Adamantinoma-Like Ewing Sarcoma Mimicking Basal Cell Adenocarcinoma of the Parotid Gland: A Case Report and Review of the Literature

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Abstract Adamantinoma-like Ewing sarcoma (AES) is a rare variant of the Ewing family of tumors that resembles classic adamantinoma of bone. AES shows epithelial differentiation and a more complex immunohistochemical expression profile with keratin and basal marker immunoreactivity and can resemble a variety of carcinomas. We report an unusual case of an AES of the parotid gland that mimicked a basal cell adenocarcinoma. Like basal cell adenocarcinoma, this AES showed a nested basaloid proliferation with peripheral palisading in tumor nests with ‘basaloid’ epithelial differentiation as highlighted by cytokeratin AE1/3 and p40 positivity. However, unlike most basal cell adenocarcinomas, this tumor demonstrated high grade morphology, showed no true ductal or myoepithelial component, and also showed a tendency towards neuroectodermal phenotype with focal rosette formation, CD99 and weak synaptophysin immunoreactivity. *EWSR1* and *FLII* fluorescence in situ hybridization confirmed the presence of a translocation supporting the diagnosis of AES. This is the first case of AES presenting as a primary

parotid mass highlighting the potential to be mistaken for primary salivary gland carcinomas, which in addition to basal cell adenocarcinoma include other basaloid tumors such as adenoid cystic carcinoma.

Keywords Adamantinoma-like · Ewing sarcoma · Parotid · Basal cell adenocarcinoma

Introduction

Mesenchymal tumors are infrequently encountered in the salivary glands, and sarcomas represent only the 0.3–1.5 % of salivary gland malignancies [1]. A recently published review of the literature between 1990 and 2010 yielded 170 case reports of malignant mesenchymal tumors arising in salivary glands that affected patients with a median age of 39 years. The majority of these tumors, 82 %, involved the parotid gland and rhabdomyosarcoma was found to be the most common tumor [1]. Although far less common at this site, Ewing family of tumors (EFT), which include Ewing sarcoma (ES)-primitive neuroectodermal tumor (PNET) spectrum of small blue round cell malignancies have also been reported in children and adult patients [2–4].

Classic ES consist of a sheet-like vaguely lobular growth pattern of monomorphic round blue cells with a rich capillary network while typical PNET morphology has more prominent rosette formation. Aside from these, 9–20 % of tumors may demonstrate variant morphologies [5, 6], which include: large cell ES, ES/PNET with hemangioendothelial features, synovial sarcoma-like ES, sclerosing ES and adamantinoma-like ES. Adamantinoma-like ES (AES) is quite rare, particularly in pure form. Like other EFT, AES express CD99 and show *EWSR1* gene rearrangements. However, as their name would indicate

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their appearance is reminiscent of adamantinoma; specifically, tumors tend to have a nested appearance and peripheral palisading as well as desmoplasia. Furthermore, AES also express cytokeratins and ‘basal’ markers like p63, unlike the classic Ewing sarcoma [5–8]. This variant morphology can be treacherously difficult to recognize in sites such as salivary gland where primary basaloid neoplasms are far more common. We report a unique case of AES that mimicked a basal cell adenocarcinoma of the parotid.

Methods

Formalin-fixed paraffin-embedded 4 μ m-thick tissue sections received in the context of a consult to one of the authors (RRS) were initially evaluated with routine hematoxylin and eosin (H&E) stain. Further evaluation was performed with periodic acid-Schiff diastase (PASD) stain and immunohistochemistry (IHC) for α -smooth muscle actin (α SMA) (prediluted solution; Cell Marque, Rocklin, CA), androgen receptor (1:100; Dako, Carpinteria, CA), AE1/AE3 (1:100, Dako), β -catenin (1:250, Dako), CD99 (1:75, Dako), chromogranin (prediluted solution; Ventana, Tucson, AZ), cytokeratin 20 (1:50, Dako), cytokeratin 7 (1:200, Dako), desmin (prediluted solution, Ventana), DOG1 (1:50; Zeta Corporation, Sierra Madre, CA), lymphoid enhancer-binding factor 1 (LEF-1) (1:10, Epitomics, Burlingame, CA), p16 (INK4a) (prediluted solution, Ventana), p40 (Δ Np63) (1:1,000; Calbiochem, Darmstadt, Germany), S100 (1:500, Dako), synaptophysin (prediluted solution, Cell Marque), and thyroid transcription factor-1 (TTF-1) (1:50, Dako). HPV detection by in situ hybridization (ISH) was performed using probes targeting HPV subtypes 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, and 52 (Y1404, Dako). High risk HPV detection was performed with Inform HPV III Family 16 Probe (B) (780-4295, Ventana) Human Papillomavirus DNA probe cocktail, with affinity to HPV subtypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 66. Fluorescence in situ hybridization (FISH) on interphase nuclei from paraffin-embedded 4- μ m sections was performed applying custom probes using bacterial artificial chromosomes (BAC), covering and flanking *EWSR1* in 22q12, and *FLII* in 11q24. BAC clones were chosen according to USCS genome browser (<http://genome.uscs.edu>). The BAC clones were obtained from BACPAC sources of Children’s Hospital of Oakland Research Institute (Oakland, CA; <http://bacpac.chori.org>) (Supplemental table 1). DNA from individual BACs was isolated according to the manufacturer’s instructions, labeled with different fluorochromes in a nick translation reaction, denatured, and hybridized to pretreated slides. Slides were then incubated, washed, and mounted with

