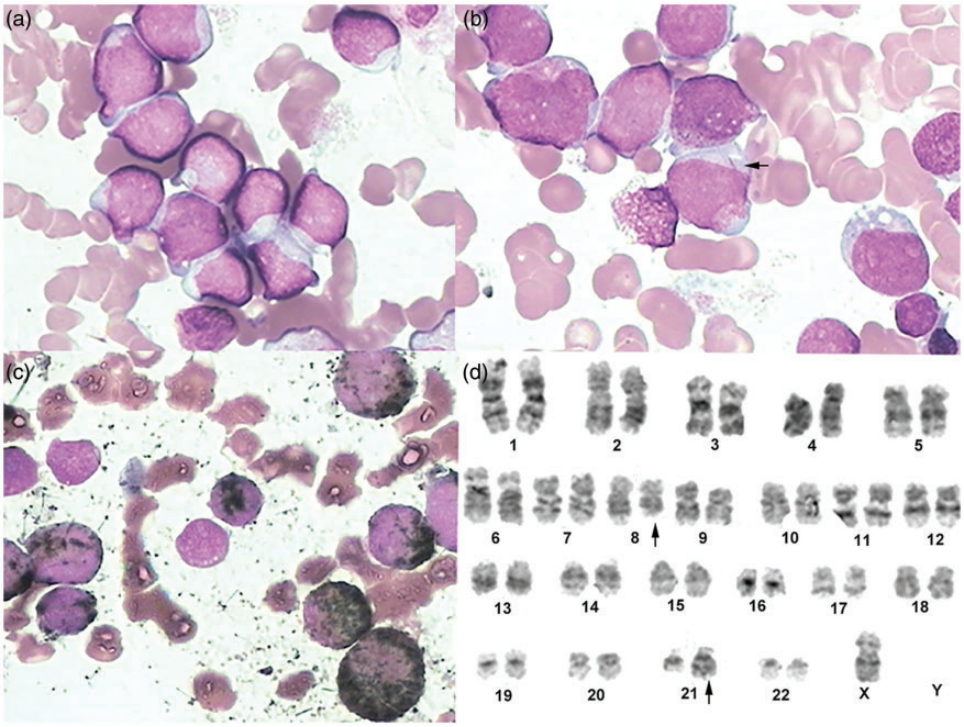

Figure 1. Bone marrow smear and cytogenetic analysis of a 54-year-old male patient in November 2013. (a) Bone marrow smear analysis revealed marked myeloid blasts with (b) visible Auer bodies. (c) Cytochemical staining was positive for peroxidase. (d) Cytogenetic analysis showed an abnormal karyotype with 45, X, -Y, t(8; 21)(q22; q22) (indicated by arrows) in four metaphases and normal karyotype with 46, XY in seven metaphases.

Hemolysis-related and immune-related examinations were negative. Leukocytosis (20.37×10^9/L), thrombocytopenia (53×10^9/L), and anemia (hemoglobin concentration was 68 g/L) were revealed by CBC analysis. Myeloid blasts were observed in peripheral blood smears, and the differential white blood cell count showed mainly neutrophils accounting for 78% (23% immature precursors, 14% band cells, and 41% segmented cells), eosinophils accounting for 4%, mature lymphocytes accounting for 16%, and monocytes accounting for 2% (monocyte count of 0.6×10^9/L). Bone marrow smears revealed marked myeloid hyperplasia with elevated erythrocytes accounting for 65%, reduced granulocytes accounting for 31% (1.5% myeloid blasts) and 29 megakaryocytes, trilineage dysplasia in granulocytes consisting of 10% P-G granulocytes and decreased cytoplasmic granules, erythrocytes consisting of 10% binuclear and trinucleate erythroid cells, and megakaryocytes consisting of 2 multinucleated and pleomorphic megakaryocytes (Figure 2a, b, c). Bone marrow biopsy exhibited no evidence of myelofibrosis. Flow cytometry showed 8.34% blasts and positive CD34, CD117, CD13, CD33, CD38, and HLA-DR expression. Cytogenetic analysis revealed a karyotype of 44, XY, -5, -6, -11, -17, -18, +mar×3 (Figure 2d), with no t(3; 3)(q21; q26), inv(3)(q21q26), or del(5q). *TP53*

