CASE SERIES

CLINICOPATHOLOGICAL FEATURES OF MYELOID SARCOMA PATIENTS FROM A SINGLE CENTER EXPERIENCE

Fatih Erkan Akay[1], Hakkı Onur Kırkızlar[2], Elif Mercan[3], Fulya Öz Puyan[3]

[1]Trakya University School of Medicine, Edirne, TURKEY
[2]Division of Hematology, Department of Internal Medicine, Trakya University School of Medicine, Edirne, TURKEY
[3]Department of Pathology, Trakya University School of Medicine, Edirne, TURKEY

ABSTRACT

Aims: This retrospective study aims to emphasize clinicopathological data and diagnosis of an uncommon myeloid neoplasm; myeloid sarcoma. ***Methods:*** Data of all patients from 2000-2019 were retrieved from the archives of Trakya University School of Medicine Hematology and Pathology Departments. Patients' charts were examined retrospectively by collecting data including age, gender, anatomic site, history of hematological malignancy, blood count, pathological characteristics and treatments administered. ***Results:*** There were 8 patients; 6 male and 2 female. The median age was 42.5 years (range: 29-69 years). The most prevalently involved sites were skin, lymph node and bone/soft tissue. There were six patients as myeloid sarcoma with preexisting or concurrent acute myeloid leukemia, one patient as de novo and one patient as acute myeloid leukemia with myelodysplasia related changes. One of the concurrent acute myeloid leukemia patients was Down syndrome related acute myeloid leukemia with myeloid sarcoma. Immunohistochemically, out of 8 patients, 4 were of myelomonocytic, 2 were of the myelocytic and 2 were of the monocytic differentiation. ***Conclusion:*** Myeloid sarcoma is a tumor mass made up of immature myeloid blasts appearing at an anatomical site other than bone marrow. Taking into account of having a challenging diagnosis, unusual cellular infiltration at any site on a patient especially with a history of acute myeloid leukemia should have myeloid sarcoma in their differential diagnosis. ***Keywords:*** Myeloid sarcoma, acute myeloid leukemia, myeloid neoplasia

INTRODUCTION

Myeloid sarcoma (MS), also previously known as granulocytic sarcoma, is a rare condition characterized by the extramedullary proliferation of a tumor mass made-up of immature myeloid cells which may end up with the destruction of the tissue found (1). MS can be seen at any age having a slight male predominance. It is mostly reported to affect the skin, bone or lymph nodes, however, there have been sites submitted throughout the whole body (2). MS, for the most part, is detected concurrently in patients with acute myeloid leukemia (AML), it may additionally occur in other bone marrow diseases like myeloproliferative neoplasms (MPNs) or myelodysplastic syndrome (MDS) and de novo which is a very rare entity (3). On the other hand, in some cases, MS may be the first evidence of AML or be a manifestation of a previously treated AML patient in remission (4).

Even with the modern diagnostic techniques including flow cytometry and immunohistochemistry, the identification of MS can be difficult. Hence, patients with a history of myeloid neoplasia exhibiting atypical cellular infiltrate at any site should be a hint for MS (4).

In this study, eight patients with MS were retrospectively analyzed from a single center aiming to emphasize their clinicopathological data and facilitate the diagnosis of an uncommon myeloid neoplasm like MS.

Address for Correspondence: Fatih Erkan Akay, Trakya University School of Medicine, Edirne, TURKEY
e-mail: erkanfatih48@gmail.com ORCID: orcid.org/0000-0001-7598-1016
Received: 09.02.2020 Accepted: 11.02.2020 • DOI:10.4274/tmsj.galenos.2020.07.01.05 Available at: tmsj.trakya.edu.tr

Cite this article as: Akay FE, Kırkızlar HO, Mercan E et al. Clinicopathological features of myeloid sarcoma patients from a single center experience. Turkish Med Stud J 2020;7(1):26-33.