Fig. 1 CT scan of the neck. Poorly delimited mass (arrow) concerning for malignancy arising in the posterior aspect of the superficial lobe of the left parotid

DAPI in an antifade solution, as previously described [9]. The genomic location of each BAC set was verified by hybridizing them to normal metaphase chromosomes. Two hundred successive nuclei were examined using a Zeiss fluorescence microscope (Zeiss Axioplan, Oberkochen, Germany), controlled by Isis 5 software (Metasystems). A positive score was interpreted when at least 20 % of the nuclei showed a break-apart signal.

Case Report

A fifty-six year-old female presented with a two-week history of a painless, palpable mass in the left side of the neck. On radiological evaluation, an ill-defined mass measuring 2.5 cm in greatest dimension was identified in the posterior aspect of the superficial lobe of the left parotid gland (Fig. 1). Fine needle aspiration biopsy revealed a basaloid neoplasm concerning for carcinoma. A left total parotidectomy with facial nerve dissection was subsequently performed and the specimen submitted to Pathology.

Gross evaluation revealed a poorly demarcated fibrotic white–gray lesion involving and infiltrating tan lobular parotid tissue. Microscopic examination of the lesion demonstrated a predominantly nested basaloid proliferation infiltrating the parotid accompanied by desmoplasia (Fig. 2a). There was angiolymphatic and perineural invasion in addition to extraparotid extension to margins. Many

Fig. 2 Adamantinoma-like Ewing sarcoma arising in parotid gland. Desmoplastic stroma surrounds tumor cells arrayed in nests and cords that replace most of the gland tissue (**a**) showing peripheral palisading (**b**) and occasionally presenting rosette-like structures (**c**; *arrows, rosettes*). The tumor is composed of cells with round nuclei, finely granular chromatin and eosinophilic cytoplasm (**d**). Synaptophysin shows weak, patchy cytoplasmic staining in tumor cells (**e**). Pankeratin is strong and diffusely positive in tumor, myoepithelial and ductal cells (**f**). p40 is positive in myoepithelial cells and most tumor cells (**g**). CD99 shows varying degrees of membrane positivity in tumor cells (**h**) (original magnifications: **a** $\times 100$; **b** $\times 200$; **c–h** $\times 400$)

of the tumor nests showed peripheral palisading (2b) reminiscent of a basal cell adenocarcinoma. However, no true ducts were noted though there were several compressed pseudorosettes (Fig. 2c). At higher power, tumor nests consisted of monomorphic cells with scant cytoplasm and occasional streaming of nuclei. Up to seven mitoses per ten high power fields were noted. Nuclei contained finely granular chromatin and occasional prominent nucleoli (Fig. 2d). No areas of necrosis were found.

Immunohistochemical stains showed weak expression of synaptophysin by subsets of tumor cells (Fig. 2e) while AE1/AE3 (Fig. 2f), p40 (Fig. 2g), and p16 were positive in the majority of the neoplastic cells. CD99 was diffusely expressed by tumor cells, though in varying degrees of intensity (Fig. 2h). Cytokeratins 7 and 20, desmin, α SMA, TTF-1, LEF-1, DOG1, androgen receptor, chromogranin and S100 were negative in tumor cells. β -catenin showed only membranous staining with no nuclear accumulation.

Fig. 3 FISH. Separation of green and red fluorescent signals indicate rearrangement in the *EWSR1* (a) and *FLII* (b) genes

A PAS after diastase was negative and showed no evidence of mucin or intracytoplasmic zymogen granules. In situ hybridization for HPV DNA was negative. FISH for both the *EWSR1* and *FLII* gene rearrangements were positive supporting the presence of a translocation (Fig. 3).

A month after the initial resection, a positron emission tomography (PET) scan was performed and showed no residual tumor. The patient was then scheduled for alternating cycles of adriamycin + cytoxan + vincristine and ifosfamide + etoposide in addition to radiation.

Discussion

Sarcomas of the parotid, both primary and secondary are rare but can potentially mimic various primary salivary gland tumors. While as expected, most spindle cell lesions will show morphologic overlap with pleomorphic adenoma or myoepithelioma, small blue round cell tumors will evoke other salivary tumor types and may also raise consideration for metastases.

