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Myeloid Sarcoma of the Paranasal Sinuses in a Patient with Acute Myeloid Leukemia

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Myeloid sarcoma (MS) is an uncommon extramedullary malignant tumor, and often represents a subgroup of acute myeloid leukemia (AML). MS of paranasal sinus origin is extremely rare. We report an uncommon case of sinonasal MS associated with AML, who was successfully treated with hematopoietic stem-cell transplantation. A 39-year-old male was admitted with complaints of left nasal obstruction and proptosis. Computed tomography and magnetic resonance imaging identified a left ethmoidal mass involving the maxillary sinus, the orbit, and the skull base. Nasal endoscopic examination detected a whitish homogeneous mass occupying the left nasal cavity. Although accumulation of atypical lymphocytes was suspected based on initial pathological inspection, immunohistochemical analysis showed myeloperoxidase-positive myeloid cells. Together with concomitant leukocytosis (149,000/μL) composed of myeloid blast cells and excess of myeloblasts in the bone marrow, the patient was diagnosed as sinonasal MS with AML with maturation (French-American-British Classification M2). The patient was treated by chemotherapy (remission induction therapy with daunorubicin and cytarabine; salvage chemotherapy with high-dose cytarabine), radiotherapy (30 Gy in 10 fractions) and allogeneic hematopoietic stem-cell transplantation, and followed up for 12 months with no recurrence. Early diagnosis is critical for the best improvement of MS. MS of the paranasal sinuses may easily be misdiagnosed as malignant lymphoma or poorly differentiated carcinoma. Prompt hematological and immunohistological investigations with suspicion of MS are essential for correct diagnosis. Furthermore, we concisely review nine previously reported patients with MS and indicate the importance of hematopoietic stem-cell transplantation for good prognosis.

Keywords: diagnosis; hematopoietic stem-cell transplantation; myeloid sarcoma; nose; paranasal sinus
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Introduction

Myeloid sarcoma (MS), or granulocytic sarcoma, is a rare extramedullary malignant tumor composed of myeloid precursor cells (Avni and Koren-Michowitz 2011; Bakst et al. 2011; Yilmaz et al. 2013). MS is often associated with acute myeloid leukemia (AML), and classified as a unique clinical presentation of any subtype of AML (Arber et al. 2016). MS occurs concomitantly, subsequently, or antecedently in 2.5%-9.1% of AML patients (Neiman et al. 1981; Bakst et al. 2011). Although MS may occur in every organ and tissue, the predilection sites are soft tissue, bone, peritoneum, lymph node, and gastrointestinal system (Yilmaz et al. 2013). Head and neck origin comprise only 12% of cases, while the most common sites are soft palate, nasopharynx, and orbit (Neiman et al. 1981). MS of paranasal sinus origin is rare (Prades et al. 2002), and a delayed or misdiagnosis can be fatal considering its poor prognosis (Yilmaz et al. 2013).

We describe an uncommon case of MS of the paranasal sinuses. Written informed consent was obtained from this patient. Moreover, we review nine cases of MS that have been reported (Prades et al. 2002; Ferri et al. 2005; Gorman et al. 2009; Jo et al. 2009; Yamamoto et al. 2010; Kuo et al. 2013; Mei et al. 2013; Kieliszak and Cosenza 2015; Gupta et al. 2017).

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Clinical Report

A 39-year-old male was admitted to the local Ear, Nose and Throat (ENT) clinic with complaints of left nasal obstruction, and was diagnosed as chronic rhinosinusitis. His past medical history was unremarkable, and past periodic health checkup did not reveal any abnormalities in complete blood count. Despite drug therapy for several months, his symptoms did not improve, and instead, left proptosis occurred. Screening brain magnetic resonance imaging (MRI) detected a paranasal sinus tumor invading the orbit. The patient was then referred to our department with suspicion of sinonasal malignancies.