MATERIAL AND METHODS

Data of all patients from the years 2000-2019 were retrieved from the archives of the Trakya University School of Medicine Hematology and Pathology Departments. Patients' charts were examined retrospectively by collecting data including age, gender, anatomic site, history of hematological malignancy, blood count, pathological characteristics, and treatments administered. Hematoxylin and eosin (H&E) stained slides and immunohistochemistry stains were analyzed, including antibodies for myeloperoxidase (MPO), CD33, CD34, CD68, and CD117 for showing the blastic cells and myeloid differentiation.

RESULTS

In our study, out of 8 patients, 6 were male and 2 were female. The median age was 42.5 (range: 29-69 years). The most commonly involved sites were skin (n=3/8) and lymph nodes (n=2/8), other sites included bone/soft tissue (n=1/8), parotid gland (1/8), testicle (n=1/8) and rectum (n=1/8). Symptoms of the patients were in accordance with the sites involved. Regional pain, lymphadenopathy and mass were the most common findings. There were six patients as myeloid sarcoma with preexisting or concurrent acute myeloid leukemia, one patient as de novo and one patient as acute myeloid leukemia with myelodysplasia related changes. One of the concurrent acute myeloid leukemia patients was Down syndrome related acute myeloid leukemia with myeloid sarcoma (Table 1). One of our patients had multiple sites involved, he was first presented with an enlarged right cervical lymph node (LN) with the progression of the disease, he later on exhibited rectal involvement as well. The odd thing about this patient's history is that his LN expressed positivity for CD7, CD43, CD34, TdT with an extensive loss of T-cells which caused his initial diagnosis to be Precursor T-cell Lymphoblastic Lymphoma. With further analysis, his bone marrow biopsy revealed he had AML. Additionally, MPO and CD68 tests were performed to patients LN biopsy validating that his first presentation was actually an MS with a TdT, CD7 co-expression (Figure 2).

On H&E stained samples MS cells were characterized by diffuse infiltration of the tissue. Morphologically most cells were intermediate to large-sized, with abundant cytoplasm, large irregular contoured nuclei along with myeloblastic, myelomonocytic or monocytic differentiation. Remaining lymphoid tissue and, follicles were present in the LNs as well as normal tissue was present in the testes, parotid gland and skin (Figures 1, 3 and 5).

Median level for hemoglobin was 7.00 (range: 6.1-10.5 g/dL), whereas median level for white blood cells was 30,740 (range: 0,1-125,000). Median for platelet was 20.500 (range: 7,000-40,000). Our patients had MPO (n=6/8) possession the most, continuing with CD117 (n=4/8) and CD68 (n=4/8) (Figure 2, 4 and 6). Immunohistochemically, out of 8 patients, 4 were of myelomonocytic, 2 were of the myelocytic and 2 were of the monocytic differentiation (Table 2).

