Myeloid Sarcoma of the Head and Neck Region

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• **Context.**—Myeloid sarcoma of the head and neck region can pose diagnostic challenges because of the low frequency of myeloid sarcoma and the potential for tumors of almost any lineage to occur in the head and neck.

**Objective.**—To study the clinicopathologic and immunohistochemical characteristics of myeloid sarcoma in the head and neck region and to review the differential diagnosis.

**Design.**—We searched for cases of myeloid sarcoma involving the head and neck region for a 24-year period at our institution. The medical records and pathology slides were reviewed. Additional immunohistochemical stains were performed.

**Results.**—We identified 17 patients, age 17 to 85 years. Most tumors involved the oral cavity. Myeloid sarcoma was the initial diagnosis in 9 patients (53%); the remaining 8 patients (47%) had a history of bone marrow disease. Immunohistochemical analysis using antibodies specific for lysozyme, CD43, and CD68 were highly sensitive for diagnosis but were not specific. By contrast, assessment for myeloperoxidase in this study was less sensitive but more specific. We also used antibodies specific for CD11c and CD35 in a subset of cases, and these reagents seem helpful as well.

**Conclusions.**—The clinical presentation of myeloid sarcoma involving the head and neck, particularly the mouth, is often nonspecific, and a high degree of suspicion for the possibility of myeloid sarcoma is needed. Immunohistochemistry is very helpful for establishing the diagnosis.


Myeloid sarcoma is defined as a tumor mass of myeloblasts or immature myeloid cells involving an extramedullary anatomic site and can occur in 3% to 8% of patients with acute myeloid leukemia (AML). These neoplasms also can occur in patients with myelodysplastic syndromes, myeloproliferative/myelodysplastic disorders, and myeloproliferative neoplasms as a manifestation of blast transformation. Myeloid sarcoma also can be the initial manifestation of AML, preceding bone marrow involvement.

The most common anatomic sites involved by myeloid sarcoma include skin, bones, and gastrointestinal tract. However, any extramedullary site in the body can be involved, including the head and neck region. Myeloid sarcoma involving the head and neck region can pose diagnostic challenges because of the low frequency of myeloid sarcoma and the potential for tumors of almost any lineage to occur in the head and neck, thereby, resulting in a broad differential diagnosis. Although others have written about the clinicopathologic and/or immunophenotypic findings of myeloid sarcoma at various sites, we found only case reports of myeloid sarcoma involving the head and neck region in our review of the literature.

In this study, we report our experience with myeloid sarcoma involving the head and neck region at a single institution. We present the clinicopathologic and immunophenotypic features of 17 patients with biopsy specimens identified during a 24-year period. We also review the differential diagnosis of myeloid sarcoma, with emphasis on lesions involving the oral cavity, and review antibodies useful for the immunohistochemical workup of these tumors.

**MATERIALS AND METHODS**

**Study Group**

A search of the archives of the Departments of Pathology and Hematopathology at The University of Texas MD Anderson Cancer Center (Houston) revealed 19 patients with biopsy specimens of the head and neck region involved by myeloid sarcoma between January 1, 1987, and December 31, 2011. We excluded 1 patient because of a complete lack of clinical information as well as 1 patient who underwent fine-needle aspiration and had no clinical follow-up, leaving 17 patients. The electronic medical records of these patients were reviewed, and relevant clinical data of these patients were abstracted, including age; sex; race; tumor site; results of laboratory studies (when available) and bone marrow examination, including ancillary data (when available); and clinical follow-up.

**Histology and Immunohistochemistry**

Hematoxylin-eosin-stained slides and immunohistochemistry slides of formalin-fixed, paraffin-embedded tissue sections prepared at initial diagnosis were reviewed.

For almost every biopsy specimen in this study, some immunohistochemical studies were performed at initial diagnosis. Those antibodies were obtained from a variety of commercial sources during the 24-year interval of the study and, therefore, are not provided. Specifically, as a part of this study, we performed...
immunohistochemical studies, depending on the panel already performed and the availability of paraffin blocks. These immunohistochemical studies included reagents specific for CD3, CD11c, CD20, CD33, CD43, CD68, CD117, CD163, lysozyme, and myeloperoxidase. The sources and dilutions of these antibodies are listed in Table 1.

