INTRODUCTION

The malignant clonal proliferation and differentiation hali of immature myeloid progenitors is known as acute myeloid leukemia (AML) (1). AML is characterized by leukemic blasts that are not limited to the bone marrow or peripheral blood. AML may be presented with granulocytic sarcoma. Leukemic cells that are located outside the blood or bone marrow are referred to as extramedullary involvement (EMI). Extramedullary disease, myeloid sarcoma, acute myeloid leukemia, and leukemic cells outside of the blood or bone marrow are called extramedullary involvement (EMI). Skin, bone, and lymph nodes are the most prevalent locations of extramedullary illness. Granulocytic sarcoma (GS) should be considered in the differential diagnosis of nodules, pustules, or plaque-like lesions, especially in patients with suspected hematological disease. No EMI-specific treatment regimens have been established; patients who are suitable for intensive therapy are typically treated with anthracycline and cytarabine-containing regimens. The most common genetic aberration in adult AML is somatic mutations in exon 12 of the NPM gene (NPM1), which affect up to 60% of individuals with normal karyotype AML and around 35% of all cases. Patients with NPM1 mutations are twice as likely to also have a FMS-like tyrosine kinase internal transmembrane duplications (FLT3-ITD) mutation as patients without NPM1 mutations.

Case: Here in this study, we report a patient diagnosed with FLT3-ITD and NPM1 double mutation AML (FAB classification M0, M1), admitted with diffuse granulocytic sarcoma.

Keywords: Extramedullary involvement, granulocytic sarcoma, acute myeloid leukemia, skin, FLT3-ITD
CASE

A 35-year-old male was admitted to a dermatology outpatient clinic with diffuse skin lesions. In the patient's physical examination, there were nodules on the neck and back that were raised from the skin, widespread, and approximately larger than 5 cm each (Figure 1). Topical treatments were recommended to the patient, however, the patient applied to the emergency service because of the complaints of fever and malaise in the follow-up. The patient's white blood cell count was 223 x 10^9/L, platelet count was 47 x 10^9/L, hemoglobin was 5 g/dL, and lactate dehydrogenase was 976 U/L. Blast cell infiltration (80%) was observed in peripheral smears and bone marrow aspiration smears. Flow cytometric findings were reported as AML M0-1. The histopathological findings of the nodule taken from the skin by punch biopsy were found to be compatible with granulocytic sarcoma. Skin biopsy sections demonstrate perivascular sheets of immature mononuclear cells, which are positive for MPO, CD33, and CD13, and negative for CD20 by immunohistochemical stains, as shown in Figure 2.

Metaphase could not be obtained by conventional cytogenetics of the patient. No pathological finding was detected in the result of FISH. The patient was started on daunorubicin and cytosine arabinoside (3+7) chemotherapy. Granulocytic sarcomas regressed from the 15th day of chemotherapy. However, after 3+7 chemotherapy, a large number of blasts were observed in the peripheral smear. Therefore, the patient was started on etoposide, mitoxantrone, and cytarabine (EMA) chemotherapy protocol.

Meanwhile, midostaurin was added to the patient's treatment because FLT3-ITD was 30% positive in the myeloid next-generation sequence panel sent at the time of diagnosis. Additionally, 49% NPM1 somatic mutation positivity was seen in this patient's myeloid next-generation sequence panel. The patient was in complete remission with EMA and midostaurin therapy. Informed consent was obtained from the patient included in the study.

Figure 1. A and B, The patient had granulocytic sarcomas, raised, erythematous, plaque-like lesions on the skin at admission to the hospital. C-D, Image of skin lesions that disappeared after daunorubicin and cytosine arabinoside (3+7) chemotherapy.

Figure 2.
DISCUSSION

Leukemic blasts can be observed in the spleen, liver, and anterior mediastinum, which are locations of normal hematopoiesis throughout and following embryonic development, in addition to peripheral blood involvement and soft tissue infiltration associated with hyperleukocytosis (e.g. the lung, retina). AML can also affect tissues where hematopoiesis isn't normally found (the skin, "leukemia cutis"), the central nervous system (CNS), and the gingivae, making proper diagnosis, prognosis, and therapy more difficult (7). It's unclear why and how EMI evolves. Cell adhesion molecules, chemokine receptor/ligand interactions, and abnormal FAS-MAPK/ERK signalling have all been studied. The notion that leukemia cells in individuals with EMI express CD56 (neural cell adhesion molecule) more often was an early theory based on the differential expression of cellular adhesion molecules (8). Homophilic CD56 binding has been proposed to increase leukemic blast binding to CD56-expressing tissues such as adipose/soft tissue, skeletal muscle, GI, testicular, and brain, which are all common locations of EMI (9). The presence of monoblastic/myelomonocytic differentiation in AML is linked to a higher risk of EMI. Leukemic cells from these subtypes have increased CD11b expression (10). The case we presented was diagnosed as FLT3-ITD mutation AML M0-1. There may be a connection between certain cytogenetic and molecular AML characteristics and the development of GS. There is also evidence that trisomy 8 positive AML and cutaneous localization of GS are related, albeit this link has to be verified (13). Rarely did an FLT3-ITD mutation occur in AML patients who presented with GS. In general, FLT3 ITD is highly correlated with poor outcomes in AML (14).

The risk level in AML FLT3-ITD+/NPM1+ depends on the AR of FLT3-ITD mutation, according to NCCN and ELN recommendations (15). Low AR is defined as being below 0.5. AR was found to be 0.61 in our case.

Given this, there is not enough data to draw any conclusions about the relationship between FLT3 ITD mutations and the development of GS. This may explain why we were unable to link the presence of the FLT3-ITD mutation to diffuse skin GS.

When EMI is identified, tissue biopsy is required for histologic and phenotypic diagnosis and cytogenetic and molecular testing; cytogenetic and molecular testing should be conducted on tissue from synchronous EMI specimens if feasible. In our case, biopsies were taken from plaques raised from the skin. The effect of EMI on prognosis in those with isolated or synchronous EMI is debatable. Although early analyses of EMI's independent prognostic effect suggested worse outcomes, later and bigger trials have found either higher EFS and OS with isolated EMI (as compared to AML without extramedullary disease) or no predictive influence at all (9, 16, 17). Patients with newly diagnosed, synchronous EMI should get systemic therapy exactly as they would if EMI were not present; patients with refractory EMI after systemic therapy should undergo local treatment such as RT (6).
In the case, we presented, both bone marrow and EMI were in remission with induction chemotherapy. No EMI-specific treatment regimens have been established; patients suitable for intensive therapy are typically treated with anthracycline and cytarabine-containing regimens (18).

CONCLUSION

The independent predictive impact of EMI on AML patient survival is uncertain, as is the best consolidative therapy. Many clinicians include alloHCT in the consolidative therapy approach for EMI patients depending on the risk of intramedullary disease (as determined by cytogenetics or molecular/mutational data) if it is present. It would make sense to base alloHCT consolidation in CR1 choices for patients with isolated EMI on the same criteria as an intramedullary disease. In conclusion, although cutaneous involvement is rare, GS should be considered in the differential diagnosis of nodules, pustules, or plaque-like lesions, especially in patients with suspected hematological disease.

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REFERENCES