The patient complained of left-sided nasal obstruction, proptosis, and nasal swelling on admission. Nasal endoscopic examination detected a whitish homogeneous mass occupying the left nasal cavity. Computed tomography (CT) and MRI identified a left ethmoidal mass involving the maxillary sinus, the orbit, and the skull base (Figs. 1 and 2). There was no cervical lymphadenopathy noted. A biopsy was performed, and examination of the tissue sections revealed diffuse infiltration of medium-sized blastic cells with a high nuclear/cytoplasmic ratio (Fig. 3A). Our initial histological diagnosis was an accumulation of atypical lymphocytes. We next planned to perform a surgery for tissue sampling, and pre-operative laboratory test showed remarkable leukocytosis (149,000/μL) composed of myeloid blast cells, mild anemia (hemoglobin: 11.1 g/dL), and thrombocytopenia (82,000/μL). An immunohistochemical analysis showed that neoplastic cells were positive for myeloperoxidase (MPO) (Fig. 3B) and CD34, but not for CD3, CD20, CD56, and terminal deoxynucleotidyl transferase. The patient was urgently transferred to the hematology department. On bone marrow aspiration, 94% of cells were myeloblasts, with some showing discrete abnormal granular maturation (Fig. 3C, D). By flow cytometric analysis, the majority of mononuclear cells were positive for CD33, CD34, and HLA-DR. CD56 was negative. Chromosome analysis revealed deletion of chromosome 5q (del(5)(q)) and monosomy 7 (-7). Leukemia fusion genes screening test (polymerase chain reaction) was negative. The patient was finally diagnosed as MS and AML with maturation (French-American-British Classification M2).

Although remission induction therapy with daunorubicin (DNR) and cytarabine (Ara-C) was performed, the patient did not achieve complete remission (CR). Salvage chemotherapy with high-dose Ara-C and radiation therapy (RT) (30 Gy in 10 fractions) were performed, and eventually CR was achieved. Bone marrow aspiration at CR period revealed megaloblasts and giant neutrophils, suggesting the presence of myelodysplastic syndrome (MDS). The patient was subsequently treated by allogeneic hematopoietic stem-cell transplantation (allo-HSCT). The patient was followed up for 12 months without any evidence of recurrence after allo-HSCT.

Discussion

MS of the paranasal sinuses is very rare, and the clinical and pathological characteristics are therefore not fully understood. In the present study, we summarized and reviewed 10 MS patients, including nine previous cases (Prades et al. 2002; Ferri et al. 2005; Gorman et al. 2009; Jo et al. 2009; Yamamoto et al. 2010; Kuo et al. 2013; Mei et al. 2013; Kieliszak and Cosenza 2015; Gupta et al. 2017) (Table 1). The median age was 59.5 years (6-95, mean 54.2) and female-to-male ratio was 4:6. Four cases had headache, four cases had facial swelling, three cases had nasal obstruction, three cases had proptosis, and two cases had visual disturbance. In general, these symptoms are similar to those of malignant sinonasal neoplasms. Future case reports of MS in the paranasal sinus are required to reveal the nature of this entity, although characteristic and

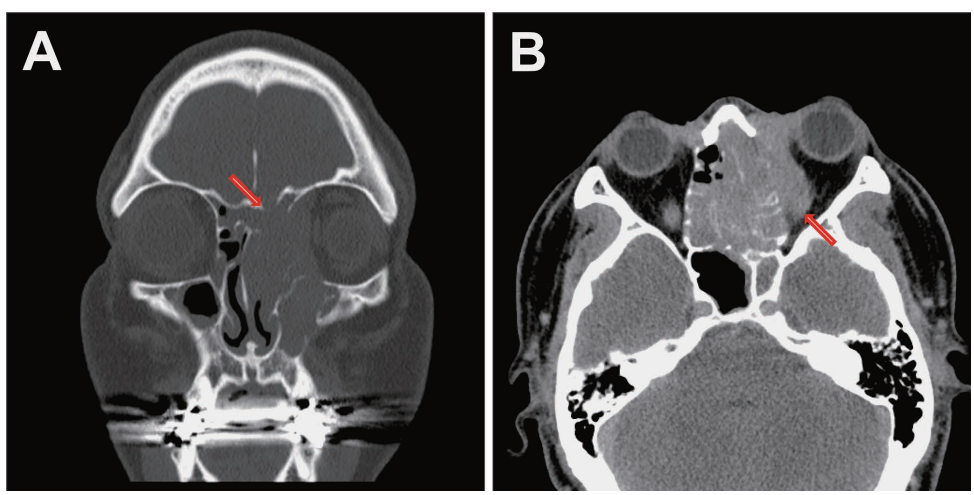

Fig. 1. CT scans of the paranasal sinuses.
Computed tomography scan showing a left ethmoidal mass (arrows) involving the maxillary sinus, the orbit, and the anterior skull base (A: coronal, B: axial).

