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Case Report

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Myeloid Sarcoma: Case Series with Unusual Locations

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ABSTRACT

Myeloid sarcoma (MS) or chloroma is a localized mass composed of blastic cells of granulocytic lineage. It is a subtype of acute myeloid leukemia and usually presents as a complication of acute myeloid leukemia, myeloid dysplastic syndrome, or myeloproliferative disorder. MS occurs in 2.5-9.1% of patients with AML, precedes the clinical disease, coincidence with the onset or at relapse and in rare conditions, it can occur with no evidence of hematologic disorders. Here, we presented seven cases of MS in unusual locations or with rare presentations at presentation or relapse. We concluded that MS should be considered in the differential diagnosis of any high-grade tumor, especially in a patient with previous history of any myeloid neoplasm.

Keywords: Non-leukemic myeloid sarcoma; Acute leukemia

INTRODUCTION

Myeloid sarcoma (MS), also known as granulocytic sarcoma, is a rare neoplasm that occurs as an extramedullary accumulation of immature myeloid cells[1]. It has also been addressed as chloroma by King in 1853 because of enzyme myeloperoxidase that turns green upon exposure to oxygen [2,3,4]. MS might be isolated or develop as part of myeloproliferative neoplasm, myelodysplastic syndrome, or acute myeloid leukemia[5]. It occurs in 2.5-9.1% of patients with AML[6], precedes the clinical disease, coincides with the onset or at relapse, especially in patients with allogeneic hematopoietic stem cell transplantation[7-11]. MS has a slight male predominance with a ratio of 1.2:1, and may occur at any age and any site of the body [12]. Most common sites include skin, lymph nodes, and bones. Other sites with less frequency include the central nervous system, the genitourinary tract, the gastrointestinal tract, peritoneum, oral and nasal mucosa, breast, pleura, and chest wall [13,14]. The most common signs and symptoms include mass effect to adjacent structures or organ dysfunction due to leukemic infiltration[15].

The diagnosis of isolated MS can be challenging for pathologists, and the rate of misdiagnosis can be in the range between 25-47%[15]. MS should be differentiated from non-Hodgkin lymphoma (lymphoblastic lymphoma, diffuse large B cell lymphoma, Burkitt's lymphoma), poorly differentiated carcinoma, blastic plasmacytoid dendritic cell neoplasm, and small round blue cell tumors such as rhabdomyosarcoma and neuroblastoma[1].

The exact mechanism of MS occurrence is not known with certainty but some hypothesis related to cytokine and adhesion molecules which leads to homing of tumor cells in a specific tissue [15].

The prognosis of isolated MS is different from MS with concomitant myeloid neoplasm so the prompt diagnosis is important for risk stratification and guidance of treatment strategies.

The current study reported seven cases of MS in unusual locations or with rare presentations at presentation or relapse.

Case presentation

Case 1

A 57-year-old male referred to our clinic with a subcutaneous scalp mass developed one month ago without any signs or symptoms of malignancy such as fever, weight loss, fatigue, organomegaly, or lymphadenopathy. Peripheral blood count and smear had no specific pathologic changes. Bone marrow aspiration and biopsy revealed trilineage hematopoietic with no increase in blast cells. Grossly, the tumoral mass had firm consistency and smooth cut surface with overlying epidermal ulceration. Microscopically, in the dermis, diffuse and dense infiltration of neoplastic cells with extension into the subcutaneous fat was observed. The cells were infiltrated around the preserved adnexa. Medium-sized tumor cells contained oval to rounded nuclei with inconspicuous nucleoli and scant cytoplasm (Figure 1). In immunohistochemistry (IHC) staining, the cells showed strong reactivity with leukocyte common antigen (LCA), CD34, CD68, CD117, and vimentin. However, these cells did not express B- or T-cell markers such as CD3, CD4, CD2, CD19, and CD20; CD30 was also negative. The Ki67 index was about 50% (Figure 1). Cytogenetic and molecular studies revealed no evidence of JAK2, t (9, 22), t (8, 21), t (15, 17), or various numerical chromosomal abnormalities. The patient underwent systemic chemotherapy as systemic acute myeloid leukemia with cytarabine and idarubicin (7+3) for induction of remission and post-remission chemotherapy with high-dose cytarabine followed by radiotherapy. In the second year of the follow-up, another subcutaneous mass developed in the upper cervical region. Core needle biopsy and IHC staining confirmed recurrence of the tumor. Bone marrow aspiration and biopsy showed normocellular marrow with no neoplastic or hematologic disorder. Clinical and lab data did not show any signs or symptoms of leukemia. At this stage, the patient was treated again with cytarabine and idarubicin (7+3) for induction of remission and post-remission chemotherapy with high-dose cytarabine. After complete remission, the patient underwent hematopoietic stem cell transplantation.

