Diagnostic confusion resulting from CD56 expression by cutaneous myeloid sarcoma

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Abstract

Myeloid sarcomas are tumor masses composed of aggregates of malignant myeloid precursors in extramedullary sites including the skin. We report a case of myeloid sarcoma in a patient who presented with an ear lobe mass and facial nerve paralysis. Expression of CD56 by the malignant cells led to an initial misdiagnosis as Merkel cell tumor. Comprehensive pathological evaluation confirmed the diagnosis of myeloid sarcoma with aberrant expression of CD56 and carrying the translocation t(8;21) (q22;q22). Aberrant antigen expression by cutaneous myeloid sarcomas can cause diagnostic confusion with other cutaneous neoplasms. This is especially relevant when myeloid sarcoma is the sole manifestation of acute myeloid leukemia.

Introduction

Certain hematopoietic neoplasms have a tendency to involve the skin. Of these the most common are CD4+/CD56+ hematodermic neoplasms (previously termed blastic natural killer (NK) cell lymphoma), myeloid sarcomas, nasal-type extranodal natural killer/T-cell lymphoma, and cutaneous T-cell lymphomas.[1] The term myeloid sarcoma refers to tumors composed of aggregates of immature leukemic myeloid precursors in extramedullary sites.[2] Myeloid sarcomas with the chromosomal translocation t(8;21) frequently express non-myeloid antigens including CD2, CD19, and CD56. Myeloid sarcomas involving the skin are a frequent cause of misdiagnosis when they express aberrant non-myeloid antigens and when the underlying leukemia is not overt. We report a case of CD56-expressing myeloid sarcoma that was misdiagnosed as Merkel cell carcinoma, and discuss the diagnostic approach toward CD56 expressing cutaneous tumors.

Case Report

A 61-year-old woman presented to her physician with a left ear lobe skin nodule, left facial nerve palsy, and deafness. Biopsy of the ear lobe lesion was interpreted initially as Merkel cell carcinoma. She was referred to our institution for further evaluation and treatment. Her past history was relevant for acute myelogenous leukemia (AML) for which she had received chemotherapy and was in remission. Imaging studies performed in our institution showed a soft tissue mass involving the left mastoid space and extending into the posterior middle cranial fossa. In addition a paravertebral mass extending from the third to sixth thoracic vertebra was noted.

The biopsy specimen from the ear lobe mass was received for consultation from the referring hospital and revealed a diffuse proliferation of atypical mononuclear cells within the dermis with an intact epidermis (Figure 1A). These cells were medium to large and had moderate amounts of cytoplasm, irregular nuclear contours, and finely dispersed chromatin (Figure 1B). Immunohistochemical stains showed the tumor cells to express myeloperoxidase (MPO) (Figure 1C). In addition they were positive for CD45 (leukocyte common antigen), CD43, CD117, CD34 (Figure 1D), and CD56 (Figure 1E). They were negative for CD20 and CD3. A diagnosis of myeloid sarcoma was made. Fluorescent *in situ* hybridization (FISH) studies were performed on the skin lesion using dual-color DNA probes: Spectrum Orange-labeled LSI RUNX1T1 (8q22) probe and Spectrum Green-labeled LSI RUNX1 (21q22) probe to identify the t(8;21) fusion signals (Abbot Molecular/Vysis, Des Plaines, IL).[3] The cells analyzed were positive for the reciprocal translocation t(8;21)(q22;q22) (Figure 1F).

A concurrent bone marrow biopsy showed a hypercellular bone marrow involved by acute myelogenous leukemia with t(8;21)(q22;q22). She received myeloablative conditioning chemotherapy and an allogeneic hematopoietic stem cell transplant, following which she developed persistent pancytopenia and died from sepsis.