Immunohistochemical analysis was performed using the Bond Max automated system of Leica Microsystems (Buffalo Grove, Illinois), according to the manufacturer’s protocol. Briefly, 4-μm sections of formalin-fixed, paraffin-embedded tissue were dewaxed, washed, and incubated with the appropriate antibody at the appropriate dilutions at room temperature for 15 minutes. The slides then were treated with Epitope Retrieval (Leica) in citrate buffer for 5 minutes after washing. Endogenous peroxidase activity was blocked by Peroxide Block (Leica) for 5 minutes. After washing, the sections were incubated with Post Primary (Leica) Immunoglobulin G (IgG) linker (Polymer Enhancer) for 8 minutes and then incubated with polymer horseradish peroxidase IgG Polymer (Leica) for 8 minutes after washing. The stain was visualized using 3,3′-diaminobenzidine and hematoxylin counterstain. Appropriate positive and negative controls were performed simultaneously.

RESULTS
Clinical Features

The clinicopathologic characteristics of these patients are summarized in Table 2. There were 12 men (71%) and 5 women (29%), with a median age of 61 years (range, 17–85 years). Twelve patients (71%) were white, 3 (18%) were African-American, and 2 (12%) were Hispanic. These patients underwent 25 biopsies, with specimens showing involvement by myeloid sarcoma. Twelve patients (71%) underwent excision or biopsy of a single site from which the diagnosis of myeloid sarcoma was established; the biopsy sites were gingiva (n = 3; 25%), lips (n = 2; 17%), skin of cheek (n = 2; 17%), tonsil (n = 1; 8%), nasal middle turbinate (n = 1; 8%), tongue (n = 1; 8%), maxillary ridge (n = 1; 8%), and mandible with adjacent soft tissue (n = 1; 8%). In addition, 1 of 17 patients (6%) underwent bilateral tonsillectomy, 1 patient (6%) had bilateral tonsillectomy with a tongue biopsy; 1 patient (6%) had excision of submandibular and parotid tail lymph nodes, 1 patient (6%) had biopsies of the buccal soft tissue and breast, and 1 patient (6%) had 5 biopsy specimens from skin of eyelid, lip, forehead (n = 2), and right flank. Overall, 12 patients (71%) had biopsy specimens from the oral cavity.

Patients Without a History of Bone Marrow Disease

Nine patients (53%) presented initially with myeloid sarcoma, without any history of bone marrow disease. The symptoms reported by these patients included skin lesion or rash (n = 2; 22%), sore/painful throat (n = 2; 22%), bleeding of the tongue or gingiva (n = 2; 22%), bulging of the eye (n = 2; 22%), a painless mass (n = 1; 11%), and jaw pain (n = 1; 11%).

A complete blood cell count was available for 7 of the 9 patients (78%) when they came to our hospital and/or at diagnosis of myeloid sarcoma. Two patients (29%) had a normal complete blood cell count, and 5 patients (71%) had abnormal results. For the patients with an abnormal complete blood cell count, the median leukocyte count was 7100/L (range, 3500–23 400/L; reference range, 4000–11 000/L), the patient with the highest leukocyte count was shown subsequently to have AML. The median red blood cell count was 3.65 × 10^6/L (range, 2.13–3.91 × 10^6/L; reference range, 4.0–5.5 × 10^6/L). The median hemoglobin level was 11.0 g/dL (range, 7.3–12.5 g/dL, reference range, 12–16 g/dL), and the median hematocrit was 33.4% (range, 21.4%–36.3%; reference range, 37%–47%). The median platelet count was 116 × 10^9/L (range, 25–244 × 10^9/L; reference range, 140–440 × 10^9/L). Eight of the 9 patients (89%) were subsequently shown to have myeloid neoplasms involving the bone marrow, including 1 myelodysplastic syndrome (MDS; 11%), 1 chronic myelogenous leukemia (11%), and 6 AML cases (67%) that were classified as acute monoblastic leukemia (n = 4), acute myelomonocytic leukemia (n = 1), and acute myeloid leukemia with maturation (n = 1). One of the 9 patients (11%) had bone marrow aspiration results within reference range.