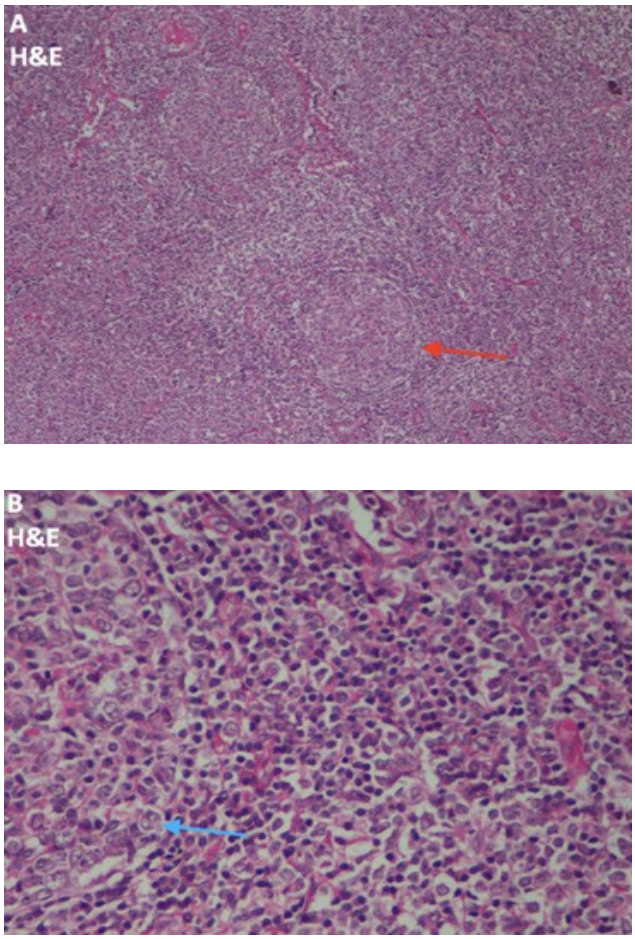

Figure 1: Case 4, lymph node involvement. A: Lymph node presenting atypical cell infiltration (blue arrow) between intact follicular structures (red arrow) (H&E, x100). B: High power examination shows diffuse infiltration of large blastic cells with clear cytoplasm (H&E, x200).

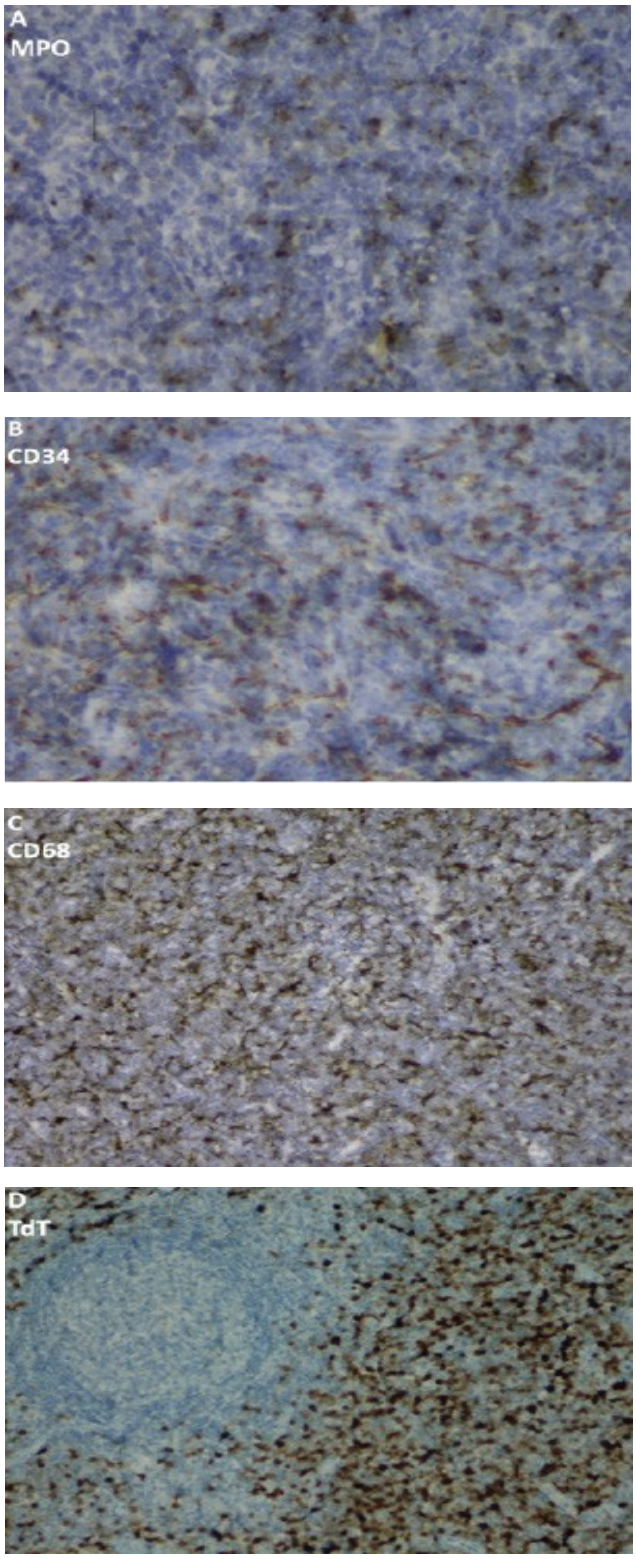

Figure 2: Immunohistochemistry of Case 4, lymph node involvement. A: Positive staining for MPO (x400). B: Positive staining for CD34 (x400). C. Diffuse positive staining for CD68 (x200). D. Diffuse positive staining for TdT on the blastic cells (x200).

