Oral Diseases (2005) 11, 109–112

http://www.blackwellmunksgaard.com

CASE REPORT

Bilateral intraosseous adenoid cystic carcinoma of the mandible: report of a case with lung metastases at first clinical presentation

S Capodiferro[1], C Scully[2], MG Lacaita[1], L Lo Muzio[3], E Maiorano[4], G Favic[1]

[1]*Department of Dental Sciences and Surgery, University of Bari, Bari, Italy;* [2]*Eastman Dental Institute for Oral Health Care Sciences, University College London, London, UK;* [3]*Institute of Dental Sciences, Università Politecnica delle Marche, Ancona, Italy;* [4]*Department of Pathological Anatomy and Genetics, University of Bari, Bari, Italy*

OBJECTIVE: Malignant epithelial tumours arising in the jaws are very rare. Adenoid cystic carcinoma (ACC) represents approximately 7.5% of all carcinomas and only a few cases of intraosseous (central) ACC have been reported in the literature.

MATERIALS: The salient clinico-pathological features of a case of ACC, bilaterally occurring in the mandible of a young caucasian woman who also had lung metastases are reported to appropriately characterize such unusual lesions and discriminate them from other tumours that more commonly affect the mandible.

RESULTS: The patient presented with a painful swelling of the right retro-molar area and paraesthesia of the ipsilateral lower lip and radiological investigations disclosed bilateral radiolucent lesions of the mandible with unequivocal signs of malignancy but without intra-lesional calcifications or association with teeth roots or cystic component. Conventional histological examination disclosed typical ACC with solid and cribriform growth patterns and extensive infiltration of the adjacent tissues.

CONCLUSIONS: The diagnosis of intraosseous malignant salivary gland type neoplasms is very difficult in view of their rarity and lack of specific signs and mainly achieved after histological examination and complete clinico-radiological work up. As surgical treatment of the patient was not indicated, due to extensive neoplastic disease, the patient is being controlled with multimodal treatment, including chemo- and radiotherapy and is alive with persistent disease 3 years after the original diagnosis.

Oral Diseases (2005) **11**, 109–112

Keywords: adenoid cystic carcinoma; salivary gland tumours; intra-osseous carcinoma; multifocal tumours; head and neck

Correspondence: Dr Saverio Capodiferro, Department of Dental Sciences and Surgery, University of Bari - piazza Giulio Cesare, 11, 70124 Bari, Italy. Tel.: +39 (080) 5478155, Fax: +39 (080) 5520505, E-mail: saveriocapodiferro@libero.it
Received 5 June 2004; revised 15 July 2004; accepted 2 August 2004

Introduction

Adenoid cystic carcinoma (ACC), originally described as 'cylindroma' by Billroth (1859), is a malignant epithelial tumour characterized by slow growth, late onset of metastasis and poor prognosis. It represents the fifth most common epithelial tumour of the salivary glands (Waldron *et al*, 1988; Ellis and Auclair, 1996), the parotid gland, the sub-mandibular gland and the palate being the most common locations.

Haematogenous metastases most frequently develop from ACCs showing cribriform and solid architecture, usually a few years after the onset of the primary tumour, and are mainly localized in bones and lungs. Very rarely, ACC may arise centrally within the jawbones, usually in the posterior mandible of adults, presenting with pain, due to the perineural infiltration (Blanchard *et al*, 1998; Favia *et al*, 2000). In such instances, the clinico-radiological features may be equivocal and usually lead to the provisional diagnosis of malignant bone tumour, unless preoperative cyto-histological examinations are performed.

Aim of this study is to report on the clinical, radiological and histopathological features of a case of ACC occurring bilaterally within the mandible of an adult caucasian woman who also showed multiple lung metastases at first clinical observation, to possibly highlight the differential diagnostic features that may help to properly identify such an entity.

Case report

A 36-year-old female was admitted with pain and swelling of the right cheek of 2 months duration, resistant to antibiotic therapy and associated with progressive paraesthesia of the ipsilateral lower lip. Clinical examination revealed a soft, non-ulcerated swelling of the right retromolar area and hypoaesthesia of the ipsilateral lower lip.