Conventional cytogenetic analysis was performed on 8 patients. In 1 patient, the bone marrow showed MDS (case 1), and the karyotype was 47,XX,+8[20]; in the patient with chronic myelogenous leukemia (case 2) the karyotype showed 46,XY,t(9;22)(q34;q11)[20]; and among the 6 patients with AML, the karyotype was abnormal in 3 patients, diploid in 2 patients, and not assessed in 1 patient. In the 3 cases of AML with abnormal cytogenetics, the karyotypes were as follows:

Case 5: 45,X,-Y,(8;21)(q22;q22),del(9)(q22)[19]
Case 7: 46,XX,t(13;16)(q21;p11.2)[20]/46,XX,del(13)(q12q22)der(16);t(13;16)(q12;p13.1)[17]/47,idem,+8[2]/48,+,+8[1]
Case 8: 46,XY,-20,+r[3]

Molecular studies were limited in these patients, in large part, because many of these cases predate the era of routine molecular diagnostics. In the case of chronic myelogenous leukemia, BCR-ABL1 was shown by reverse transcriptase polymerase chain reaction. NPM1 mutation was identified in 1 patient (case 7).

Patients With a History of Bone Marrow Disease

Eight patients (47%) had a history of bone marrow disease before the diagnosis of myeloid sarcoma, including 3 patients (38%) with AML, 2 patients (25%) with MDS, 2 patients (25%) with chronic myelomonocytic leukemia, and 1 patient (13%) with acute biphenotypic T/myeloid cell leukemia. At diagnosis of myeloid sarcoma, the results of bone marrow examination showed AML (n = 3; 38%), MDS (n = 2; 25%), chronic myelomonocytic leukemia (n = 2; 25%), and 1 patient (13%) had uninvolved bone marrow. The latter patient, a 17-year-old girl, had undergone stem cell transplant for acute biphenotypic T/myeloid cell leukemia previously and, at time of diagnosis with myeloid sarcoma, had a diploid male karyotype (case 17). Conventional cytogenetic analysis was available for 5 patients; of which, 3 patients (60%) had very complex karyotypes (cases 13, 14, and 16; see Table 2) and 2 patients (40%) had diploid karyotypes.

Follow-up

At last clinical follow-up of the 17 patients, 5 (29%) were alive, and 10 patients (59%) died of their disease. Two patients (12%) were lost to follow-up.

Pathologic Findings

The neoplasms involved tissue sites in a diffuse pattern. In lymph nodes and tonsils, the neoplasms preferentially involved the paracortical regions. In submucosa and soft
tissue, the neoplastic cells infiltrated around small blood vessels and nerves and between adipocytes (Figure 1). One case involving the tongue showed mild to moderate pseudoepitheliomatous hyperplasia (Figure 2, inset). In the cases that involved the mouth, plasma cells were intermixed with the neoplastic cells, and in some areas, plasma cells were numerous (Figure 2).

Using traditional cytologic criteria, 11 of 17 tumors (65%) showed evidence of maturation, including 10 with some degree of maturation, and 1 with extensive maturation. The remaining 6 tumors (35%) were completely blastic, without any evidence of maturation (Figure 3, A through C).

The tumors with evidence of maturation had either granulocytic and/or monocytic features. In granulocytic tumors, the neoplastic cells had granular cytoplasm, and the granules had either neutrophilic or eosinophilic features. Eosinophilic metamyelocytes were present in 5 cases (29%). In monocytic tumors, the neoplastic cells lacked cytoplasmic granules and had either oval or reniform nuclei. In 2 monocytic tumors, many of the nuclei were folded, consistent with promonocytes. In 2 other purely monocytic tumors that involved lip and skin, the neoplastic cells were arranged in a single-file pattern (Figure 4); in 1 case, the stroma of a skin biopsy specimen had a myxoid appearance with extensive coagulative necrosis. The single case of myeloid sarcoma with extensive maturation was composed predominantly of myelocytes and metamyelocytes and arose

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<td>5D11</td>
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Abbreviations: MPO, myeloperoxidase; N/A, not applicable.