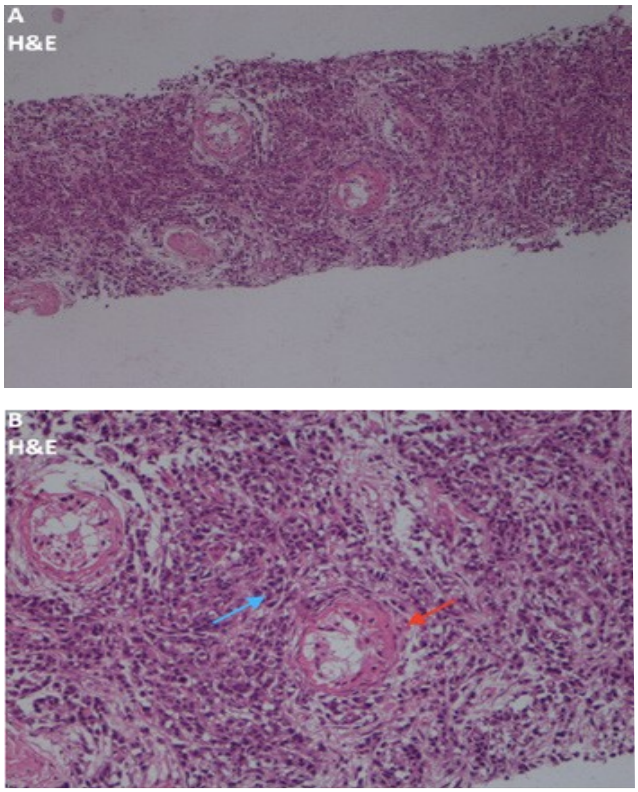

Figure 3: Case 3, testicular involvement. A: Diffuse blastic infiltration of testicular parenchyma (H&E, x100) B: High power examination of atypical cells surrounding (blue arrow) with abundant eosinophilic cytoplasm and pleomorphic/hyperchromatic nucleuses seminiferous ducts (red arrow) (H&E, x100).

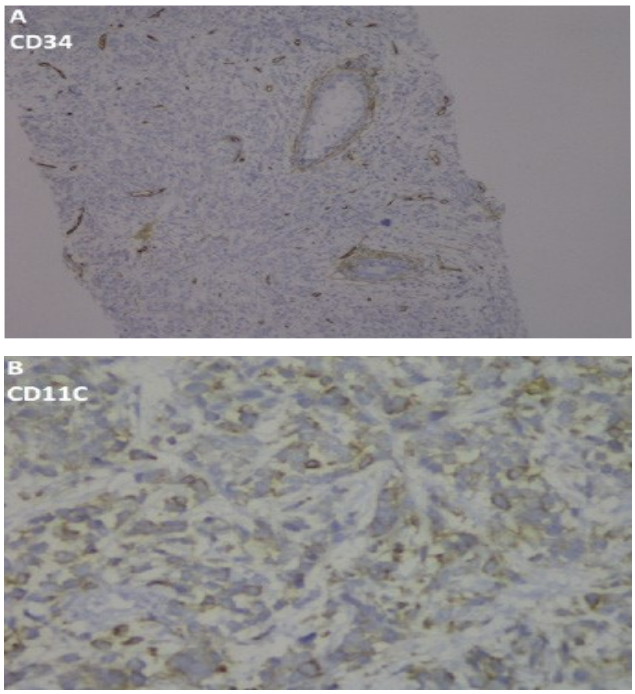

Figure 4: Immunohistochemistry of case 3, testicular involvement. A: Negative staining for CD34 (x100). B:Positive staining for CD11c (x400).

