Primary Intraosseous Adenoid Cystic Carcinoma with Widespread Skeletal Metastases Showing Features of High-Grade Transformation

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Abstract

Malignant salivary gland carcinomas arising primarily within the jaw bones are extremely rare. The most common salivary malignancy in these locations is mucoepidermoid carcinoma followed by adenoid cystic carcinoma and adenocarcinoma. The clinical picture and imaging studies of these malignancies may be confused with odontogenic lesions which are more common in this location. Adenoid cystic carcinomas have a prolonged clinical course, tendency for perineural invasion and distant metastasis and multiple recurrences. The diagnosis of these tumors requires thorough histopathologic examination. Immunohistochemical studies may be required in cases showing solid growth pattern. High-grade transformation, earlier termed as dedifferentiation, has been observed in several salivary gland carcinomas including adenoid cystic carcinoma. These transformed tumors are reported to have an extremely poor prognosis. Here, we report a case of primary intraosseous adenoid cystic carcinoma with extensive skeletal metastases which showed a negative staining with p63 and positive staining with CD117. The tumor had a predominant solid growth pattern with areas indicative of high-grade transformation. A negative p63 staining may indicate an incomplete or focal loss of abluminal layer and this is one of the criteria for high-grade transformation in adenoid cystic carcinoma.

Keywords Adenoid cystic carcinoma · Salivary gland neoplasms · Head and neck neoplasms · Mandible · Humans · Female · Immunohistochemistry · Paraesthesia

Introduction

Malignant salivary gland tumors are uncommon accounting for only 3% to 5% of all head and neck neoplasms [1]. Mucoepidermoid carcinoma and adenoid cystic carcinoma (ACC) are the commonly seen salivary gland malignancies. Salivary gland carcinomas located centrally within the mandible are rare, comprising less than 0.4% of all salivary gland carcinomas [2]. Primary intraosseous adenoid cystic carcinoma (PIACC) of the jaws is extremely uncommon. ACC typically presents with slow, indolent growth, but there is a high incidence of local recurrence and metastasis, which results in the low long-term survival rate [3]. The lung and bone are the most common sites of distant spread, but the extremely slow growth pattern of the tumor and the gradual

appearance of metastasis allow patients to lead a normal life for many years [3]. We report a case of a female patient who presented with jaw swelling accompanied by pain and paraesthesia. A diagnosis of PIACC with widespread skeletal metastases was confirmed with imaging techniques and immunohistochemical studies on biopsy sample.

Case Report

A 54-year-old female patient was referred to the Oral & Maxillofacial Surgery unit of our Institution. She had a complaint of ill-fitting complete dentures due to swelling, pain and paraesthesia for three months and had visited a local dental clinic for the same. On examination, she was found to have mild expansion of mandible. Panoramic radiograph taken showed a radiolucent lesion in the angle and ramus of mandible on the right side. An incisional biopsy was done by the dental practitioner at the local clinic and a diagnosis of ameloblastoma was given. She was referred to our Institution for further treatment. On examining the patient at our

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Institution, a diffuse swelling on the right side of the face extending from the corner of mouth to the ear lobe and superiorly extending from zygomatic arch to inferiorly below the lower border of mandible was noted. The overlying skin was normal. It was firm and tender on palpation. There was paraesthesia of the lower lip on the right side along with lack of tonicity. Intraoral examination showed edentulous arch with vestibular obliteration on the right side. The overlying mucosa was normal and there was bicortical expansion.

Multi-detector computed tomography (MDCT) of neck was done and showed the presence of a lytic expansile lesion with destruction of bony cortices involving the body, ramus of mandible on the right side extending up to mandibular notch and involving the coronoid process (Fig. 1). Soft tissue density component was seen within and around the lytic lesion and extending into adjacent masseter, pterygoids and temporalis muscle on the right side. Sub-centimetric lymph nodes were seen bilaterally in Ib level and in the right I and II levels.