* Dako, Carpinteria, California; Novocastra, Newcastle upon Tyne, UK.

**Table 1. List of Antibodies Used for Immunohistochemistry in the 24-Year Study of Myeloid Sarcoma Involving the Head and Neck Region**

Figure 1. The neoplastic cells diffusely and extensively infiltrate skeletal muscle and adipose tissue (hematoxylin-eosin, original magnification ×100).

Figure 2. Inset, This tongue biopsy specimen shows pseudoepitheliomatous hyperplasia overlying myeloid sarcoma. High-power magnification of the specimen in Figure 2 shows many reactive plasma cells, intermixed with the neoplastic myeloid cells. In the mouth, the presence of many plasma cells can obscure or distract from the diagnosis of myeloid sarcoma (hematoxylin-eosin, original magnifications ×20 [inset] and ×1000).

Figure 3. A, In this neoplasm (immature type), the cells have immature nuclear features, but a subset of cells has eosinophilic, granular cytoplasm, suggesting the possibility of myeloid sarcoma. B, In this neoplasm (blastic type), most of the cells have finely granular or blastic nuclear features, and very few cells exhibit evidence of cytoplasmic maturation. C, In this neoplasm (differentiated type), most of the neoplastic cells are granulocytes that exhibit substantial maturation (hematoxylin-eosin, original magnifications ×1000 [A through C]).
in a patient with a history of MDS. Mitotic figures were infrequent in that case.

In blastic tumors without maturation (n = 6; 35%), the neoplastic cells had very immature or blastic chromatin. One of these cases involving tonsil had a prominent starry-sky pattern (Figure 5). Mitotic figures and apoptotic cells were found in all cases of myeloid sarcoma but were more frequent in blastic tumors.

Five tumors (29%) were assessed with naphthol-ASD chloroacetate esterase stain. Four of 5 tumors (80%) stained positively in a subset of neoplastic cells; 1 blastic tumor (20%) was negative.

**Figure 4.** This case of myeloid sarcoma, in a patient with a history of chronic myelomonocytic leukemia, shows a single-file pattern of infiltration in the skin. This pattern is very common in monocytic forms of myeloid sarcoma (hematoxylin-eosin, original magnification ×400).

**Figure 5.** This case of myeloid sarcoma shows a prominent starry-sky pattern (hematoxylin-eosin, original magnification ×400).

**Figure 6.** Examples of immunohistochemical results in cases of myeloid sarcoma. A, Lysozyme. B, CD43. C, CD68 (immunohistochemistry with hematoxylin counterstain, original magnifications ×400).

**Figure 7.** In this example of myeloid sarcoma, the neoplastic cells are monocytic and a subset of cells has prominently folded nuclei, resembling, in part, the horseshoe-shaped nuclei that can be observed in anaplastic large cell lymphoma (hematoxylin-eosin, original magnification ×1000).
The results of immunohistochemical studies, including those performed at initial diagnosis, as well as for those in this study, are summarized in Table 2. All cases assessed (n = 17, 100%) were positive for at least one myeloid marker.

**Immunohistochemical Findings**

The results of immunohistochemical studies, including those performed at initial diagnosis, as well as for those in this study, are summarized in Table 2. All cases assessed (n = 17, 100%) were positive for at least one myeloid marker.
myeloperoxidase. Six of 10 cases (60%) were positive for CD117, but the reactivity was often dim or present in a subset of cells. Six of 9 cases (67%) assessed were positive for CD163; reactivity often varied in a subset of cells. CD11c was positive in all 5 cases assessed (100%), but highlighted only a subset of cells in 1 case. CD33 was positive in 6 of 7 cases (86%) assessed. All cases (100%) assessed for CD3 (n = 15) and CD20 (n = 15) were negative.