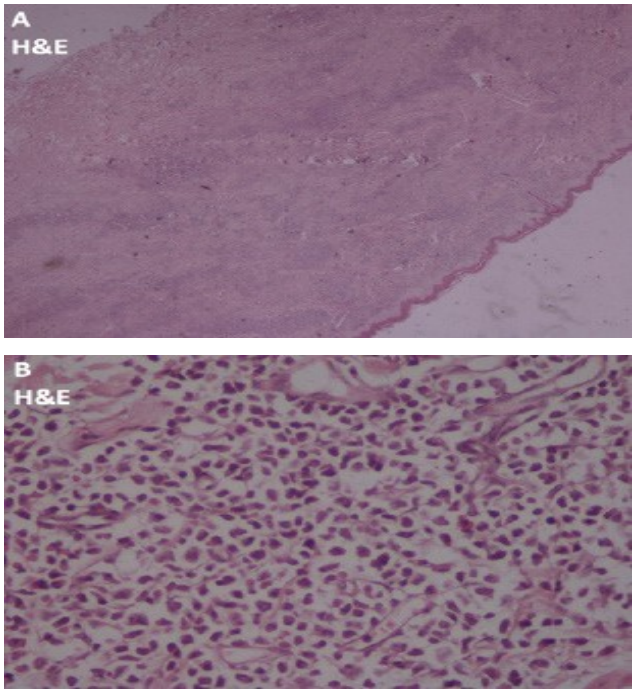

Figure 5: Case 2, skin involvement, A: Atypical cell infiltration in the dermis surrounding vascular and adnexal structures causing a detachment in collagen bands (H&E, x40). B: High power examination of monoblastic cells with eosinophilic cytoplasm and large nucleus (H&E, x400).

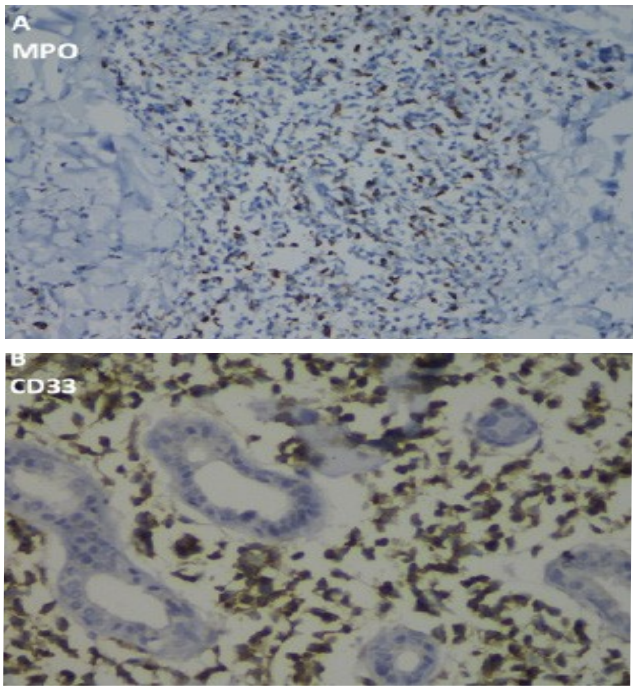

Figure 6: Immunohistochemistry of Case 2, skin involvement. A: Scattered positive staining for MPO (x200). B: Diffuse positive staining for CD33 (x400).

Our patients had MPO (n=6/8) positivity the most, continuing with CD117 (n=4/8) and CD68 (n=4/8) (Figure 2, 4 and 6). Immunohistochemically, out of 8 patients, 4 were of myelomonocytic, 2 were of the myelocytic and 2 were of the monocytic differentiation (Table 2).

Median level for hemoglobin was 7.00 (range: 6.1-10.5 g/dL), whereas median level for white blood cells was 30, 740 (range: 01-125,000). Median for platelet was 20.500 (range: 7,000-40,000).

Table 1: Clinical feature of patients.

