Primary Intranodal Epithelioid Rhabdomyosarcoma

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Abstract

We report an unusual, rare case of primary epithelioid rhabdomyosarcoma of a lymph node in the parotid basin. A 72-year-old man with a history of squamous cell carcinoma of the forehead and cheek had a 5-cm mobile nontender mass of the parotid tail and right level II region. A positron emission tomography/computed tomography scan confirmed a hypermetabolic soft tissue mass in the right parotid gland. Histologic sections showed an intraparotid lymph node almost completely effaced by a centrally necrotic malignant epithelioid neoplasm consisting of uniform-appearing dyshesive cells exhibiting rhabdoid morphologic features with abundant eosinophilic fibrillary cytoplasm, eccentric nuclei, and prominent nucleoli. Bizarre cells were not seen. In immunohistochemical studies, neoplastic cells expressed desmin and myogenin. Electron microscopy showed a mixture of thick and thin filaments, primitive Z-band formation, and well-formed sarcomeres. Fluorescence in situ hybridization studies for FOXO1, PAX3, and/or PAX7 rearrangements were negative. An extensive clinical and radiologic workup showed no evidence of primary tumor elsewhere. Complete resection of the tumor was performed, and adjuvant chemotherapy was given; patient was disease free 12 months after surgery.

Sarcomas occurring primarily in lymph nodes are exceedingly rare events. With the exception of histiocytic sarcoma, Langerhans cell sarcoma, follicular dendritic cell sarcoma, interdigitating dendritic cell sarcoma, and dendritic cell sarcoma not otherwise specified known to occur within lymph nodes,1 only a few others are known to occur in lymph nodes. Kaposi sarcoma constitutes by far the largest number of cases of primary lymph nodal involvement, and cases are known to occur in the setting of both immunocompetent and immunocompromised immunologic states.2-9 There have been sentinel reports in the literature of leiomyosarcoma, epithelioid hemangioendothelioma, and schwannoma developing solely within lymph nodal tissue.10-12

Rhabdomyosarcoma occurs mainly in children and young adults (typically the embryonal and alveolar types) and is rare in adults (usually the pleomorphic type).13 Alveolar rhabdomyosarcoma not infrequently manifests with nodal metastasis, although a primary site is generally identified during further workup. Adult rhabdomyosarcomas constitute a small percentage of soft tissue sarcomas (~2%-5%) that exhibit variable morphologic features in adults and, besides the pleomorphic variant, include other rarer types such as sclerosing rhabdomyosarcoma and the epithelioid variants.14-17 The existence of the epithelioid type was only recently characterized and known to have a predilection for older adults in a short series.17 Two of the cases reported in the series (in a platform presentation) had nodal disease for which no other primary sites were identified.17 We report an unusual case of primary intranodal epithelioid rhabdomyosarcoma occurring in the parotid basin, a tumor that could easily be mistaken for other neoplasms such as poorly differentiated carcinoma or melanoma.
Case Report

A 72-year-old man had a mass in an antero-inferior position in relation to his right ear that had been progressively enlarging for 5 months. The specimen from a fine-needle aspiration done at an outside institution was diagnosed as non–small cell carcinoma. His medical history was significant for squamous cell carcinoma of the right side of the forehead and right cheek that was treated with excisional biopsy in 2005.

Physical examination revealed a 5-cm, mobile, nontender mass involving the parotid tail and right level II region. In addition, there was a concerning 1-cm scaly brownish area within the previous cheek cancer excision site. The forehead excision site contained a 2- to 3-cm well-healed scar without any worrisome skin changes.

A staging positron emission tomography/computed tomography scan Image II showed a hypermetabolic soft tissue mass adjacent to the right parotid gland with a peak standard uptake value of 11.0. It was unclear whether the mass was arising from within the parotid parenchyma or adjacent to the gland inferiorly. There was no adjacent cervical lymphadenopathy.

The patient underwent right superficial parotidectomy with facial nerve dissection and right supraomohyoid neck dissection. In addition, 2 small excisional biopsies of “suspicious” skin lesions in the temporal and preauricular area were done.

Materials and Methods

Pathologic Studies

The resected specimen was fixed in 10% formaldehyde, embedded in paraffin, sectioned, and stained with H&E. An extensive panel of immunohistochemical stains were done using commercially available antibodies, steam-induced epitope retrieval, and the DAKO EnVision detection system (DAKO, Carpinteria, CA) on paraffin-embedded sections. The antibodies included desmin (D33, dilution 1:100; DAKO), myogenin (F50, dilution 1:100; DAKO), HHF-35 (HHF-35, dilution 1:150; DAKO), CD10 (56C6, dilution 1:150; Novocastra, Newcastle upon Tyne, England), vimentin (V9, dilution 1:200; DAKO), S-100 (rabbit polyclonal, dilution 1:3,000; DAKO), HMB-45 (HMB45, dilution 1:50; DAKO), Melan-A (A103, dilution 1:100; DAKO), pancytokeratin cocktail (combination of AE1, Cam5.2, and MAK-6, dilution 1:100; DAKO, Becton Dickinson [San Jose, CA], and Zymed [South San Francisco, CA], respectively), p63 (4A4, dilution 1:80; DAKO), smooth muscle actin (SMA; 1A4, dilution 1:200; DAKO), calponin (Calp, dilution 1:100; DAKO), renal cell carcinoma (PN-15, dilution 1:30; Cell Marque, Rocklin, CA), and MOC-31 (MOC-31, dilution 1:40; DAKO).