Case 2

A 66-year-old male presented with left nasal congestion, left periorbital swelling, and mild proptosis from one month ago. Radiologic examination showed significant soft tissue edema with a hyperdensity area around orbital cavity, maxillary sinus opacification, and left frontal sinus. Based on the clinical suspicion to sinus tumor, endoscopic sinus surgery was performed and the specimen was sent for histopathologic evaluation. Microscopic examination showed diffuse interstitial infiltration of mononuclear cells with a high N/C ratio containing hyperchromatic nuclei with disruption of glandular structures. In immunohistochemical staining, these cells showed immunoreactivity for LCA, MPO, CD117, and CD68 and negativity for CD34, CD10, CD20, CD23, CD5, CD2, CD7, CD56, CD7, CD138, CD99, and cytokeratin (Figure 2). Subsequent bone marrow aspiration and biopsy showed trilineage hematopoiesis with no increase in blast count. Other patient lab data including complete blood count was within normal limits. Thus, the patient diagnosed with aleukemic MS was treated with AML induction chemotherapy followed by radiotherapy. The treatment course was uneventful.

Case 3

A 26-year-old woman presented with abdominal pain and referred to an emergency ward with signs and symptoms of bowel obstruction. An abdominopelvic computerized scan showed a large mass (5 cm) in the right lower quadrant area with peripheral lymphadenopathy. Peripheral blood was within normal limits.

At laparotomy, a large cecal mass with evidence of ischemia in ileum was observed, and thus, right

hemicolectomy with appendectomy was performed. Pathologic examination reported diffuse infiltration of atypical mononuclear cells and showed immunoreactivity for LCA and CD56 with the Ki 67 index of about 30%. The tumor cells were negative for CD20, CD3, CD10, BCL2, BCL6, CD138, Cytokeratin, DOG1, Vimentin, S100, Synaptophysin, and chromogranin with diagnosis of undifferentiated lymphoma. The slides were reviewed in another pathologic center with diagnosis of unclassifiable high grade lymphoma. Moreover, malignant cell infiltration was not observed on bone marrow aspiration and biopsy. Finally, the slides were referred to our institute for further analysis. Few additional markers were tested in our center, which were positive for MPO, CD117, and CD 45 and negative for PAX5, CD30, CD5, and CD3. The final diagnosis of MS was made, and the patient was treated with standard AML induction chemotherapy (Figure 3).

Case 4

A 53-year-old female with past medical history of AML on remission for 6 years presented with a recurrent genital ulcerative lesion from 2 mouths prior to admission. The lesion was treated with initial diagnosis of pyoderma gangrenusome. However, due to lack of response to therapy, skin re-biopsy was performed and the patient was referred to our institution for pathologic examination. Microscopic examination showed surface ulceration with interstitial infiltration of blastoid cells with hyperchromatic nuclei admixed with some eosinophils and monocytoid cells. IHC study showed positivity for MPO, CD117, and CD34. The Ki67 index was 30-40% of the cells (Figure 4). Bone marrow aspiration and biopsy did not reveal any increase in the blast percentage. With final diagnosis of MS, the patient was treated with AML induction therapy and genital ulcers were completely resolved.

Case 5

A 32-year-old male presented to our institution with dry cough and dyspnea on exertion from 2 months before admission. Clinical examination revealed collateral engorged vessels on the patient's chest wall. The computed tomography of neck and chest demonstrated mediastinal mass involving anterior, posterior, and middle mediastinum with pressure effect on esophagus, pulmonary arteries, and superior vana cava. The patient underwent core needle biopsy of mediastinal mass, and corticosteroid was initiated for him. A pathologist reported high-grade undifferentiated non-Hodgkin lymphoma after immunohistochemistry of tissue biopsy. The patient received a course of hyper-CVAD, but did not respond to chemotherapy. Thus, his pathology slides were reviewed by another pathologist, and the diagnosis of MS was confirmed (Figure 5). Bone marrow aspiration and biopsy showed normal histology and no evidence of increased blastic cells. The patient received the AML induction chemotherapy protocol, and all of his symptoms improved.