Case	*Age/Gender*	*Involved Site*	*Clinical Manifestation*	*Associated Hematological Disorder*	*Systemic Treatment received*
1	35/M	Bone and Soft Tissue	Pain in left ankle	Concurrent AML	Remision induction 3+7 (Idarubicin+Cytosine arabinoside)
2	69/F	Skin	Ecimosis and Bullous Lesions on arms and legs	AML with Myelodisplasia related changes	4 cycles of azacitidine (due to MDS), 1 cycle of high dose Cytosine arabinoside
3	41/M	Testicle	Mass in right testicle	Concurrent AML	Remision induction 3+7 (Idarubicin+Cytosine arabinoside) 3 cycles of high dose Cytosine arabinoside, 1 cycle of FLAG-Ida
4	58/M	LN (Primary IS)	Mass in right cervical LN	De novo	Remision induction 3+7 (Idarubicin+Cytosine arabinoside), 3 Cycles of high dose Cytosine arabinoside
		Rectum	Anal pain and mass in rectum		
5	29/M	Skin	Nodular lesion on left arm	Concurrent AML, AML induced hemophagocytic lymphohistiocytosis (HLH)	Remision induction 3+7 (Idarubicin+Cytosine arabinoside) 3 cycles of high dose Cytosine arabinoside, 1 cycle of FLAG-Ida, Etoposide (due to HLH)
6	44/M	Parotid gland	Left preauricular mass	Down Syndrome Related Concurrent AML	Remision induction 3+7 (Idarubicin+Cytosine arabinoside) 3 cycles of high dose Cytosine arabinoside, 1 cycle of FLAG-Ida
7	36/F	Skin	Lesion on left ankle	Concurrent AML	Remision induction 3+7 (Idarubicin+Cytosine arabinoside) 3 cycles of high dose Cytosine arabinoside
8	57/M	Lymph Node	Left axillar mass	Concurrent AML	Remision induction 3+7 (Idarubicin+Cytosine arabinoside) 3 cycles of high dose Cytosine arabinoside

M: *Male,* ***F:*** *Female,* ***IS:*** *Involved Site,* ***LN:*** *Lymph Node,* ***AML:*** *Acute Myeloid Leukemia,* ***MDS:*** *Myelodysplastic Syndrome*

Table 2: Laboratory and Pathological features of patients.

Case	Routine Blood Test			Involved Site	IHC markers on MS biopsies
	Hb (g/dL)	WBC ($x10^3$)	Platelet ($x10^3$)		
1	10.2 g/dL	7,000	25,000	Bone and Soft Tissue	MPO, CD11c, CD33, CD34, CD68, CD117, Ki-67 70-80%
2	6.3 g/dL	44,000	23,000	Skin	MPO, CD11C, CD25, CD33, CD68, CD34, CD117, CD138
3	6.1 g/dL	125,000	7,000	Testicle	CD11C, CD117
4	10.5 g/dL	31,480	27,000	LN (Primary IS)	MPO, CD10, CD11C, CD20, CD33, CD68 TdT, Ki-67 70-80%
				Rectum	MPO, CD7, CD34
5	7.0 g/dL	0,1	10,000	Skin	CD68, CD117
6	7.1 g/dL	2,500	13,000	Parotid Gland	CD11C, CD33, CD34. CD68
7	6.9 g/dL	40,000	40,000	Skin	MPO, CD34
8	6.1 g/dL	30,000	18,000	Lymph Node	MPO, CD34

Hb: *Hemoglobin,* ***WBC:*** *White Blood Cell,* ***IS:*** *Involved Site,* ***LN:*** *Lymph Node,* ***IHC:*** *Immunohistochemistry,* ***MS:*** *Myeloid Sarcoma*

DISCUSSION

Myeloid sarcoma is a rare myeloid neoplasm presented as a tumor mass made up of immature myeloid blasts localised at an anatomical site other than bone marrow. Broad classification for MS according to the European Society for Hematology may ocur in the following circumstances: 1. concurrent with AML; 2. extramedullary relapse of AML or following a bone marrow transplantation; 3. occurring with other MPNs including CML, MDS or bone marrow fibrosis; and 4. isolated MS which has normal bone marrow biopsy and blood count lacking any history of myeloid neoplasia (4). Likewise, in our study, 7 patients out of 8 developed MS concurrent with AML, and one patient exhibited MDS at the beginning of the disease, later on, turned into AML also having a manifestation of MS. Békássy et al.'s (5) retrospective analysis of 5824 patients who underwent hematopoietic stem cell transplantation (HSCT) for AML, CML or MDS from 1981 to 1992, found that 26 of the patients had evidence of MS.