Ultrastructural Examination

Representative portions of tumor fixed in 3% glutaraldehyde were selectively sent for electron microscopic examination.

Fluorescence In Situ Hybridization

To determine the presence or absence of FOXO1, PAX3, and PAX7 rearrangements, bicolor fluorescence in situ hybridization studies were performed on 4-μm-thick unstained tissue sections of lesional tissue using the Vysis LSI FOXO1 dual-color break-apart probe (Abbott Molecular, Des Plaines, IL) and custom-designed PAX3 and PAX7 break-apart probe sets as previously described. Briefly, the PAX3 and PAX7 break-apart probes were directly labeled by nick translation with SpectrumGreen or SpectrumOrange-dUTP using a modification of the manufacturer’s protocol (Abbott Molecular). After pretreatment of the slides, the cells and probes were codenatured at 75°C for 1 minute and incubated at 37°C overnight using the HYBrite instrument (Vysis). Posthybridization washing was performed in 0.4× saline sodium citrate (SSC)/0.3% NP-40 at 72°C for 2 minutes, followed by 2× SSC/0.1% NP-40 at room temperature for 1 minute. The slides were air dried in the dark and counterstained with 4’,6-diamidino-2-phenylindole (DAPI II, Vysis). Hybridization signals were assessed in 200 interphase nuclei with strong and well-delineated signals by 2 molecular pathologists. Images were acquired by use of the CytoVision Image Analysis System (Applied Imaging, Santa Clara, CA).
Results

Pathologic Findings

The resection specimen consisted of a 7.9 × 3.5 × 2.7-cm parotid gland with a 3.6 × 3.2 × 2.8-cm well-circumscribed nodular mass at the parotid tail. Grossly, the mass was soft, tan-gray, hemorrhagic, and focally necrotic. The remainder of the parotid parenchyma was unremarkable.

Histologic sections showed a circumscribed intraparotid lymph node with near replacement of the nodal parenchyma by a malignant epithelioid neoplasm consisting of dyshesive cells with abundant eosinophilic fibrillary cytoplasm, eccentric nuclei imparting rhabdoid-like morphologic features (although perinuclear cytoplasmic inclusions were absent), prominent nucleoli, and punctuated by areas of coagulative tumor necrosis Image 2A, Image 2B, and Image 2C. Mitosis was estimated at approximately 6 per 10 high-power fields (×400).

In immunohistochemical studies, the neoplastic cells were uniformly positive for desmin, myogenin, HHF-35, CD10, and vimentin and negative for S-100, HMB-45, Melan-A, pancytokeratin cocktail, p63, SMA, calponin, renal cell carcinoma, and MOC-31 Image 2D and Image 2E. Ultrastructurally, the tumor cells had a mixture of intermediate thin and thick filaments, thick filament ribosomal complexes, primitive Z-band formation, and even well-formed sarcomeres. Primitive intercellular junctions were also noted. These findings are diagnostic of rhabdomyosarcoma Image 2F.

Fluorescence in situ hybridization studies using the Vysis LSI FOXO1 dual-color break-apart probe and custom-designed FOXO1, PAX3, and PAX7 break-apart and/or spanning probe sets for the PAX3-FOXO1, PAX7-FOXO1, or PAX3 variant fusions characteristic of alveolar rhabdomyosarcoma were negative. Three additional intraparotid nodes were positive for isolated tumor clusters. The specimen from the right side of the neck contained another 4 lymph nodes that had no evidence of tumor. Both skin biopsy specimens were consistent with actinic keratosis.

Additional workup included magnetic resonance imaging of the head and neck that showed that brain parenchyma, intraorbital contents, and paranasal sinuses were all normal in appearance. The nasopharynx and oropharynx were also unremarkable. A testicular ultrasound performed to evaluate for possible germ cell tumors was also within normal limits, revealing only a small inguinal hernia. Thus, no primary site of tumor origin was identified.

Adjuvant chemoradiation treatment with the protocol of vincristine, dactinomycin, cyclophosphamide, and mesna in combination was successfully completed. At 12 months after surgery and chemoradiation, the patient was alive and well without evidence of recurrence.

Discussion

Rhabdomyosarcoma is the most common primary sarcoma in children, commonly occurring as the embryonal or alveolar subtypes, which have definable molecular genetics that result in diagnostic, therapeutic, and prognostic implications. Adult rhabdomyosarcomas are extremely rare and frequently of the pleomorphic type with a predilection for the extremities. Only recently in an abstract, Jo and Fletcher described a series of 15 cases of a morphologically distinct variant of rhabdomyosarcoma, called epithelioid rhabdomyosarcoma, that are characterized by cells with abundant amorphophilic cytoplasm, minimal pleomorphism, large vesicular nuclei with prominent nucleoli, prominent necrosis, and phenotypic expression of myogenic markers. Two of the patients in the series had nodal disease with no known primary sites.