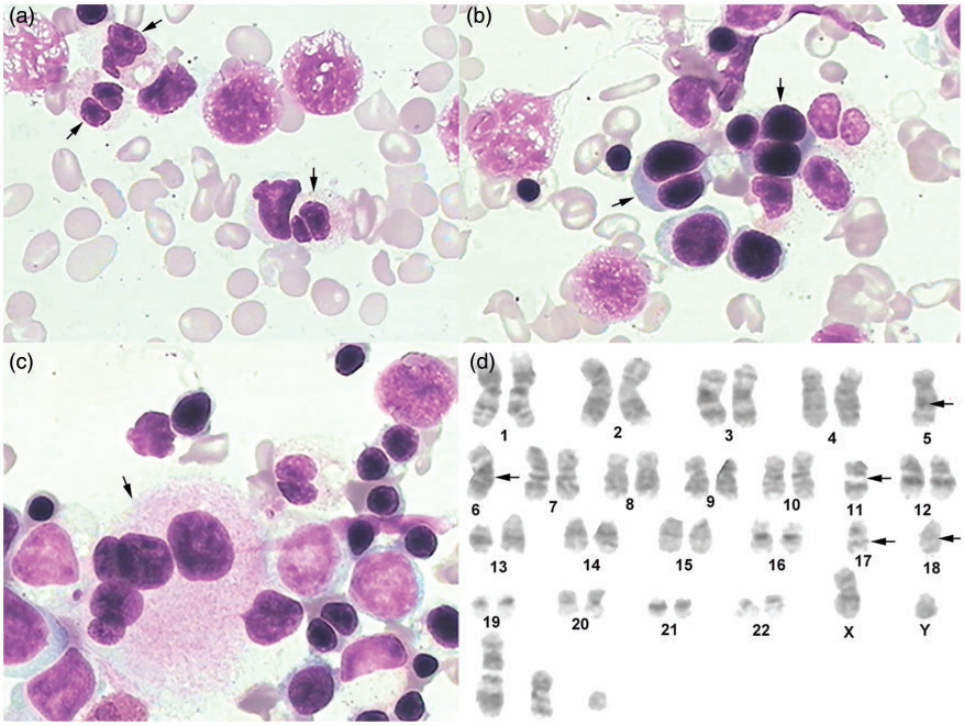

Figure 2. Bone marrow smear and cytogenetic analysis of a 54-year-old male patient in March 2018. Bone marrow smear analysis showed multilineage dysplasia, including (a) P-G granulocytes, (b) binuclear and trinucleate erythroid cells, and (c) multinucleated megakaryocytes (all indicated by arrows). (d) Cytogenetic analysis showed an abnormal karyotype with 44, XY, -5, -6, -11, -17, -18, +mar×3 in all 10 metaphases in March 2018.

mutation was positive, and there was no evidence of *RUNX1*/*RUNX1T1*, *BCR*/*ABL1*, platelet-derived growth factor receptor A (*PDGFRA*), *PDGFRB*, and fibroblast growth factor receptor 1 (*FGFR1*) rearrangement or pericentriolar material 1 (*PCM1*)-Janus kinase 2 (*JAK2*) gene fusion. More than 100 gene mutations were detected. *DNMT3A*, Tet methylcytosine dioxygenase 2 (*TET2*), ASXL transcriptional regulator 1 (*ASXL1*), and *JAK2* mutations were negative, and clonal hematopoiesis of indeterminate potential was largely ruled out. With the absence of mutations in *JAK2*/*V617F*, calreticulin, or *MPL*, there was no evidence meeting the WHO criteria for primary myelofibrosis, BCR-ABL1$^+$ CML, CMML, aCML, or other myeloid neoplasms. Additionally, he had not been recently exposed to cytotoxic drugs or hematopoietic growth factors. The diagnosis of MDS/MPN-U was established clearly. However, the patient refused to receive further examinations and treatment for personal reasons and remained alive for 26 months until the last follow-up on 30 May 2020. The reporting of this study conforms to CARE guidelines.[3]