The etiology of MS remains ambiguous; therefore, diagnosis may be challenging. Patients' clinical features, radiology findings, immunohistochemistry, and cytogenetic features should evaluated for a more accurate diagnosis. For visualization techniques, Positron Emission Tomography/Computed Tomography has been shown to be more beneficial in the localization of tumors (6). Radiologically guided core biopsy, which offers more reliable results, should be performed, rather than traditional fine-needle aspiration biopsy (7). H&E stained slides usually reveal infiltrating myeloid cells at different stages of maturation possessing either granulocytic or monocytic maturation, also seen in AML. With the purpose of making a more reliable diagnosis; immunohistochemistry, flow cytometry, fluorescence in situ hybridization (FISH), real-time protein chain reaction analysis, and next-generation sequencing have been shown to increase the accuracy (1, 4).

A systematic review carried out by Magdy et al. (8) reported similar immunohistochemical results with ours; MPO, CD34, CD68, CD117, and lysozyme were the most common antigens possessed. In comparison with other retrospective studies; skin, LN, bone, soft tissue, and gastrointestinal tract are the most commonly involved sites which correlate with our results as well (1, 9).

Along with a known poor prognosis, there still hasn't been a large prospective study conducted to report the actual prognosis for MS. It may depend on tumor location, genetics, the stage at diagnosis, and treatment strategy. It is usually known to be 10 to 12-month period, with rare reported cases over >16 years of follow-up (3, 10). However, a bigger study done by Movassaghian et al. (11) revealed a higher 3-year survival. Site involved had an important impact on the survival with better reported prognosis for isolated MS sites involving gastrointestinal mucosa, pelvis, eyes/gonads (11). On the contrary, patients with isolated MS report a longer overall survival (3). Pileri et al. (1) attempted to identify poor prognostic factors by showing that neither disease course nor answer to therapy are influenced by location, age, being concomitant with AML or not, and morphology. Interestingly CXCR4 protein determined by immunohistochemistry was related to increased overall survival in a recent study done by Kawamoto et al. (12).

Misdiagnosis frequently occurs and needs to be differentiated from non-Hodgkin lymphomas, histiocytic lymphoma, mucosa-associated lymphoid tissue lymphoma, anaplastic large-cell lymphoma (ALCL), lymphoblastic lymphoma/leukemia (LBL), melanoma, Ewing sarcoma, and thymoma. Having similar morphological findings like diffuse infiltration of tumor cells, MS has immature granulocytic infiltration being negative for CD3, CD20, CD79a, and PAX-5 and positive for myeloid differentiation antigens (3, 8). The most common misdiagnosis usually happens between LBL/leukemia and ALCL, starry sky appearance with a lack of nucleolus for LBL/Leukemia and CD30 positivity for ALCL are helpful morphological characteristics for differentiation (3). Since MS may have coexpression of T-cell markers, immunohistochemical expression of MPO, lysozyme, CD34, CD68, and CD117 should be analyzed with a bone marrow biopsy for AML to verify your results (9). Given that one of our patients had an MS with the coexpression of Tdt and T-cell markers.

When it comes to treatment strategies due to deficient prospective studies, there still has not been a proper chemotherapy protocol developed for MS. According to patient's age, performance, and underlying disease (de novo, secondary to AML, secondary to MDS, etc.), treatment protocol can vary from induction, consolidation salvage chemotherapy and/or to allogenic HSCT depending on degree of patient's suitability, on a side note addition of clinical studies testing monoclonal antibody for treating MS are still ongoing (3). After the disease is under control, local therapy including surgery and radiotherapy simultaneously may be performed on sites with MS involvement, which have been demonstrated in retrospective studies to not affect overall survival and prognosis (3).