Other markers performed at initial diagnosis and not specifically for this study were reviewed. Markers that were positive included CD45/LCA (8 of 8 [100%], with variable intensity in 4 cases, CD4 (4 of 6 [67%]), TdT (2 of 3 [67%]), in a subset of cells), CD31 (1 of 1 [100%]), CD34 (1 of 5 [20%]), and CD56 (1 of 2 [50%]). Markers that were negative (0%) included CD30 (n = 6), κ light chain (n = 2), λ light chain (n = 2), CD8 (n = 2), CD1a (n = 1), CD2 (n = 1), CD5 (n = 1), CD7 (n = 1), CD15 (n = 1), CD45RO (n = 1), CDw75 (n = 1),

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CD79a (n = 1), CD123 (n = 1), CD138 (n = 1), PAX5 (n = 1), TCL-1 (n = 1), and anaplastic lymphoma kinase (ALK; n = 1).

**COMMENT**

In this study, 12 of 17 patients (71%) had myeloid sarcoma involving the oral cavity, indicating this site is common for myeloid sarcoma of the head and neck. This finding is in keeping with a case report and review of the literature by Pau and colleagues who tabulated 45 cases of myeloid sarcoma involving the oral cavity. In their review, the gingiva was most commonly involved by myeloid sarcoma, and that was also true in our study. Other common sites of myeloid sarcoma in the mouth are the buccal mucosa and palate. Osterne et al reported that myeloid sarcoma tends to affect women slightly more than men, but that was not the case in our study group, where 71% of patients were men. Myeloid sarcoma does not seem to show racial preference; our patient cohort was composed of white (71%; 12 of 17), African-American (18%; 3 of 17), and Hispanic (12%; 2 of 17) patients in proportions that are in keeping with the general racial composition of persons in the United States.

The clinical presentation of myeloid sarcoma is often nonspecific. In this study, patients presented with sore throat, jaw pain, sinus pain, skin lesions, tonsillar enlargement, or lymphadenopathy. In the skin, myeloid sarcoma can present as papules, nodules, or a rash. In the mouth, others have emphasized that myeloid sarcoma can mimic pyogenic granuloma, abscess, or other inflammatory processes thereby delaying biopsy and diagnosis.

In this study, in biopsy specimens from the oral cavity, we observed histologic features that can distract one from the correct diagnosis. Plasma cells can be numerous, suggesting the possibility of plasmacytoma. However, the plasma cells are cytologically bland and express polytypic immunoglobulin light chains unlike a plasma cell neoplasm. The presence of mucosal ulcer with superficial acute inflammation, often associated with plasma cells, can mimic, in part, a benign process, particularly pyogenic granuloma and chronic gingivitis. In one case, a biopsy specimen of the tongue showed myeloid sarcoma associated with pseudoepitheliomatous hyperplasia and marked plasmacytosis (Figure 2), mimicking a reactive lesion. Therefore, a high index of suspicion and recognition of immature myeloid cells associated with the reactive cells are required to establish the diagnosis of myeloid sarcoma. For patients in whom the biopsy specimen is involved by malignant neoplasm, the histologic features of myeloid sarcoma can be difficult to recognize and the differential diagnosis is broad. However, once myeloid sarcoma is considered as a potential diagnosis, immunohistochemical analysis can definitively establish the correct diagnosis. The findings in this study are in accord with the work of others that has shown that antibodies specific for lysozyme, CD43, and CD68 are highly sensitive, although not specific.

Assessment for antibodies specific for lysozyme, CD43, and CD68 are helpful but are more often negative in blastic tumors that lack granulocytic or monocytic differentiation, respectively. Based on our experience, a number of antibody panels can be designed to address the possibility of myeloid sarcoma using immunohistochemical methods. We suggest that assessing a lesion for lysozyme, CD68, and myeloperoxidase offers a good balance of sensitivity and specificity. Our results also suggest that antibodies specific for CD11c and CD33 are helpful, but only a few cases were studied. Obviously, a useful antibody panel for diagnosis of myeloid sarcoma also needs to include antibodies that will help exclude lymphomas and solid tumors.

