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Case Report

Sea-blue histiocytosis in a patient with acute myeloid leukemia with myelodysplasia-related changes harboring isolated trisomy 9: pathognomonic or a coincidence?

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Abstract: Although isolated trisomy 9, a form of chromosome aneuploidy, is rare in acute myeloid leukemia (AML), up to 30 cases of AML involving isolated trisomy 9 have been reported to date. We report the case of a 77-year-old female with AML, in which trisomy 9 was detected as an isolated aberration. In addition, the patient's bone marrow displayed so-called sea-blue histiocytosis. The accumulation of further cases of isolated trisomy 9-harboring AML involving sea-blue histiocytosis is necessary to determine whether the coexistence of these findings is pathognomonic or a coincidence.

Keywords: Acute myeloid leukemia, trisomy 9, sea-blue histiocytosis

Introduction

Trisomy 9 is a genetic disorder, characterized by an extra chromosome 9. Among hematological malignancies, trisomy 9 is most frequently seen in polycythemia vera; however, isolated trisomy 9 is a recurrent, but rare, chromosomal aberration in acute myeloid leukemia (AML), and only 30 AML cases harboring this abnormality have been reported [1-21]. Regarding its morphology, the disease does not exhibit any particular characteristics, expect that no cases of AML-M3 or M7 (French-American-British classification) have been reported. On the other hand, only one case exhibiting sea-blue histiocytosis has been reported [21]. Herein, we report the second case of AML with myelodysplasia-related changes to exhibit isolated trisomy 9 and sea-blue histiocytosis in the bone marrow, which was diagnosed based on the detection of trilineage dysplasia in the patient's bone marrow cells.

Case presentation

A 77-year-old female was referred to our hospital due to anemia and thrombocytopenia. Her laboratory values on admission included a white blood cell count of 9.6×10^9/L with a blast frequency of 0.5%, a hemoglobin concentration of 9.7 g/dL, a platelet count of 25×10^9/L, and a lactate dehydrogenase level of 189 IU/L. A bone marrow examination revealed a hypercellular bone marrow with a blast frequency of 38.2%. Morphologically, the patient's bone marrow cells demonstrated trilineage dysplasia, accompanied by proliferating histiocytes, containing blue-green colored cytoplasmic granules with vacuolation, which seemed to represent so-called sea-blue histiocytosis (**Figure 1**). In surface marker analysis, the blasts displayed CD13, CD34, and human leukocyte antigen (HLA)-DR expression, but were negative for CD33. Karyotype analysis of the patient's bone marrow cells detected the following karyotype: 47,XX,+9[4]/46,XX[16] (**Figure 2**). A diagnosis of AML with myelodysplasia-related changes was made because of the dysplasia seen in the bone marrow cells. The patient received various chemotherapies, including azacitidine monotherapy and anthracycline-based intensified chemotherapy (daunorubicin and cytosine arabinoside, and mitoxantrone and cytosine arabi-