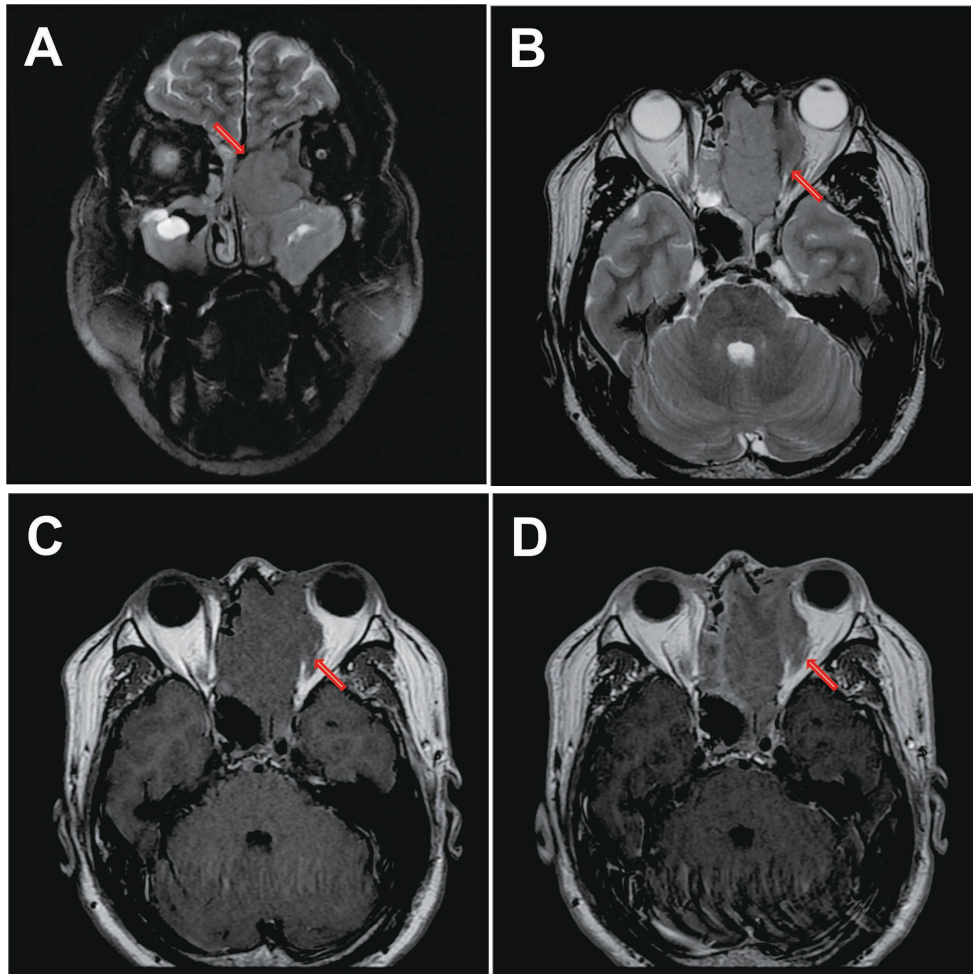

Fig. 2. MR images of the paranasal sinuses.
Magnetic resonance image showing a left ethmoidal mass (arrows) involving the maxillary sinus, the orbit, the right paranasal sinuses, and the skull base (A: coronal T2-weighted image, B: axial T2-weighted image, C: axial T1-weighted image, D: axial T1-weighted image with gadolinium).

specific symptoms may not be found.

MS is mainly associated with AML, but MS can be classified into three groups according to the onset of the disease: (1) an extramedullary presentation of acute leukemias, detected simultaneously with the disease, during the course of the disease, or at disease relapse; (2) an extramedullary presentation of MDS, chronic myeloid leukemia, or other myeloproliferative diseases; and (3) an extramedullary tumor preceding the onset of AML at which the bone marrow aspiration reveals no hematological disease (Yilmaz et al. 2013). The last group is regarded as an exceedingly rare case, and is termed primary, nonleukemic, or isolated MS (Yilmaz et al. 2013). However, two out of 10 sinonasal MS cases are primary in our review (Prades et al. 2002; Mei et al. 2013) (Table 1), which may suggest the sinonasal area as a predilection site of primary MS.

The precise onset of MS in our patient was unclear. Although translocation t(8;21) and inversion of chromosome 16 have been reported as common cytogenetic abnormalities of MS (Avni and Koren-Michowitz 2011), we did not find such abnormalities in this patient. As we found del(5q) and -7, which are common karyotype abnormalities of MDS (Haase et al. 2007), and megaloblasts and giant neutrophils in bone marrow aspiration during the period of CR, we suspect that this patient developed MS during the course of MDS, and MDS transformed into AML.