Case 6

A 72-year-old female presented with left sided neck lymphadenopathy for a duration of 4 weeks. The patient was a known case of AML on remission. The cytogenetic study on her first bone marrow specimen showed +8 chromosomal abnormalities. The cervical lymph node was excised and showed complete effacement with infiltration of blastic cells. The IHC study was positive staining for CD117 and CD34 and negative for MPO, CD20, CD3, and high Ki67. Bone marrow aspiration and biopsy showed normal hematopoietic elements. Thus, MS was diagnosed and the patient was treated with AML standard chemotherapy.

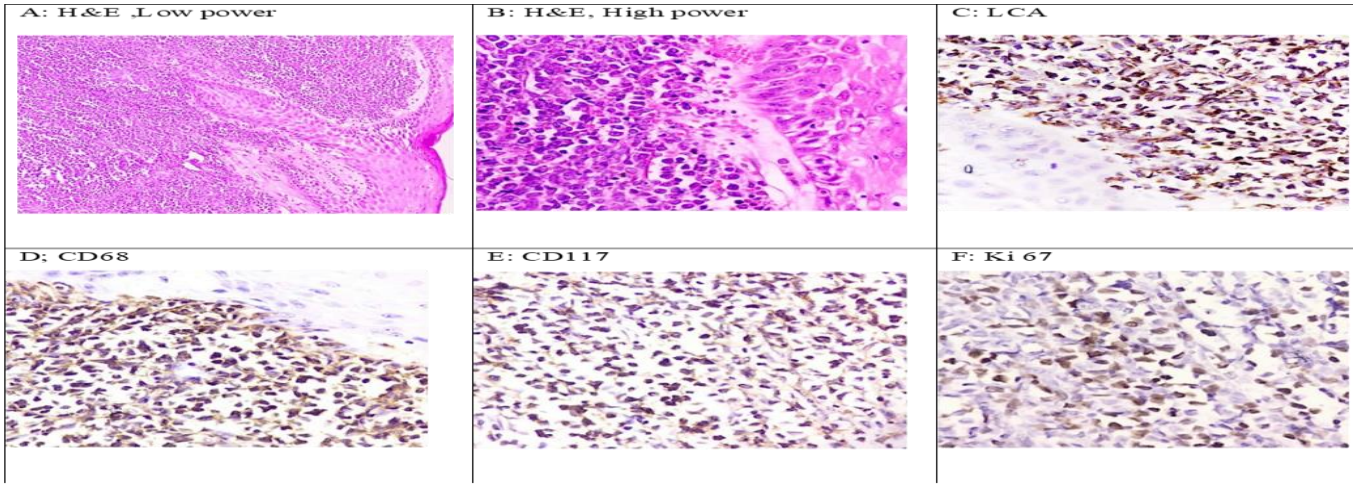


Figure 1. a) Low power magnification of skull granulocytic leukemia diffuse infiltration of neoplastic cells. b) High power examination reveal monotonous infiltration of blastic cells with gray zone between dermis and epidermis (H&E staining). C,d,e, and F**:** Immunostin for LCA, CD68 , CD117 and Ki 67 in skull skin nodule