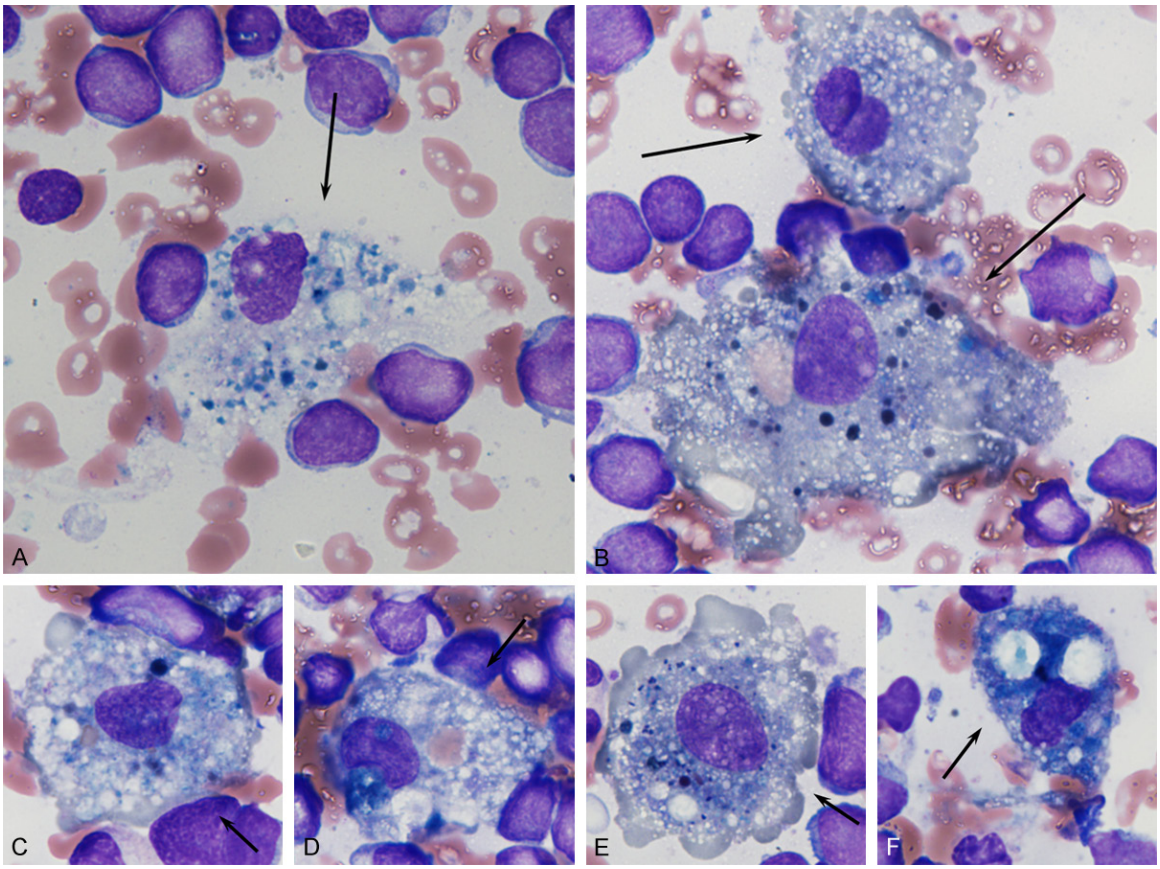

Figure 1. The May-Giemsa-stained sea-blue histiocytes seen in the bone marrow (A-F, ×1000). The sea-blue histiocytes (arrows) demonstrated morphological diversity and included relatively large cells, containing scattered blue-green granules (A, B); medium-sized cells with sparse granules and vacuoles (C-E); and medium-sized cells packed with condensed granules (F).

noside); however, her disease gradually became refractory, and she eventually died 17 months after the initial diagnosis.

Discussion

Trisomy occurs as a sole cytogenetic abnormality in 7.7% of cytogenetically analyzed cases of AML. The five most common types of trisomy are +8, +13, +11, +21, and +4 [22]. Among hematological malignancies, trisomy 9 is most frequently seen in polycythemia vera, and it was previously considered to be disease-related rather than be a secondary effect of therapy [23]. However, it is currently assumed to represent a gain-of-function mechanism with respect to *JAK2* at 9p24.

Regarding chromosome 9 abnormality in cases of AML, deletions of the long arm of chromosome 9 are relatively common, occurring in approximately 2% and 5% of adult and childhood cases, respectively [24, 25]. On the other hand, the occurrence of trisomy 9 alone is rare in AML, and only 30 such cases of AML have been reported to date [1-21].

As for the morphological classification of disease, Mark et al. [15] reported that the M2, M4, and M5 subgroups of the French-American-British classification dominate in AML patients with trisomy 9, irrespective of whether the trisomy 9 is primary or secondary. However, cases of M0 [20], M1 [7, 9], M2 [10, 14, 17, 19], M4 [1, 4, 15, 21], M5 [10, 11], and M6 [12] disease have been reported. Hence, the disease does not exhibit any obvious morphological characteristics at present, expect that no cases of AML-M3 or M7 have been reported.

Unfortunately, most of the reports about previous cases mainly focused on the chromosomal aberration itself, or information about individual cases was not available because the cases