The rate of misdiagnosis of primary MS has been reported in the range of 25-47% (Yamauchi and Yasuda 2002; Antic et al. 2013), and many primary MS patients are misdiagnosed with lymphoma (Meis et al. 1986; Yamauchi and Yasuda 2002). In the present case, we performed the nasal biopsy without any blood tests because the patient was young, and had no past medical histories and no systemic complaints. We finally noticed the concurrent AML when we performed a routine examination before surgery. This suggests that a blood test should be performed as a routine test for the different diagnosis of sinonasal tumors. Moreover, otolaryngologists and pathologists must list MS as a differential diagnosis of sinonasal malignancies. As MS is usually composed of mononuclear cells with a high

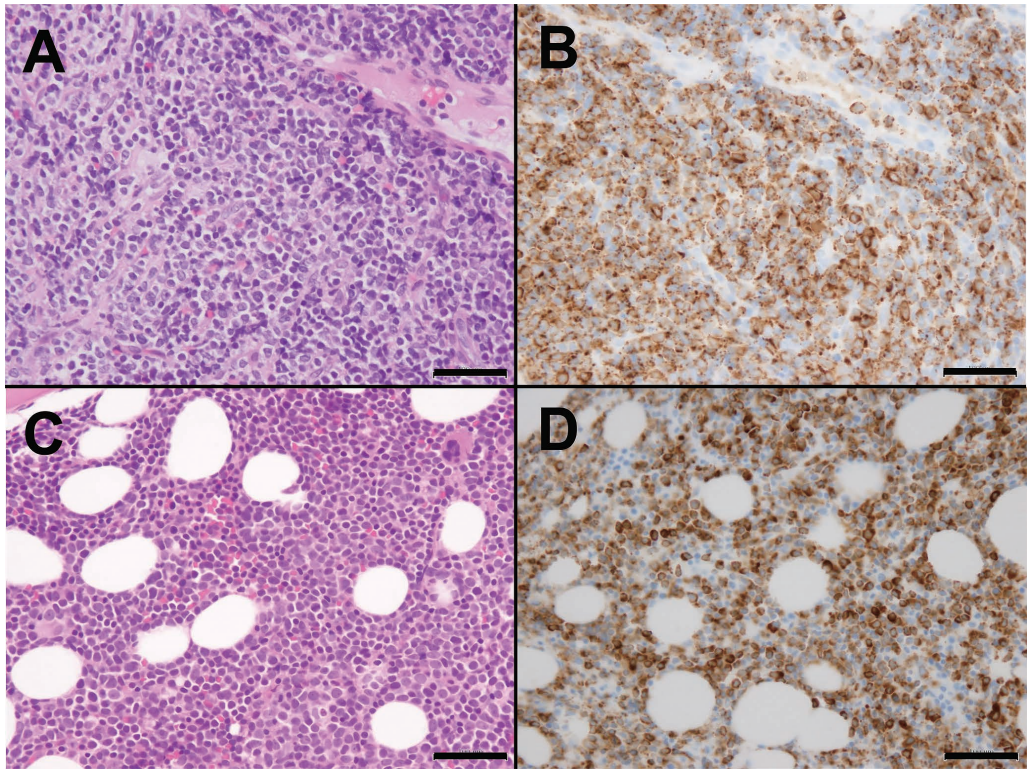

Fig. 3. Histopathological and cytopathological findings.
A nasal biopsy showing infiltration of myeloperoxidase (MPO)-positive medium-sized blastic cells with a high nuclear/cytoplasmic ratio (A: H&E staining, × 200; B: MPO immunostaining, × 200). Bone marrow aspiration showing diffuse infiltration of MPO-positive myeloid blasts (C: H&E staining, × 200; D: MPO immunostaining, × 200). Scale bar; 100 μm.

nuclear/cytoplasmic ratio, it can be misdiagnosed as lymphoma or other poorly-differentiated malignant neoplasm in the absence of peripheral blood and bone marrow involvement (Siraj et al. 2017). Immunohistochemistry is crucial for correct diagnosis of MS, and an antibody against MPO is most commonly used. In our review, the positive rate of MPO is 100% in seven described cases (Table 1). However, in general, the positive rate of MPO does not reach 100% because monoblastic MS does not express MPO (Pileri et al. 2007; Wang and Li 2016). An immunohistochemical panel including CD43, lysozyme, MPO, CD68, CD117, CD3 and CD20 will be useful to identify the vast majority of MS variants (Alexiev et al. 2007).