Discussion

MDS/MPN-U is the most heterogeneous and least well-characterized entity; it primarily occurs in older adults and generally

invades the peripheral blood, bone marrow, spleen, liver, and other extramedullary tissues. Common somatic mutations in patients with MDS/MPN-U include *ASXL1, TET2, JAK2*, and *SRSF2* (>20%).[4] MDS/MPN-U remains one of the most challenging malignancies to diagnose, with no currently recognized specific molecular findings or consensus on which therapy (if any) should be given for patients who are candidates for allogenic hematopoietic stem cell transplantation (allo-HSCT). Augmented leukocyte proliferation is generally managed using cytoreductive agents, such as hydroxyurea, or immunomodulation with interferon-α, but hypomethylating agents (HMAs) and lenalidomide may be an option in cases of prevailing cytopenias.[5] JAK inhibitors alone or in combination with HMAs are also potential therapeutic options.[6] When patients are progressing to AML, induction chemotherapy should be used as a bridge to allo-HSCT. The MDS/MPN-U category appears to have an inferior prognosis, with median survival times of 12.4 and 21.8 months.[4]

The pathogenesis of MDS/MPN-U is unclear and may be related to age, prior history of MPN or MDS, and recent cytotoxic or growth factor therapy, according to the WHO MDS/MPN Diagnostic Criteria.[2] MDS/MPN has a high risk of converting into AML, at approximately 23% to 54%.[7–9] However, reports of patients who develop MDS/MPN after diagnosis of AML are rare.

The present case was identified as AML with t(8; 21)(q22; q22) initially, with a superior prognosis, and this patient achieved deep molecular remission after regular induction chemotherapy and consolidation chemotherapy. After 4 years, leukocytosis and thrombocytopenia occurred, and less than 20% myeloid blasts were observed in the blood. Marked myeloid hyperplasia predominantly in erythroid cells and trilineage dysplasia were detected. Cytogenetic analysis revealed a complex karyotype without *RUNX1/RUNX1T1, BCR/ABL1, PDGFRA, PDGFRB*, and *FGFR1* rearrangement or *PCM1-JAK2* gene fusion. Therefore, the diagnosis of MDS/MPN-U was confirmed. Disease progression in most cases involves general transformation from MPN, MDS, or MDS/MPN into AML, and transformation from AML into MPN, MDS, or MDS/MPN is extremely rare. Hyrenius-Wittsten et al.[10] reported the genomic profiling and direct ex vivo drug analysis of an MDS/MPN-U that progressed into AML. Takeshita et al.[11] described a case of therapy-related aCML after achieving complete remission from APL, and the aCML rapidly underwent clonal evolution and transformed into CD56-positive AML. Ide et al.[12] reported that FGFR1-mutated B-cell acute lymphoblastic leukemia transformed into a myelodysplastic/myeloproliferative neoplasm and AML. However, there are no reports on the transformation of AML into MPN, MDS, or MDS/MPN. Secondary hematopoietic malignancies can be attributed to cytotoxic drugs, and the cause of these transformations may be therapy-related. Therapy-related acute myeloid leukemia (t-AML) accounts for approximately 10% to 20% of all AML cases. t-AML/MDS is an important subset associated with exposure to alkylating agents, topoisomerase II inhibitors, and radiation therapy. Several studies demonstrated a poor prognosis with a median overall survival of less than 12 months for these patients.[13–20] We reviewed the available literature (Table 1), and the overall incidence of t-AML/MDS is low. Additionally, the occurrence of hematologic tumors (such as Hodgkin lymphoma, Non-Hodgkin lymphoma, acute lymphoblastic leukemia, and chronic lymphocytic leukemia) is relatively more frequent in contrast to solid tumors (such as gynecologic cancer, breast cancer, Ewing sarcoma, and primitive neuroectodermal

Table 1. Literature on hematological malignancy and solid tumor transformation into t-AML/MDS.

Primary cancer	Number of patients	Therapy	Median latency time for t-AML/MDS	Incidence of t-AML/MDS	Median OS of t-AML/MDS
HL[12]	754	MOPP or ABVD or PAVe ±IFRT	55.2 months	24/754 (3.2%)	0.7 (0–1.7) years
Indolent NHL[13]	563	Fludarabine-based chemotherapy	25 months (6–168)	12/563 (2.1%)	NA
DLBCL[14]	1280	PCB+epidoxorubicin/ idarubicin/sequential or CHOP or CHOP-like	43 months (30–127)	8/1280 (0.625%)	0.75 (0.4–1.4) years
ALL[15]	54068	Epipodophyllotoxin/cyclo-phosphamide/6-mer-captopurine/CNS irradiation	32.4 months (21.6–54)	255/54068 (0.47%)	NA
CLL[16]	234	Fludarabine	32.4 months (13.2–93.6)	12/234 (5.1%)	NA
Ovarian cancer[17]	33910	Platinum-based chemotherapy	47 months	47/33910 (0.14%)	3 months
Cervical[17]	11659	Platinum-based chemotherapy	34.5 months	14/11659 (0.12%)	7 months
Uterine cancer[17]	14561	Platinum-based chemotherapy	38.5 months	18/14561 (0.12%)	4 months
Breast cancer[18]	9926	AC/AC+TAC/F	25 months (18–95)	9/9926 (0.09%)	13.78 months
EWS or primitive neu-roectodermal tumor of bone[19]	578, median age 12 (0–30) years	VAdCA or VAdCA+I/E or VAdCA* and I/E*	36 months	11/578 (2% 5 years)	NA