A repeat incisional biopsy showed the presence of fibro-collagenous tissue with an invasive neoplasm composed of cells arranged mainly in solid nests (Fig. 2), trabecular pattern, nests, cords and focal cribriform pattern (Fig. 3a, b). Cells were round to oval with uniform nuclei, fine granular chromatin, inconspicuous nucleoli and scant to moderate pale eosinophilic cytoplasm. Admixed oval to spindle shaped cells with hyper chromatic nuclei and scant cytoplasm were noted. Some of the solid islands showed comedonecrosis (Fig. 4a, b). Vascular invasion of tumor cells and invasion into the adjacent adipose tissue was also seen (Fig. 5a, b). Micropapillary growth pattern, clear cell changes, ductal pattern and desmoplasia were seen in focal areas (Fig. 6a–d). Occasional atypical mitotic figures were noted (0–1/10hpf).

Fig. 1 MDCT* showing the lytic expansile lesion with destruction of bony cortices involving the body of mandible on right side with soft tissue density component seen within and around the lytic lesion.
*Multidetector computed tomography

Fig. 2 Histologic findings of incision biopsy showing an invasive neoplasm composed of cells arranged mainly in solid nests ($\times 10$, H&E*). *Haematoxylin & eosin

A diagnosis of poorly differentiated carcinoma was given and a differential diagnosis of adenoid cystic carcinoma, polymorphous adenocarcinoma, odontogenic carcinoma NOS, basaloid squamous cell carcinoma and metastatic carcinomas were considered. Immunohistochemistry (IHC) was performed with the tumor cells showing strong positivity for CK7 and CD117 and focal positivity for S100 while CK20, synaptophysin, ER, TTF1 and p63 were negative (Fig. 7a–d). The overall histopathologic and IHC features were suggestive of PIACC with high-grade transformation. The slides of the original biopsy were reviewed and also showed a histopathologic picture composed primarily of biphasic tumor cells arranged in solid islands. The intraosseous location and the absence of a cribriform pattern may have led to an initial diagnosis of ameloblastoma especially the basal cell variant.

A whole body Position emission tomography (PET) CT imaging (head to mid-thigh) was performed on a GE Discovery PET 8 slice CT scanner and revealed flourodeoxy glucose (FDG) avid multiple lytic lesions with soft tissue component involving right temporal/sphenoid bones, entire right side of mandible along with lytic lesion involving D5 (dorsal or thoracic 5) vertebrae, sacrum and right ischium (Fig. 8a–d). Bilateral level Ib lymph nodes were noted but no other possible primary malignancy could be detected. A final diagnosis of high-grade transformation in a PIACC with widespread skeletal metastases was given. However, the patient was unwilling for any further treatment and hence, palliative care was advised.

Fig. 3 Histologic picture showing arrangement of tumor cells. **a** Arranged in nests, cords and focal cribriform pattern ($\times 5$, H&E*). **b** High power of cribriform pattern ($\times 40$, H&E*). *Haematoxylin & eosin

Fig. 4 Histologic picture showing solid islands. **a** Low power of solid islands showing comedonecrosis ($\times 10$, H&E*). **b** High power view of one island showing predominantly round to oval cells with fine granular chromatin and scant cytoplasm (arrow) admixed with

few spindle to oval cells with hyperchromatic nuclei and scant cytoplasm (arrowhead). The center of the island shows comedonecrosis (asterisk). ($\times 40$, H&E*). *Haematoxylin & eosin

Fig. 5 Histologic picture showing invasion. **a** Vascular invasion of tumor cells ($\times 20$, H&E*). **b** Invasion into the adjacent adipose tissue ($\times 20$, H&E*). *Haematoxylin & eosin

Fig. 6 Histologic picture showing special features. **a** Islands of clear cells ($\times 20$, H&E*). **b** Micropapillary growth pattern ($\times 20$, H&E*). **c** Stromal desmoplasia ($\times 5$, H&E*). **d** Ductal pattern ($\times 20$, H&E*). *Haematoxylin & eosin

Discussion

ACC was first described by Robin and Laboulbène over 150 years ago as a “tumeur heteradenique,” the name “adenoid cystic carcinoma,” (coined by Spies) was popularized by Foote and Frazell [4]. Earlier it was thought to be a benign variant of mixed salivary gland tumour and its malignant nature was emphasized by Dockerty and Mayo only in 1943 [5]. ACC is generally a slow-growing but highly malignant neoplasm with a remarkable capacity for recurrence [6]. Long-term follow-up is essential regardless of the site because ACC is prone to undergo late recurrence and metastasis. Most patients eventually develop distant metastases, mainly in the lungs and bone, despite the local control of the tumor. The natural history of ACC is characterized by slow, but relentless growth; multiple local recurrence and hematogenous dissemination mainly to the lung, liver, bone and brain [7]. The occurrence of bone metastasis usually corresponds to rapid tumor dissemination and death of the patient, whereas lung metastases demonstrate a less aggressive clinical course [6].