A panoramic radiograph revealed a large radiolucent lesion in the right angle of the mandible, showing

irregular but well-defined borders, erosion of the cortical bone, interruption of the superior mandibular margin, and extension into the soft tissues. Another radiolucent area of smaller size but with similar radiological features was simultaneously detected in the opposite mandibular angle (Figure 1). The lesion in the right mandible measured approximately 39.1 × 36.3 mm on CT scans (Figure 2), while three-dimensional CT reconstruction showed interruption of the cortical bone of both mandibular lesions (Figure 3). Both lesions did not display intra-lesional calcifications, association with teeth roots or cystic components.

Under local anaesthesia, incisional biopsies were performed bilaterally, and the surgical samples, consisting of greyish firm tissue, were fixed in 10% neutral buffered formalin and embedded in paraffin for routine histological examination on haematoxylin–eosin stained slides. The morphological features of both lesions were similar and consisted in large irregular clusters and sheets of cubic to polyhedral epithelial cells, displaying solid or cribriform growth pattern, with prominent neoplastic infiltration of the retromolar mucous salivary glands and peri-tumoural neural structures (Figures 4 and 5). The tumour cells had scarce eosinophilic cytoplasms and irregular nuclei showing clumped chromatin and evident nucleoli. The neoplastic clusters were frequently surrounded by dense basement membrane-like material that was also detectable in smaller amounts

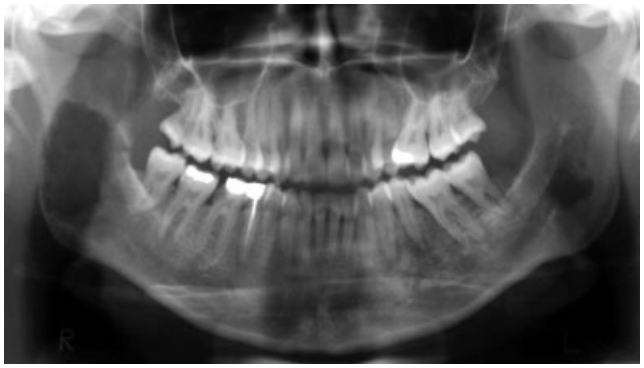

Figure 1 Bilateral intraosseous ACC: a large radiolucent area of the right mandibular angle/ascending ramus is evident associated with a smaller radiolucent area of the left ramus. Intralesional calcifications or association with teeth roots are not detectable

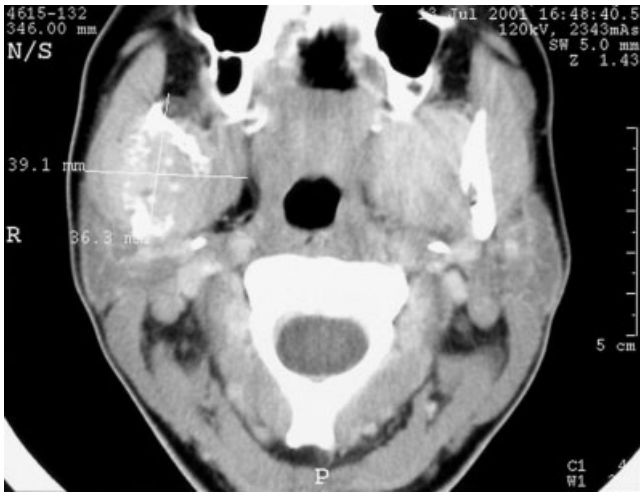

Figure 2 Axial CT: the larger lesion (right side) measures approximately 39.1 × 36.3 mm and extensively erodes the cortical plate and invades adjacent tissues