The leading differential diagnostic consideration in this case was basal cell adenocarcinoma. Basal cell adenocarcinoma is the malignant counterpart of basal cell adenoma and is typically a tumor of adulthood with the parotid gland being the major site of involvement. Like basal cell adenoma, basal cell adenocarcinoma may demonstrate tubular, trabecular, solid and membranous (dermal analogue) morphologies, though the solid growth pattern is more common. Basal cell adenocarcinomas also tend to have peripheral palisading in tumor nests, and may show true squamous and sebaceous elements [10–12]. It is, thus, understandable that AES presenting in the parotid may masquerade as a basal cell adenocarcinoma, which would statistically be more prevalent. However, most basal cell adenocarcinomas are low grade, and unlike this current case, do not have a highly infiltrative growth pattern or high mitotic rate. This aggressive appearance is in fact what prompted us to consider something other than basal cell adenocarcinoma. Additionally, basal cell adenocarcinomas are ‘biphasic’ salivary tumors with a distinct ductal component of varying prominence [13]. Our case did not

demonstrate true ducts, morphologically or immunophenotypically. Also, basal cell adenocarcinomas often have a myoepithelial subpopulation (typically the outermost palisaded layer of cells in tumor nests), which could not be demonstrated here. Finally, unlike our case, many basal cell adenomas and adenocarcinomas can show nuclear β -catenin reactivity [14].

Along these lines, other basaloid salivary gland malignancies can be considered as well. The most relevant among these would be solid patterned adenoid cystic carcinoma. This is the most aggressive of the growth patterns in conventional adenoid cystic carcinoma, and can be considered a small blue round cell tumor with a potentially highly infiltrative growth similar to our case. However, peripheral palisading is generally not a feature of solid adenoid cystic carcinoma, and adenoid cystic carcinoma also is a biphasic tumor with a peripheral myoepithelial layer and solid ductal overgrowth more centrally. Furthermore, even solid adenoid cystic carcinoma typically shows the characteristic myxohyaline stroma surrounding tumor nests, if not within nests as seen in cribriform adenoid cystic carcinoma [13].

Aside from primary tumors, metastatic squamous cell carcinoma to the parotid, often originating at cutaneous sites and involving intraparotid lymph nodes, can be considered [15]. While a majority of tumors are keratinizing, pleomorphic and moderately to poorly differentiated [16], metastatic squamous cell carcinoma from an oropharyngeal primary site may also present in the parotid and show a deceptively ‘basaloid’ and monomorphic appearance reminiscent of our case. In a series of 1,500 cases of oropharyngeal squamous cell carcinoma only 0.8 % metastasized to the parotid [17]. But conversely, these tumors have been reported to represent up to 10 % of all metastatic disease at this site [18]. Our case was additionally p16 positive which added further confusion since p16 is often used as a surrogate marker for oncogenic high risk HPV. However, the diffuse expression of CD99 and the presence of pseudorosettes were helpful in delineating our AES from an oropharyngeal squamous cell carcinoma metastasis, and indeed in situ hybridization for HPV was negative.

As with any small blue round cell tumor, the possibility of a neuroendocrine neoplasm, primary or metastatic (e.g. Merkel cell carcinoma), needed to be ruled out although the occurrence of these tumors in the parotid gland is certainly rare [19]. Here, the immunohistochemical stains played an important role, showing no reactivity for chromogranin with only weak staining for synaptophysin. Other round blue cell sarcomas can be considered as well, specifically, desmoplastic small round cell tumor. Although desmoplastic small round cell tumor is not common outside of the abdominal cavity, it has also been reported involving the parotid gland [20]. The tumor cells in this entity are similar to those of ES, and like our case the stroma is characteristically desmoplastic (hence the name). These tumors are also characterized by *EWSR1* rearrangement, but with *WT1* as a translocation partner [21, 22]. However, in our case the tumor was negative for desmin, and the translocation partner here was confirmed to be *FLII*.

Finally, as a technicality, a poorly differentiated version of hyalinizing clear cell carcinoma may be conjectured as a potential pitfall since both this entity and AES have *EWSR1* translocations. Hyalinizing clear cell carcinoma is a primary salivary gland tumor characterized by a nested clear cell to eosinophilic proliferation of squamoid cells embedded in a mixed hyaline and desmoplastic stroma [23]. The hyalinization is typically peritumoral and sharply delineated from the remainder of the intervening fibrocellular stroma. Most tumors are low grade and clear to eosinophilic in appearance but high-grade transformation may occur [24]. In our case the absence of any typical hyalinizing clear cell carcinoma stromal or cytonuclear features, the CD99 reactivity, pseudorosette formation and ultimately the presence of a *FLII* partner excluded hyalinizing clear cell carcinoma, which shows *ATF1* as *EWSR1* translocation partner.

Similar to other EFTs, AES were initially described to mainly affect the long bones of the extremities and only rarely other areas like the head and neck [7, 25–27]. However, cases genotypically and phenotypically compatible with this tumor have also been reported to affect soft tissue and even viscera with or without associated osseous involvement [5, 28–30]. Interestingly, two of these cases arose in the soft tissue of the neck affecting the vagus nerve [28, 29]. As these cases would imply, not all EFT fit cleanly into one histologic subtype. For instance even in our case, there were PNET like areas and few vaguely spindled areas as well.

In summary, we describe a rare parotid AES mimicking the appearance of salivary basal cell carcinoma as a potential pitfall. It is thus important to recognize the spectrum of EFT involving the parotid so they can be considered when the morphologic and immunohistochemical criteria

for the usual spectrum of basaloid salivary gland malignancies are not met.

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