PIACC generally occurs in 4th to 6th decade without gender predilection [8]. The most common site involved is the posterior body and angle of mandible [2]. Pain and swelling are the most common symptoms reported followed by paraesthesia, tooth mobility and trismus [8]. Our patient was a female in the 6th decade. Though there was pain, swelling and paraesthesia, the primary complaint was the inability to wear dentures.

Radiographically, destruction of the bone with infiltrative margins is seen in most of the cases. A few cases have reported tooth resorption, expansion of bone and involvement of inferior alveolar canal [8]. Batsakis, in 1979, proposed a diagnostic criteria for central salivary gland neoplasm: (1) radiographic evidence of osteolysis, (2) presence of intact cortical plates, (3) presence of intact mucous membrane overlying the lesion, (4) absence of primary tumor in major or minor salivary glands and (5) histological confirmation of the typical architecture and morphological features of salivary gland tumor [2]. Our case fulfills all these criteria except the presence of intact cortical plates. However, as we strongly feel that the tumor originated centrally in the mandible and eroded the cortical plates, we can

Fig. 7 Immunohistochemical staining. **a** Positivity with CK7. **b** Negative staining with p63. **c** Focal staining with S100. **d** Positive staining with CD117

consider that criteria as being fulfilled. Regarding staging, some studies have suggested that PIACC should be staged on the basis of damage to the mandible, rather than tumor size, as follows: no changes in the morphology and integrity of the bone cortex surrounding the lesions and the presence of surface periosteum (stage I); intact surface of the bone cortex with a certain degree of swelling (stage II); and damage to the bone cortex, periosteum rupture, or lymph node metastasis (stage III) [1, 9]. The stage I and stage II tumors maybe mistaken for odontogenic lesions.

Histologically, ACC is a biphasic tumor composed of ductal and basal/myoepithelial components and shows three main growth patterns mainly cribriform, tubular and solid. These growth patterns forms the basis of histological grading, and the quantity of solid component is considered to be the most significant adverse prognosticator [4]. Patey and Thackray were the first to note that the solid pattern in ACC imparted a poor prognosis [10, 11]. Grading of ACC depends upon the predominant growth pattern: grade I is tubular, grade II is cribriform and grade III is solid. Generally, a tumor with greater than 30% solid component belongs in the ‘grade III’ category and it is suggested that any solid

component imparts a poor prognosis [11]. The incision biopsy of our case showed a predominantly solid growth pattern with a focal area of cribriform pattern. A diagnosis of poorly differentiated carcinoma with differential diagnosis of adenoid cystic carcinoma, polymorphous adenocarcinoma, odontogenic carcinoma NOS, basaloid squamous cell carcinoma and metastatic carcinoma were considered. Ameloblastoma was the diagnosis given at the outside institution. Central ameloblastoma is far more common than PIACC and its basal cell variant can be considered as a differential diagnosis for ACC. However, we did not consider ameloblastoma due to the presence of focal cribriform pattern in our slides which was not seen in the previous biopsy slides. Whole body imaging to rule out metastatic carcinoma and IHC studies were then done. PET imaging showed the presence of multiple lytic lesions in near and distant skeletal sites along with the mandibular lesion. The tumor stained positively with CK7 and negatively with CK20, p63, synaptophysin, ER, TTF1. This excluded basaloid squamous cell carcinoma, neuroendocrine tumors, metastatic breast, lung and thyroid carcinomas. S100 showed only focal positivity in some cells whereas in polymorphous adenocarcinoma