In our case, the diagnosis of epithelioid rhabdomyosarcoma was substantiated by the sheets of dyshesive epithelioid cells with copious fibrillar eosinophilic cytoplasm imparting a rhabdoid appearance to the cells, prominent vesicular nuclei, and nucleoli with diffuse reactivity for desmin, myogenin, and demonstration of Z bands on electron microscopy, similar to the cases reported by Jo and Fletcher. In view of the prominent epithelioid morphologic features and immunophenotypic expression, the differential diagnosis for this case included metastatic epithelioid rhabdomyosarcoma of soft tissue, poorly differentiated myoepithelial carcinoma, embryonal rhabdomyosarcoma (with predominant rhabdoid morphologic features), metastatic malignant melanoma, occult germ cell tumor with sarcomatous component, extrarenal rhabdoid tumor, and proximal-type epithelioid sarcoma. Although it is absolutely difficult to exclude a metastasis from an entirely occult site or a previously resected rhabdomyosarcoma of soft tissue, the results of a detailed history and extensive clinical and radiographic examinations were negative.

The diagnosis of rhabdomyosarcoma is seldom challenging, particularly in the appropriate clinical setting. However, the occurrence of primary intranodal epithelioid rhabdomyosarcoma without a known primary tumor can pose considerable diagnostic challenge because of phenotypic mimicry with other entities (as listed in the preceding text) that are far more common, leading to erroneous diagnosis and inappropriate treatment.

Malignant melanoma is by far a more common clinical scenario and could manifest as a metastatic lesion with or without known primary sites, and, not uncommonly, it can exhibit rhabdoid features with copious amelanotic eosinophilic cytoplasm. Melanomas are often positive for one or a combination of melanocytic markers (S-100, Melan-A, and HMB-45) and will be negative for myogenin, myoglobin, or myoD1.

Metastatic poorly differentiated carcinoma, such as a myoepithelial carcinoma of the salivary gland, usually exhibits
**Image 2** A, Intraparotid lymph node with replacement of the nodal parenchyma by tumor cells with focal necrotic areas (H&E, ×40). B, Low-power view of sheets of uniform epithelioid rhabdoid-appearing cells (H&E, ×100). C, High power showing mild cellular pleomorphism, rhabdoid morphologic features with copious fibrillary eosinophilic cytoplasm, prominent nucleoli, and mitosis (H&E, ×200). D, Diffuse desmin reactivity (×400). E, Scattered nuclear reactivity for myogenin (×400). F, Electron microscopy showing thick and thin filaments with prominent Z bands.
a rhabdoid (or plasmacytoid) appearance with characteristic immunophenotypic expression of pancytokeratin and myoepithelial markers (p63, calponin, and SMA). In the present case, no tumor was present in the parotid gland, and the marker immunoprofile was different.

Embryonal rhabdomyosarcoma, on rare occasions (especially in tumor recurrence after therapy), could consist of well-differentiated skeletal muscle with prominent rhabdoid morphologic features and could be extremely difficult to distinguish from epithelioid rhabdomyosarcoma. However, in those cases, the predominant cell type consists of well-differentiated skeletal muscle with an extremely low mitotic rate. Coagulative tumor necrosis and pleomorphism are not common features. In addition, embryonal rhabdomyosarcoma often occurs in the younger population, compared with epithelioid rhabdomyosarcoma, which has a predilection for older age groups. Germ cell tumors could harbor sarcomatous components that could be of any histologic type, and embryonal rhabdomyosarcoma is the most common type in the largest published series. The absence of any clinical evidence of a mass lesion in the gonadal or extragonadal sites makes this an unlikely scenario in our patient.

Malignant extrarenal rhabdoid tumor has typical rhabdoid morphologic features, thus mimicking rhabdomyosarcoma, but these tumors, besides expression of vimentin and epithelial markers and loss of INI1, are negative for the myogenic markers. Proximal-type epithelioid sarcoma is a histologic mimic of epithelioid rhabdomyosarcoma but will always show expression of epithelial markers, whereas CD34 is positive in about 50% to 60% of cases, and they also show loss of INI1 protein expression and are uniformly negative for myogenic markers.

We report the clinical, pathologic, and molecular genetic features of a case of primary intranodal epithelioid rhabdomyosarcoma occurring in the parotid nodal basin of an elderly man. A high index of suspicion, expanding the differential diagnosis of rhabdoid-appearing cells with eosinophilic fibrillar cytoplasm to include malignant mesenchymal tumors such as rhabdomyosarcoma, and using appropriate ancillary diagnostic techniques are critical in facilitating the correct diagnosis and instituting appropriate therapy. The origin of this tumor within the lymph node is not certain, but it putatively might arise from perinodal or capsular intermediate elements or undifferentiated mesenchyme within the node. In the report of a series of epithelioid rhabdomyosarcoma, Jo and Fletcher suggest that epithelioid rhabdomyosarcoma has aggressive biologic behavior. The natural history of primary intranodal epithelioid rhabdomyosarcoma remains to be established.

References