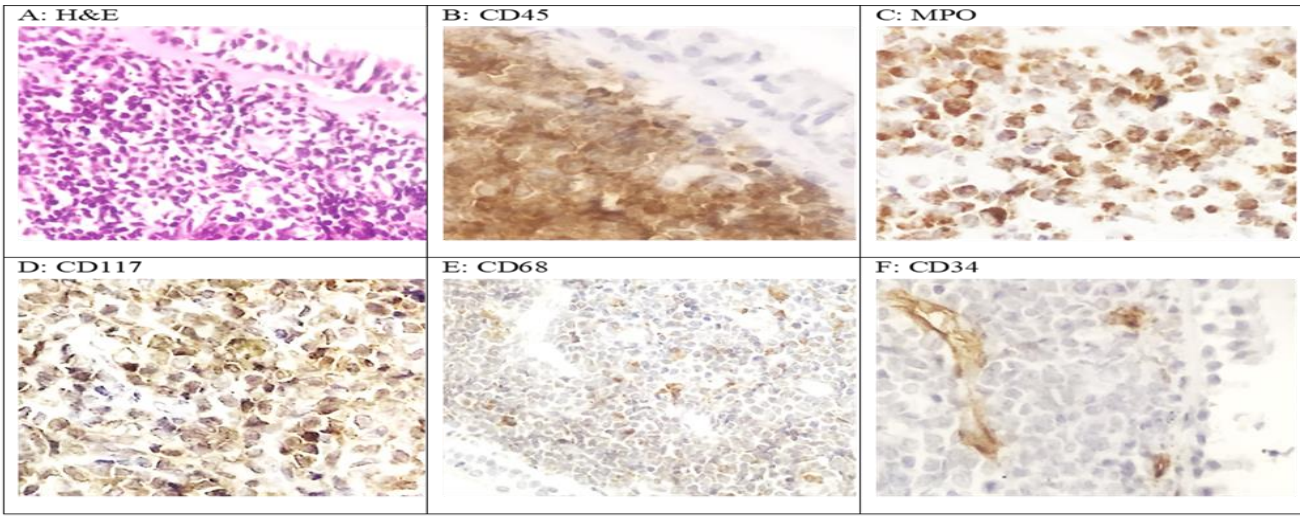


Figure 2. a) Maxillary sinus mass with diffuse infiltration of blastic cells beneath the surface respiratory epithelium. b,c ,d,e and f : Immunostin for LCA,MPO , CD117 CD68 and CD34

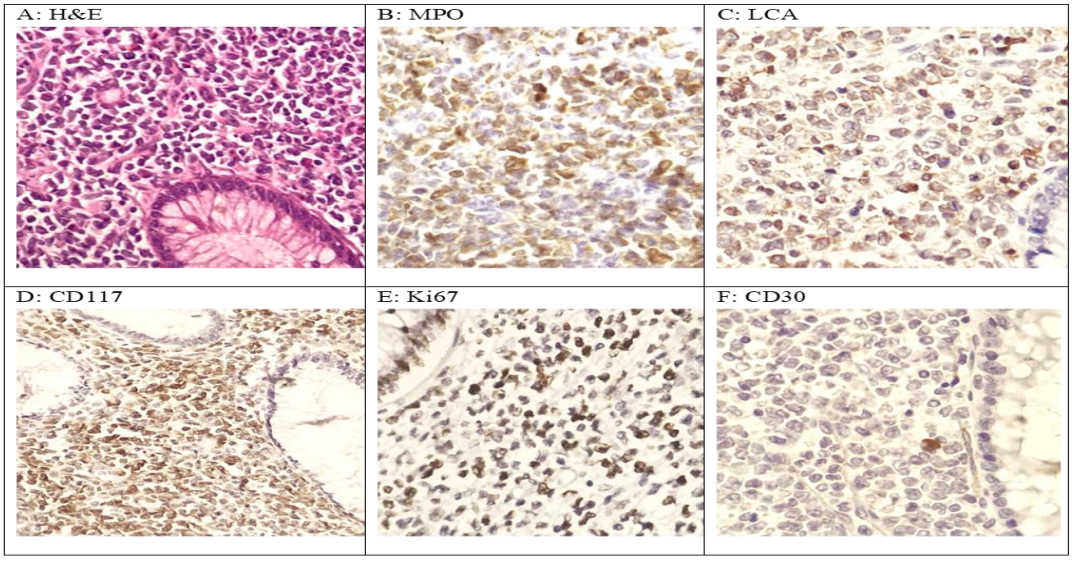


Figure 3 a: Diffuse and compact infiltration of blastic cells between intestinal glands.
b, c, e and f ;Immunohistrochemistry staining with MPO, LCA, CD117, CD30 and ki67