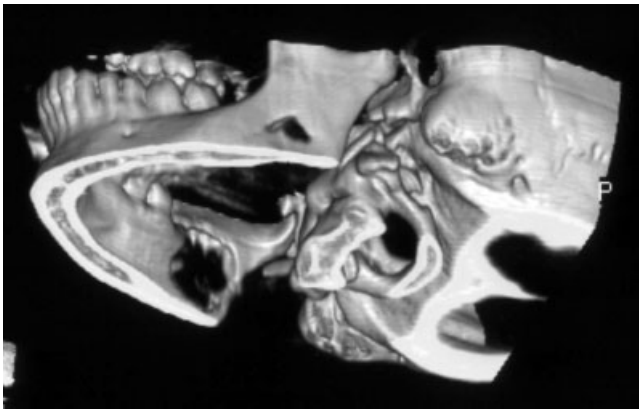

Figure 3 Three-dimensional CT reconstruction: the erosion of the mandibular cortical bone is evident on both sides

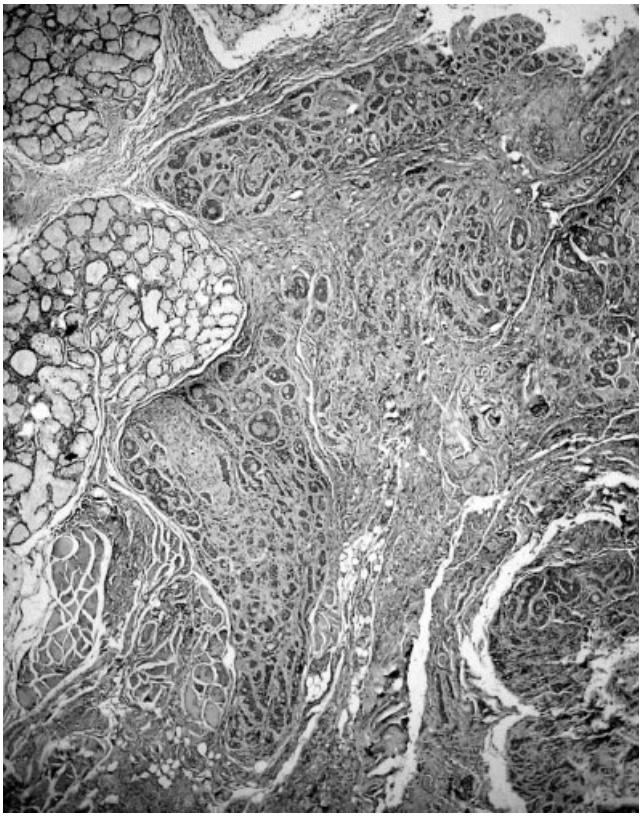

Figure 4 Histological features of the intraosseous ACC at low power magnification: the tumour grows in irregular clusters and sheets and infiltrates the retromolar mucous glands and skeletal muscle (haematoxylin–eosin, ×40)

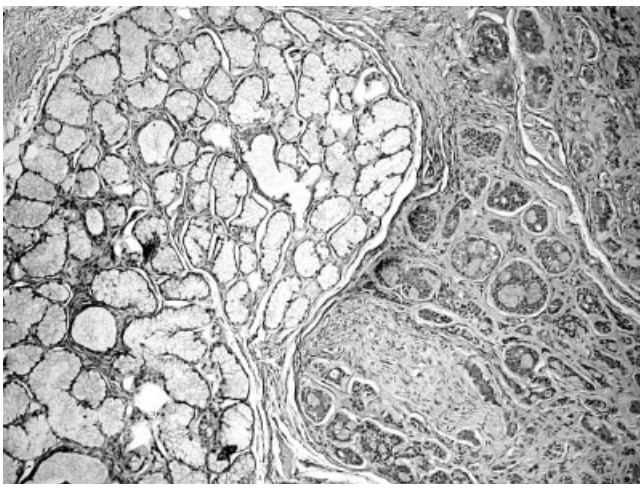

Figure 5 At higher magnification the tumour is composed by cuboidal to polyhedral cells arranged in cribriform structures and surrounded by large amounts of dense basement membrane-like material (haematoxylin–eosin, ×160)

within them. Based on these typical morphological features the diagnosis of ACC was formulated.

Due to the simultaneous bilateral occurrence of the neoplasm, the possibility of its metastatic nature was considered and extensive clinico-radiological investigations, including clinical inspection of the neck and oral cavity, gynaecological examination, ultrasonography and repeated CT scans of the head and neck area, along with chest radiograms, mammography, whole-body CT scan and bone scintigraphy were carried out that revealed multiple nodular lesions in both lungs (Figure 6), but no additional tumour deposits in the head and neck or elsewhere. The pulmonary lesions were subjected to percutaneous fine needle aspiration cytology that confirmed the malignant epithelial nature of the nodules and showed occasional cribriform pattern, consistent with ACC.