MOPP: mechlorethamine, vincristine, procarbazine, prednisone; ABVD: doxorubicin, bleomycin, vinblastie, dacarbazine; PAVe: procarbazine, melphalan, vinblastine; IFRT: involved-field radiation therapy; PCB-epidoxorubicin: ProMECE-CytaBOM (methylprednisolone, cyclophosphamide, epidoxorubicin or doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate); PCB-idarubicin: ProMICE-CytaBOM (methylprednisolone, cyclophosphamide, idarubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate); PCB-sequential: sequential ProMECE instead of the classical cycling regimen; CHOP: cyclophosphamide, doxorubicin vincristine, prednisolone; AC: doxo-rubicin hydrochloride, cyclophosphamide: F: 5-fluorouracil; TAC: paclitaxel; VAdCA, vincristine, doxorubicin, cyclophosphamide, and dactinomycin; I/E: ifosfamide and etoposide; VAdCA* and I/E*: high-intensity vincristine, doxorubicin, cyclophosphamide, dactinomycin, ifosfamide, and etoposide; HL: Hodgkin lymphoma; NHL: Non-Hodgkin lymphoma; ALL: acute lymphoblastic leukemia; CLL: chronic lymphoblastic leukemia; DLBCL: diffuse large B cell lymphoma; OS: overall survival; EWS: Ewing sarcoma; NA: not applicable.

bone tumors) (2.299% vs. 0.494%). In hematologic and solid tumors, the median latency time for transformation into t-AML/MDS was 25 to 55.2 months and 25 to 47 months, respectively (Table 1). Therefore, transformation from AML into MDS/MPN may have occurred due to therapy-related reasons in the present case, who had a history of chemotherapy with topoisomerase II inhibitors (doxorubicin, daunorubicin, and mitoxantrone). Additionally, as people age, their tissues accumulate an increasing number of somatic mutations. When this occurs in the hematopoietic system, a substantial proportion of circulating blood cells may derive from a single mutated stem cell. This is termed clonal hematopoiesis (CH) and is highly prevalent in the elderly population.[21] Individuals with CH are at greater risk for hematological malignancies, cardiovascular disease, and increased mortality from non-hematological cancers. As organisms age, there is increasing evidence that cells acquire somatic mutations or encounter environmental mutagens that induce mutations.[22] Time and environmental exposure can cause cancer and malignant development whereby a proliferative cell acquires a series of mutations that can lead to unrestrained growth; for our patient, who is older and has a history of malignancy, and who is genetically susceptible to cancer, it is possible for this to occur. In addition, there might have been two types of clones at first, with acute myelogenous leukemia as the main clone of concern and MDS/MPN-U as the masked subclone. With the treatment of AML, the subclone became evident. In previous studies, aberrant signaling caused by mutations in the RAS/RAF/MEK/ERK pathway and its upstream activators critically contributed to AML or MDS/MPN development.[10,23,24] For this patient, the AML might have alterations in the MEK/ERK pathway. Four years after chemotherapy, because of external environmental exposure or changes in the internal microenvironment, the MEK pathway may have been altered again, leading to the development of MDS/MPN.

In our patient, AML transformation into MDS/MPN-U may be a possible pathogenic mechanism. Nevertheless, there are few previous reports on the transformation of AML into MDS/MPN. Although the simultaneous existence of two clones in a patient is possible, the incidence is very low and only sporadically reported.[25,26] Similarly, the presence of both acute and chronic leukemia in an individual is rare.

We suggest that chemotherapy in patients with leukemia may lead to stem cell damage and treatment-related non-AML myeloid tumors. Therefore, patients with deep remission of AML should be followed up regularly, focusing on the possibility of MDS, MDS/MPN, and other diseases.

Ethics statement

Ethical approval was not required because this was a retrospective study. Written informed consent was obtained from the patient.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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