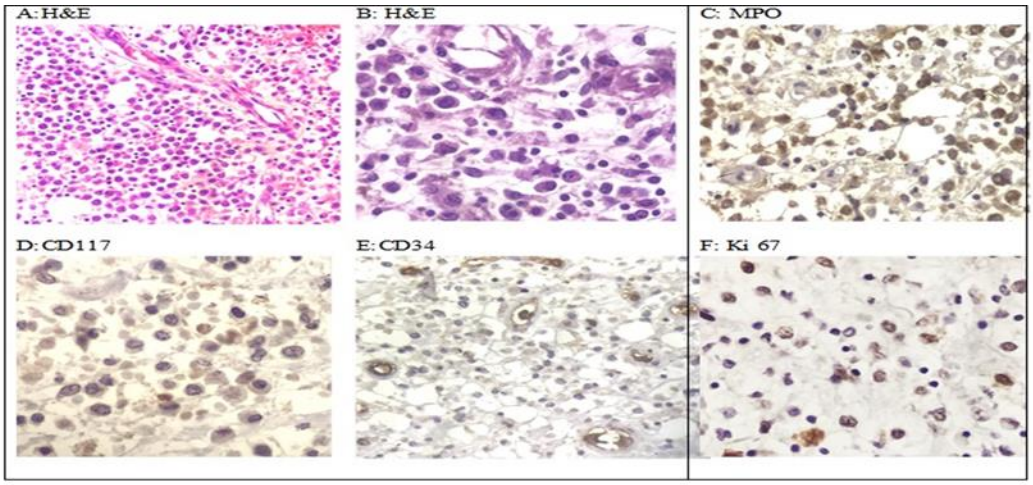
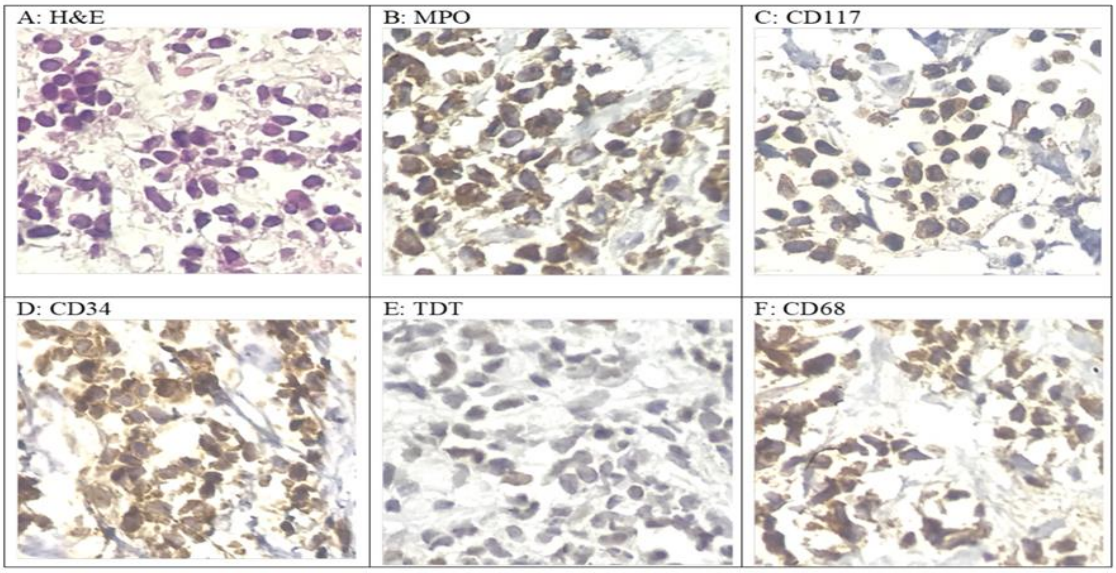


Figure 4. a and b : Diffuse infiltration of blastic cells .
C, d, e, and f ;Immunohistrochemistry staining with MPO, CD117, CD34 and ki67



Figur 5. a) Diffuse infiltration of blastic cells .
B, c, d, e and f ;IHC staining with MPO, CD117, CD34, TDT and CD68