Although there is no consensus on the treatment of MS (Avni and Koren-Michowitz 2011), current MS treatments are largely dependent on whether they develop at initial diagnosis or at relapse (Bakst et al. 2011). Concurrent MS with bone marrow involvement is generally treated with chemotherapy directed at the underlying leukemia (Avni and Koren-Michowitz 2011; Bakst et al. 2011). For primary MS, recent reviews have reported that systemic treatment is recommended for all primary MS patients because there is a higher rate for progression to leukemia especially in patients given local treatments alone (88-100%) compared with patients given systemic chemotherapy (42%) (Avni and Koren-Michowitz 2011; Bakst et al. 2011; Yilmaz et al. 2013). The usefulness of HSCT for MS has been reported (Pileri et al. 2007; Chevallier et al. 2008), and Chevallier et al. (2008) reported that the 5-year overall survival was 47% after allogeneic HSCT. In our review, only two cases underwent HSCT including our case, and satisfactory short-term survival was achieved (Prades et al. 2002) (Table 1). Considering that 0% (0/5) of the sinonasal MS patients without HSCT achieved no longer than 2-year survival (Ferri et al. 2005; Jo et al. 2009; Yamamoto et al. 2010; Kuo et al. 2013; Kieliszak and Cosenza 2015) (Table 1), we hypothesize that effective chemotherapy and follow-up HSCT are essential for good prognosis. We performed RT as a local treatment. RT is worth considering when we cannot achieve CR with chemotherapy alone (Bakst et al. 2011), because incomplete MS response after chemotherapy is a significant risk for early bone marrow relapse (Byrd et al. 1995). Consequently, both sufficient local and systemic therapies are important to treat the sinonasal MS.

In conclusion, MS of the paranasal sinuses is an uncommon disease. Considering the rapid progression of concurrent hematological disorders, early and correct diagnosis is necessary for best prognosis. Prompt hematological and immunohistological investigations in cases with suspected MS are essential for the correct diagnosis of this rare entity.

Table 1. Summary of sinonasal MS cases.

Author	Year	Age	Sex	Symptoms	Past HD	Present HD	Locations	MPO	Other positive marker	Chemotherapy	RT	HSCT	Follow-up
Prades	2001	20	female	nasal obstruction	no	no	NC, M, S	N.D.	CD34	DNR+Ara-C, MTX-Ara-C		Yes	survive (18M)
Ferri	2005	72	female	facial, eyelid swelling, fever	AML (M0)	AML (M0)	NC, E, M, Or	positive	CD34				dead (10D)
Gorman	2009	55	male	headache, double vision, proptosis	CML	CML	NC, E, F, Or	N.D.		chemotherapy			N.D.
Jo	2009	63	male	cheek swelling	MDS	AML (M4), CMML-2	M	positive	Lys, CD68, CD99	chemotherapy			dead (2Y from the first symptom)
Yamamoto	2010	95	female	nasal obstruction	MDS?	AMMoL	NC	positive	Lys, AAT, CD4, CD68	ACR+Ara-C, Ara-C			dead (4M, heart attack)
Kuo	2013	73	male	temporal and orbital pain, proptosis	AML (M6)	AML (M7)	NC, E, Or, SB	positive	CD117		Yes		dead (2M)
Mei	2013	56	male	cheek swelling	no	no	M, ST	positive	CD34, CD45, CD56, CD117	ACR+Ara-C			N.D.
Kieliszak	2015	63	male	frontal bone tenderness, rhinorrhea	no	AML (M5b)	F, ST	N.D.		DNR+Ara-C			dead
Gupta	2017	6	female	nasal bleeding, nasal swelling, blurring of vision	no	AML with aberrant CD19 expression	NC, E, Or, ST	posotive	LCA	DNR+Ara-C			lost to follow up
Suzuki	2018	39	male	nasal obstruction, headache, proptosis	MDS?	AML (M2)	NC, E, M, Or, SB	posotive	CD34	DNR+Ara-C, high-dose Ara-C	Yes	Yes	survive (12M)

The features of nine previously reported cases are summarized, together with the present case. The first author of each cited reference is shown as Author, and the publication year is shown as Year.

HD, hematological disease; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndromes; MDS?, suspected myelodysplastic syndromes; CMML, chronic myelomonocytic leukemia; AMMoL, acute myelomonocytic leukemia; NC, nasal cavity; M, maxillary sinus; S, sphenoid sinus; E, ethmoid sinus; Or, orbit; F, frontal sinus; SB, skull base; ST, subcutaneous tissue; MPO, myeloperoxidase; N.D., not described; Lys, lysosome; AAT, alpha-1-antitrypsin; LCA, leukocyte common antigen; DNR, daunorubicin; Ara-C, cytarabine; MTX, methotrexate; ACR, aclarubicin; RT, radiotherapy; HSCT, hematopoietic stem cell transplantation.

Conflict of Interest

The authors declare no conflict of interest.

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