Discussion

Our case highlights a pitfall in the diagnosis of cutaneous myeloid sarcomas that express CD56, a non-myeloid antigen. CD56 or neural cell adhesion molecule (NCAM) is a cell membrane protein involved in adhesion of neural cells. CD56 is expressed on NK cells, on a subset of peripheral $CD8^+$ T-cells, on neural or neuroendocrine cells, and on peripheral blood monocytes.[4,5] Hematopoietic and non-hematopoetic neoplasms that express CD56 can involve the skin. Cutaneous non-hematopoietic tumors that are CD56 positive include Merkel cell carcinomas and metastases to the skin from other primary neuroendocrine carcinomas. Merkel cell carcinomas present as dermal nodules mainly involving the head and neck regions, with a characteristic salt-and-pepper nuclear chromatin histologically.[6-8] The tumors are CD45 negative and stain for cytokeratin 20 (CK20), CAM 5.2, and CD56. Metastatic neuroendocrine tumors to the skin have an immunophenotype similar to the primary tumor and frequently express CD56.

A review of CD56 positive hematological neoplasms presenting in the skin, conducted by the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer,[1] recognizes four different subtypes of proliferations with CD56 expression: (i) $CD4^+/CD56^+$ hematodermic neoplasms (previously designated as blastic NK-cell lymphomas); (ii) skin infiltration by CD56 positive acute myelogenous leukemia (myeloid sarcoma); (iii) nasal-type extranodal NK/T cell lymphomas; and (iv) "classical" cases of cutaneous T-cell lymphoma (CTCL) with coexpression of the CD56 molecule.

CD4 and CD56 positive hematodermic neoplasm is a recently recognized entity that originates from plasmacytoid dendritic cells (pDC), has a high incidence of skin involvement and leukemic dissemination, an aggressive clinical course, and a dismal prognosis.

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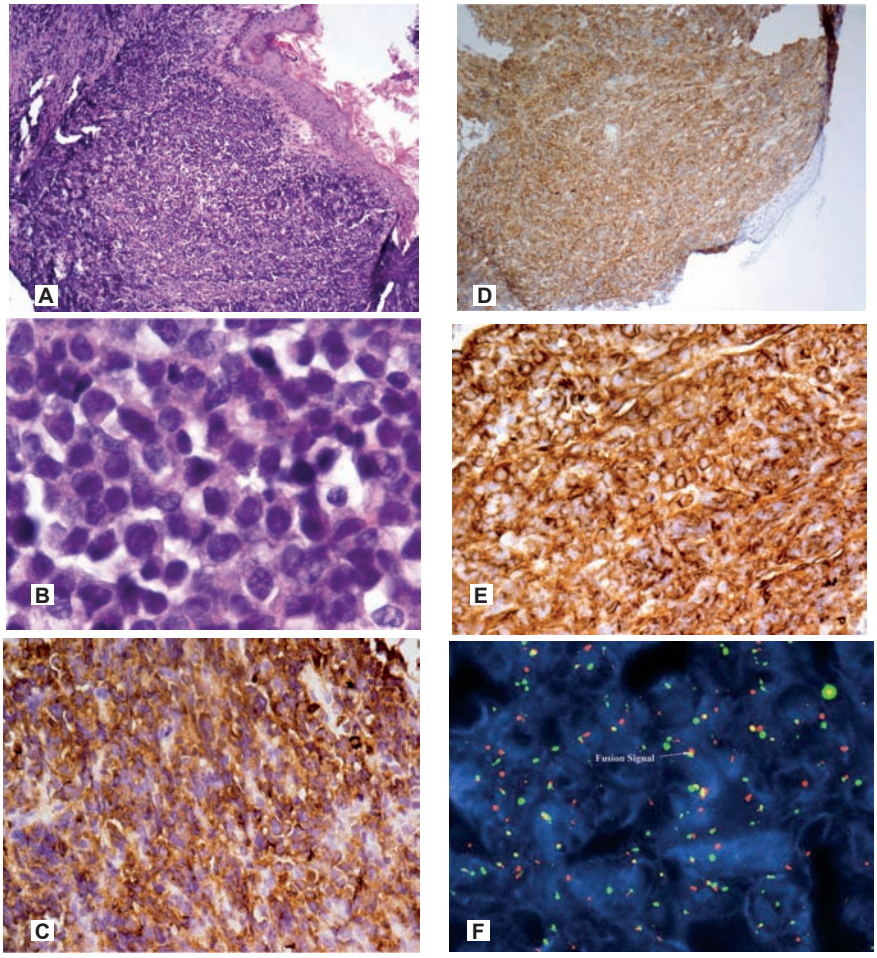