DISCUSSION

Extramedullary MS is a tumor mass composing of myeloid precursors with a variable degree of maturation or monoblastic cells which can infiltrate anywhere outside the bone marrow. According to WHO classification, if there is a simultaneous involvement of bone marrow, it is not considered as MS[16]. MS may be seen isolated or developed as AML relapse, blastic crisis of myeloproliferative neoplasms, MDS/MPN, or myelodysplatic syndrome[1,19]. Moreover, MS is regarded as isolated MS that is also called non-leukemic and leukemic MS. Non-leukemic MS may also precede the development of leukemia by months or years [20]. The ability of blastic cells to invade extramedullary tissues depends on multiple factors such as expression of surface molecules (i.e., CD56) and cytogenetic abnormalities[1]. The most common sites of extramedullary MS are soft tissues, bones, skin, lymph nodes, and the gastrointestinal tract. Uncommon sites include jaw, nasal cavity, cervix, facial nerve, and breast, although it may be presented in any extramedullary site [21,22,23]. Skin involvement by infiltration of leukemic cells is called leukemia cutis. Leukemic involvement of the skin is often associated with systemic leukemia. Very rarely, leukemia cutis may precede clinically detectable systemic leukemia, the so-called aleukemic leukemia cutis[24,25,26]. The most common type of MS is the granulocytic type that is composed of myeloblastic, promyelocytic, or neutrophilic cells[6,16]. Rarely, MS occurs with trilineage hematopoiesis, erythroblasts, or predominance of megakaryoblasts that may occur due to myeloid neoplasm transformation [16]. Histologically, MS mostly shows infiltrative and diffuse patterns of mononuclear cells, sometimes with other hematopoietic elements, which can be a diagnostic clue to the myeloid origin of neoplastic cells. In fact, malignant populations containing blastic cells with round or folded nuclei and fine chromatin are easily mistaken for a variety of malignancies, including high-grade B-cell lymphoma. Therefore, in the absence of systemic acute leukemia, immunostaining has a significant role in proper diagnosis of MS [16,24]. Most useful diagnostic markers are MPO, CD68, CD33, CD34, CD117, and CD56. MPO and CD117 are the most sensitive markers for myeloid differentiation whereas monocytic precursors strongly express CD68 and CD163; therefore, association of CD68, CD33, and MPO can diagnose 100% of leukemia cutis [26,16, 19].

In a study by Benet et al., non-leukemic MS demonstrated variable reactivity for these markers.

Cytogenetic studies have shown that de novo MS is carried by about 50% of individuals with normal karyotype. Moreover, by using cytogenetic and FISH methods in 55% of MS cases, chromosomal abnormalities including trisomy 8, monosomy 7, and KMT2A abnormality can be identified[16,5]. Some studies have also shown that about 16% of MS containing the NPM1 mutation are histologically more monoblastic or myelomonoblastic and that cells are CD34 negative and have a normal karyotype[16]. Due to its rarity, non-leukemic MS is frequently misdiagnosed as other common malignancies such as non-Hodgkin lymphoma, burkitt lymphoma, small round cell rumor, malignant melanoma, and metastatic tumors[16,21,22]. Therefore, in cases of undifferentiated tumor in any part of the body, MS is a major differential diagnosis. Overall therapies include local radiation, systemic chemotherapy, immunotherapy, surgery, hematopoietic stem cell transplantation, target therapy, donor lymphocyte infusion, and combination therapy [17,18].

Optimal therapy for non-leukemic MS is not definitely determined, but several studies have shown that most of patients with non-leukemic GS who are treated with local excision or radiotherapy eventually develop overt systemic leukemia within a few months. Optimal therapy is not definitely determined for non-leukemic MS; however, systemic chemotherapy regimens for AML are currently accepted as appropriate treatment for MS[12,15]. Radiotherapy is also recommended in MS and cases with inadequate responses to systemic chemotherapy, recurring following stem cell transplantation and when rapid symptom relief is needed[15]. Some authors suggest bone marrow transplantation after the first induction of remission, but there is no consensus on this issue [16,17]. The non-leukemic period after diagnosis of MS is significantly longer in patients treated with systemic chemotherapy. However, the overall long-term prognosis of these patients remains poor [12].

CONCLUSION

MS as a subtype of AML may present de novo, as relapse of AML, or may present as a blastic transformation of a prior MDS, myeloproliferative neoplasms, or MDS/MPN. Due to marrow or peripheral blood involvement, pathological diagnosis of MS is difficult, especially in the absence of systemic leukemia. Early diagnosis of MS has an extremely significant prognostic value; thus, MS should be considered in differential diagnosis of any undifferentiated tumor.

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