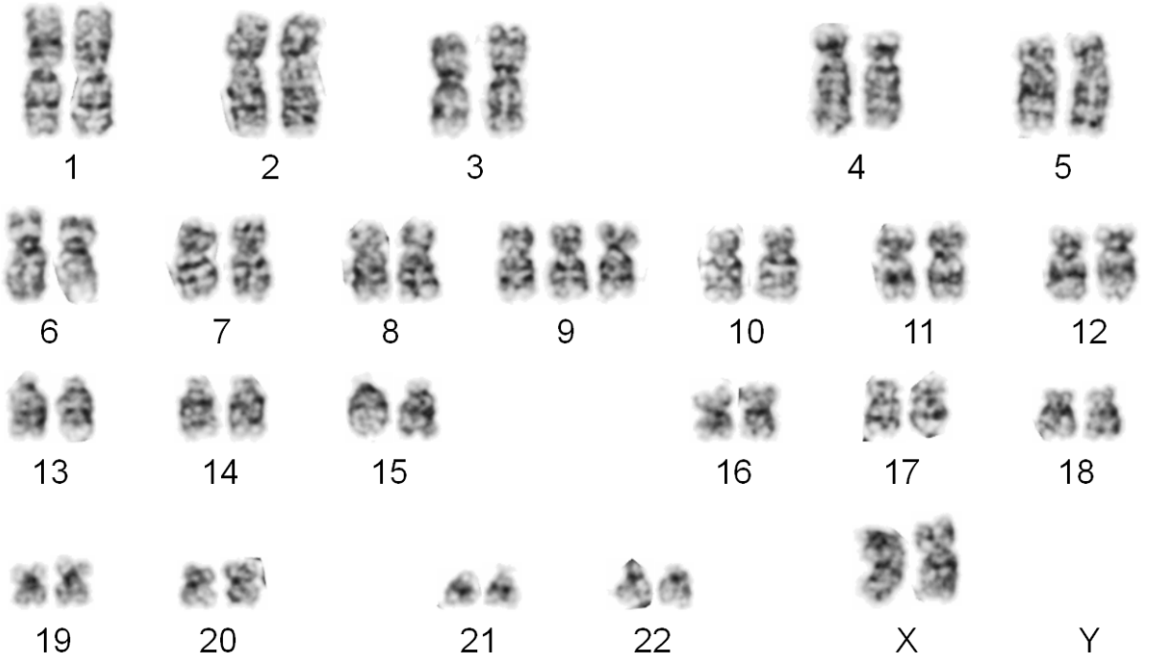

Figure 2. The G-banded karyogram obtained in this case (47,XY,+9).

were reported as part of a series. Therefore, it seems that the clinical and prognostic impact of isolated trisomy 9 in AML has not been fully elucidated. We consider that further accumulation of cases of AML harboring isolated trisomy 9 is necessary to allow the impact of isolated trisomy 9 on the prognosis and clinical course of AML to be evaluated.

Regarding the sea-blue histiocytosis seen in the bone marrow in the present case, it is a morphological finding that has been described in the setting of high rates of intramedullary cell death, e.g., due to lysosomal lipid storage disorders, such as Gaucher disease or Niemann-Pick disease, or hematological diseases, such as myelodysplastic syndromes, myeloproliferative disorders, lymphoma, chronic immune thrombocytopenia, or β-thalassemia major [26]. The sea-blue histiocytes seen in our case varied from cells containing scattered blue-green granules to densely packed cells. This finding was considered to be part of the morphological diversity reported by Howard and Kesteven [27]. In terms of clinical significance, it was suggested that sea-blue histiocytosis arises as a result of ineffective hematopoiesis, leading to increased destruction of erythrocytes, leucocytes, and platelets in myelodysplastic syndrome [27]. Thus, cases involving sea-blue histiocytosis might display more marked cytopenia than those without sea-blue histiocytosis, as has been observed in cases of drug-induced [26] or malnutrition-induced [28] sea-blue histiocytosis. Two cases of AML harboring sea-blue histiocytosis have been reported previously [21, 29]. These cases and the present case share several things in common, e.g., the patients were all elderly, Japanese, and had poor prognoses (**Table 1**). However, it is unclear whether these points are actually characteristics of sea-blue histiocytosis-containing AML because so few cases have been reported. With regard to the association between trisomy 9 and sea-blue histiocytosis, only one case of AML harboring both trisomy 9 and sea-blue histiocytosis has been reported [21]. Unfortunately, it was unclear whether the coexistence of isolated trisomy 9 and sea-blue histiocytosis in the current case was pathognomonic or a coincidence. Although we were not able to perform any detailed evaluations of the mechanisms responsible for the formation of the sea-blue histiocytes in the present case, it might be possible to determine the molecular biological mechanisms responsible for sea-blue histiocytosis, even in AML cases involving trisomy 9, in the near future.

Table 1. Cases of acute myeloid leukemia involving sea-blue histiocytosis

Case no.	Age/Sex	Diagnosis	WBC ($\times 10^9$/L)	Hb (g/dL)	Plt ($\times 10^9$/L)	Chromomal abnormality	Subsequent therapy and clinical course	Author
1	74/M	AML-MRC	7.2	7.4	21	trisomy 9	Aclarubicin and cytarabine (resistant), salvage chemotherapy (progression); died of leukemia (11 months)	Yamamoto K (2016)
2	80/M	AML-M4	5.27	NR	NR	t(8;22)(p11;q13)	Low-dose cytarabine; died of leukemia	Imataki O (2020)
3	77/F	AML-MRC	9.6	9.7	25	trisomy 9	Azacitidine (progression), anthracycline-containing chemotherapy (progression); died of leukemia (17 months)	present case

AML: acute myeloid leukemia; MRC: myelodysplasia-related changes; NR: not reported.

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Written informed consent was obtained from the patient's daughter.

Disclosure of conflict of interest

None.

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