Figure 1. (A) Skin lesion from the left ear, showing intact epidermis with large mononuclear cells within the dermis (hematoxylin and eosin stain, 40X). (B) Skin lesion from the left ear, showing large mononuclear cells with fine chromatin, and moderate amounts of granular cytoplasm (hematoxylin and eosin stain, 400X). (C) Cytochemical staining for myeloperoxidase shows cytoplasmic positivity in the malignant cells (400X). (D) CD34 immunohistochemical staining shows strong positivity in the malignant cells (400X). (E) CD56 immunohistochemical staining identifies the neoplastic cells (100X). (F) FISH studies of the skin lesion 8q22 (red); 21q22 (green); fusion (yellow) signals consistent with t(8;21)(q22;22).

Extranodal NK/T cell lymphoma most commonly occurs in the nasopharngeal area and frequently shows an angiocentric growth pattern with prominent necrosis, and once was referred to as lethal midline granuloma. Most cases are associated with Epstein Barr Virus (EBV) and express cytotoxic molecules such as perforin, granzyme B, and TIA-1. Occasionally, CD56 may be expressed also by cutaneous T-cell lymphoma such as primary cutaneous CD30$^+$ lymphoproliferations, anaplastic large cell lymphomas (ALCL), and subcutaneous panniculitis-like T-cell lymphomas. Results from this study showed that CD56$^+$ cutaneous lymphoproliferative disorders, with the exception of CD56$^+$ CTCL, have a very poor prognosis.

Previous reports have highlighted the difficulty in the diagnosis of cutaneous myeloid sarcomas owing to the aberrant expression of lymphoid antigens. Kurata *et al.*[10] have described a case of a 39-year-old man who presented with a forehead cutaneous nodule that was positive for CD45 and CD56, and negative for CD3, CD20, CD34, TIA-1, and TdT. Only a limited panel of immunostains was performed, hence leading to a misdiagnosis of NK cell lymphoma. The initial biopsy specimen when re-evaluated showed expression of myeloid antigens, namely myeloperoxidase (MPO), and the diagnosis of myeloid sarcoma was made finally. Beswick *et al.*[11] described a case of a 65-year-old man who presented with a nodule on the back that was diagnosed as high-grade T-cell lymphoma by virtue of CD3 expression. He received chemotherapy and three years later developed violaceous nodules over his trunk and limbs. Biopsy of this mass and a detailed immunohistochemistry panel revealed a myeloid sarcoma that was positive for CD45, CD43, CD4, CD31, and chloroacetate esterase. The initial biopsy was reviewed and was found to be a myeloid sarcoma and not a T-cell lymphoma.

A recent report by Pileri *et al.* reviewing 92 cases of myeloid sarcomas in adults has heightened our knowledge on myeloid sarcomas. They have illustrated that the tumor cells in myeloid sarcomas most commonly expressed CD68/KP1 (100%), followed in decreasing order by myeloperoxidase (83.6%), CD117 (80.4%), CD99 (54.3%), CD68/PG-M1 (51%), CD34 (43.4%), CD56 (13%), CD61 (2.2%), CD30 (2.2%), and glycophorin A and CD4 (1.1%).[12] Chromosomal abberations were detected in about 54% of cases and monosomy 7 (10.8%), trisomy 8 (10.4%), and mixed lineage leukemia-splitting (8.5%) were the commonest abnormality.

Since detection of genetic lesions is critical for classification, prognostic stratification, and monitoring of AML, it is very important that FISH studies on the paraffin-embedded tissue for chromosomal abnormalities, namely monosomy 7, trisomy 8, 11q23 rearrangement, and t(8;21), are performed to aid in further prognostication when myeloid sarcoma is the sole manifestation of acute myeloid leukemia. This is mainly owing to the fact that since the diagnosis of myeloid sarcoma frequently is unexpected, fresh cells are not available usually for cytogenetic and/or molecular studies.

In summary, myeloid sarcoma should be considered in the differential diagnosis of cutaneous CD56 positive tumors that are CD45 positive and lack expression of cytokeratin and other neural markers.

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