Fig. 8 PET* imaging studies showing lytic lesions with increased uptake in **a** right temporal/sphenoid bones. **b** Right side of mandible. **c** Right ischium. **d** Dorsal 5 (T5) vertebrae. *Positron emission tomography

strong diffuse positivity with S100 is usually seen [11]. S100 is a sensitive, but not specific, marker for myoepithelial cells [12]. Considering the presence of focal cribriform areas, focal S100 positivity and the absence of other primary site on imaging studies, ACC was considered and IHC staining with CD117 was done even though p63 was negative. The strong positivity obtained with CD117 confirmed the diagnosis of ACC. ACC usually demonstrates strong positive staining for CD117 (c-kit) and the expression is predominantly located in the inner ductal cells of the tubular and

cribriform patterns and is homogeneously expressed in the solid form [12, 13]. Molecular studies have shown that aberrations in MYB gene can be used to confirm ACC diagnosis [1]. Due to the nonavailability of MYB molecular analysis in our Institution, and also due to the patients non-affordability to be referred to another centre, molecular study was not done in this case.

p63 is expressed by the abluminal cells of normal salivary gland and it is usually expressed by the same component in conventional ACC [4, 14, 15]. High grade transformation

in salivary gland carcinomas including ACC (ACC-HGT) has been previously reported [4, 10, 16]. Cheuk et al. were the first to recognize these tumours as a distinct form of ACC, calling them “dedifferentiated ACC [4, 16]. Histologic hallmarks of this high-grade transformation in ACC are necrosis, high mitotic rate, and the loss of the biphasic ductal-myoepithelial differentiation [4]. In their study, Seethala et al. [4] have compared solid ACC with ACC-HGT and listed some criteria to differentiate between the two and recommended the presence of at least three major criteria for diagnosis of ACC-HGT. The major criteria listed by them include (1) nuclear size at least 2–3 times the size of grade I-II ACC nuclei, (2) growth in solid confluent sheets often filling a $\times 40$ high power field (hpf), (3) fibrocellular desmoplastic stroma, (4) unique features like micropapillae and squamoid areas, (5) incomplete or focal absence of abluminal layer as confirmed by IHC and (6) strong p53 expression. The minor criteria include (1) vesicular or heterogeneously dispersed chromatin, (2) thickened or irregular nuclear membrane, (3) prominent central nucleoli, (4) scant to moderate cytoplasm, (5) punctuate to large areas of comedonecrosis, (6) presence of microcalcifications, (7) mitosis of more than 10/hpf and (8) Ki 67 expression of more than 50%. They felt that the morphologic features that were unique to ACC-HGT included the presence of micropapillae and squamoid areas, fibrocellular desmoplasia, and the loss of an abluminal layer of myoepithelial cells confirmed by IHC and the presence of these features in any ACC should warrant examination for other supportive criteria of ACC-HGT. Our case satisfies 4 of the major criteria namely presence of solid confluent sheets filling a $\times 40$ hpf, fibrocellular desmoplastic stroma, presence of micropapillae and absence of abluminal layer confirmed by negative p63 IHC staining. Vesicular chromatin, scant to moderate cytoplasm and large areas of comedonecrosis were the minor criteria noted in our case. In addition, lymphovascular invasion has been frequently reported in these cases [4, 16] and was observed in our case. Thus, this case warrants a diagnosis of high grade transformation in PIACC with skeletal metastases. The pathogenesis of ACC-HGT is not well understood though studies have shown abnormalities in p53, cyclin D1 and Her2/neu [4, 17]. HGT-ACC has an exceptionally poor prognosis with a median survival ranging from 12 to 36 months and may thus be even more aggressive than solid ACC [11]. Metastasis to lymph nodes is frequent and radical surgery along with radiotherapy is considered the best treatment option. Unfortunately, due to the presence of widespread skeletal metastasis along with the patient’s unwillingness for further treatment, palliative chemotherapy was the only option in our case.

In conclusion, ACC with high grade transformation refers to the presence of a pleomorphic mitotically active high grade carcinoma component arising in an otherwise

conventional adenoid cystic carcinoma of any pattern/grade [11]. However, there is a lot of morphologic overlap between solid conventional ACC and high grade transformation and the transition from conventional adenoid cystic to high grade transformation may often be gradual. As solid PIACC is an uncommon tumour, it requires thorough evaluation to rule out high grade transformation. The presence of unique features like micropapillae and microcalcifications in addition to the large nuclear size, fibrocellular desmoplasia, large areas of comedonecrosis and high mitotic activity may serve as useful clues. The absence of p63 IHC staining can be considered as a useful diagnostic tool for ACC-HGT.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest to disclose.

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