In conclusion, MS which is an uncommon diseases should be taken into consideration as a differential di-

agnosis of any unusual cellular infiltration at any site, particularly if a patient has a history of AML. Comprehensive diagnostic work-up and comprising genetic profile should be done in all cases. Earlier induction therapy may result in better outcomes, furthermore, prospective multicenter controlled trials that integrate novel targeted therapies for refining and taking one step closer to better understanding the disease are needed.

Ethics Committee Approval: N/A
Informed Consent: Informed consents were obtained from patients for this study.
Conflict of Interest: The authors declared no conflict of interest.
Author contributions: Concept: FEA, OPF, KHO Design: FEA, OPF, KHO Supervision: FEA, OPF, EM, KHO Resources: FEA, OPF, EM, KHO Materials: FEA, OPF, EM, KHO Data collection and/or processing: FEA, OPF, EM, KHO Analysis and/or Interpretation: FEA, OPF, EM, KHO Literature Search: FEA, OPF, KHO Writing Manuscript: FEA, OPF, KHO Critical Review: FEA, OPF, KHO
Financial disclosure: The authors declared that this study received no financial support.
Editor-in-chief's Note: One of the authors of this article, Fatih Erkan Atay is a member of the editorial board of Turkish Medical Student Journal. However, he did not take place in any stage on the editorial decision of the manuscript. The editors who evaluated this manuscript are from other institutions.

REFERENCES

1. Pileri SA, Ascani S, Cox MS et al. Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. Leukemia 2007;21(2):340-50.
2. Claerhout H, Sophie Van Aelst S, Melis C et al. Clinicopathological characteristics of de novo and secondary myeloid sarcoma: a monocentric retrospective study. Eur J Haematol 2018;100(6):603-12.
3. Wilson CS, Medeiros LJ. Extramedullary manifestations of myeloid neoplasms. Am J Clin Pathol 2015;144(2):219-39.
4. Almond LM, Charalampakis M, Ford SJ et al. Myeloid sarcoma: presentation, diagnosis, and treatment. Clin Lymphoma, Myeloma Leuk 2017;17(5):263-7.
5. Békássy AN, J Hermans J, Gorin NC et al. Granulocytic sarcoma after allogeneic bone marrow transplantation: a retrospective European multicenter survey. Acute and Chronic Leukemia Working Parties of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 1996;17(5):801-8.
6. Stolzel F, Rollig C, Radke J et al. F-FDG-PET/CT for detection of extramedullary acute myeloid leukemia. Haematologica 2011;96(10):1552-6.
7. Campidelli C, Agostinelli C, Stitson R et al. Myeloid sarcoma: extramedullary manifestation of myeloid disorders. Am J Clin Pathol 2009;132(3):426-37.
8. Magdy M, Abdel Karim N, Eldessouki I et al. Myeloid sarcoma. Oncol Res Treat 2019;42(4):219-24.
9. Kaygusuz G, Kankaya D, Ekinci C et al. Myeloid sarcomas: a clinicopathologic study of 20 cases. Turk J Haematol 2015;32(1):35-42.
10. Yamauchi K, Yasuda M. Comparison in treatments of nonleukemic granulocytic sarcoma: report of two cases and a review of 72 cases in the literature. Cancer 2002;94(6):1739-46.
11. Movassaghian M, Brunner AM, Blonquist TM et al. Presentation and outcomes among patients with isolated myeloid sarcoma: a Surveillance, Epidemiology, and End Results database analysis. Leuk Lymphoma 2015;56(6):1698-703.
12. Kawamoto K, Miyoshi H, Yoshida N et al. Clinicopathological, cytogenetic, and prognostic analysis of 131 myeloid sarcoma patients. Am J Surg Pathol 2016;40(11):1473-83.