The differential diagnosis of myeloid sarcoma in the head and neck region includes several types of malignant lymphoma (B cell and T cell); blastic plasmacytoid dendritic cell neoplasm; solid tumors, such as carcinoma and melanoma; and small blue cell tumors of childhood. The most common error is to misdiagnose cases of myeloid sarcoma as diffuse large B-cell lymphoma. This is particularly likely for cases of immature myeloid sarcoma, where no evidence of differentiation is observed. In general, the cells of diffuse large B-cell lymphoma have thick nuclear membranes and basophilic nucleoli, unlike myeloblasts or monoblasts, which have thin nuclear membranes and pinpoint nucleoli. In addition, cases of diffuse large B-cell lymphoma express pan–B-cell antigens and are negative for myeloid antigens. Myeloid sarcoma also can exhibit a prominent, starry-sky appearance with numerous apoptotic cells and mitoses and resemble Burkitt lymphoma. However, immunohistochemical studies readily distinguish myeloid sarcoma from Burkitt lymphoma because the latter is positive for pan–B-cell antigens, CD10, and BCL-6, and is negative for myeloid antigens. Some blastic cases of myeloid sarcoma can resemble lymphoblastic lymphoma/leukemia. The presence of a starry sky pattern and expression of CD34, CD43, or TdT (although usually variable) in a subset of myeloid sarcomas also can contribute to an erroneous diagnosis. Furthermore, lymphoblastic lymphoma/leukemia can express myeloid-associated antigens, such as CD13 and CD33. In general, most cases of lymphoblastic lymphoma/leukemia involving extramedullary sites are of immature T-cell lineage, express a variety of T-cell antigens as well as CD10 and TdT (bright, often uniform), and are negative for myeloperoxidase, lysozyme, and CD68. Rarely, B-cell lymphoblastic lymphoma/leukemia also can involve tissues of the head and neck; these tumors express TdT (bright), CD10, and one or more pan–B-cell antigens and are negative for lysozyme. Rarely, cases of B-lymphoblastic lymphoma/leukemia have been reported to express myeloperoxidase, another potential diagnostic pitfall. Expression of CD43 by myeloid sarcoma might raise the possibility of peripheral T-cell lymphoma.
lymphoma cases are positive for a variety of pan–T-cell antigens. Rarely, cases of myeloid sarcoma, particularly monocytic tumors, can be composed of larger cells with folded nuclear contours that can resemble, at least in part, hallmark cells, as are observed in anaplastic large cell lymphoma (Figure 7). However, anaplastic large cell lymphoma is a T-cell neoplasm that is uniformly and brightly positive for CD30 in a membranous and Golgi pattern. In addition, a large subset of anaplastic large cell lymphoma cases are positive for ALK. Although CD30 is uncommonly positive in myeloid sarcoma cases, myeloid sarcomas lack the uniform and membranous pattern of CD30 expression.

Blastic plasmacytoid dendritic cell neoplasm, also known as CD4+, CD56+ hematodermic neoplasm, is a rare disease that commonly involves skin and can involve regional lymph nodes and other systemic sites. Histologically, the blastic plasmacytoid dendritic cell neoplasm is composed of medium-sized, monotonous, blastlike cells, with a high mitotic rate. These cells are positive for CD4, CD56, CD123, CD303/BDCA-2, and TCL-1, and variably express TdT. Cases of blastic plasmacytoid dendritic cell neoplasm are invariably negative for myeloperoxidase, which is very helpful in the differential diagnosis. For blastic plasmacytoid dendritic cell neoplasms in which myeloperoxidase is negative, Cronin and colleagues19 suggested recently that a panel of antibodies specific for CD4, CD56, CD123, and TCL-1 is useful, although not completely specific, for the differential diagnosis.

Poorly differentiated carcinoma can be considered in the differential diagnosis because the mouth is a common site of carcinomas and cases of myeloid sarcoma with monocytic differentiation can exhibit a single-file pattern of infiltration that mimics adenocarcinoma.20 Expression of keratin and differentiation can exhibit a single-file pattern of infiltration differential diagnosis because the mouth is a common site of differential diagnosis. TCL-1 is useful, although not completely specific, for the panel of antibodies specific for CD4, CD56, CD123, and CD303/BDCA-2, and TCL-1, and variably express TdT. Myeloid sarcoma needs to be remembered in the differential diagnosis of poorly differentiated tumors involving the head and neck region. Harris NL, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: IARC Press; 2008:140–141.