Consequently, the final diagnosis was of central and bilateral ACC of the mandible, with lung metastases.

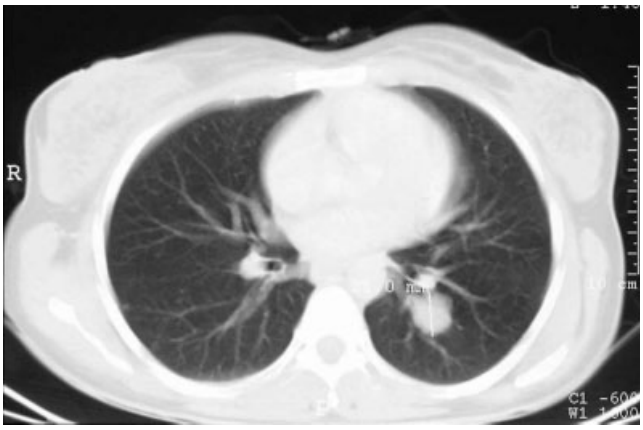

Figure 6 Chest axial CT showing multiple and bilateral nodular lesions, the largest measuring approximately 2.1 cm, consistent with metastatic deposits

The disease was beyond radical surgical salvage and, therefore, radiotherapy of the mandibular lesions (6480 cGy) was administered, in combination with poly-chemotherapy (2 cycles of *cis*-platin + 5 fluorouracil, followed by 1 cycle with taxol + carboplatin + cyclophosphamide, 6 cycles with epirubicin + cyclophosphamide, and another 6 cycles with gemcitabine). The patient is still being monitored and, after 3 years of follow up, is alive with persistent disease in the right hemi-mandible and lungs. Nevertheless, all lesions have considerably shrunk (down to 20–30% of their original size) following multimodal treatments and the patient is being considered for adjunctive radiotherapy in case disease progression will become evident.

Discussion

Adenoid cystic carcinoma represents approximately 7.5% of all carcinomas and 4% of both benign and malignant salivary gland tumours (Ellis and Auclair, 1996). While it is known that salivary gland type carcinomas may occasionally occur primarily within the jaws, these more frequently are mucoepidermoid carcinomas, while central (intraosseous) localizations of ACC are very unusual.

Up to January 2004, 16 cases of ACC arising centrally in the mandible have been reported (Brookstone and Huvos, 1992; Blanchard *et al*, 1998), most commonly occurring in the posterior mandible of adults, with a peak incidence in the 4th–6th decades, and presenting as painful enlargements, possibly associated with different paraesthetic symptoms. The malignant nature of ACC, especially of those showing prevalence of the solid growth pattern, is manifested by haematogenous metastases to lungs and bones, more than lymphatic spread to cervical lymph nodes. In this setting, counter-lateral mandibular metastases have not been described previously (Brookstone and Huvos, 1992; Ellis and Auclair, 1996) and the occurrence of simultaneous and bilateral primary ACC within the mandible is very unlikely. In addition, primary ACC may seldom arise in the trachea and lungs (Favia *et al*, 2000) but the possibility that such cancers metastasize to the jawbones is exceedingly rare. In addition, ACC very rarely arise in different parts of the body, such as breast, uterine cervix, external ear, lacrimal glands and paranasal sinuses but the possible origin from these sites could be excluded, based on repeated clinical examinations and extensive radiological work-up.

The purported origin of intraosseous salivary gland type cancers is from ectopic mucous glands of the retromolar area, entrapment within the bone of glandular remnants during the development of the submandibular gland, or, more convincingly, from neoplastic transformation of the mucous cells constituting the epithelial lining of dentigerous cysts or odontogenic epithelium (Brookstone and Huvos, 1992; Favia *et al*, 2000).

As to the current case, the simultaneous detection of multiple ACC localizations within the jawbones and

lungs pointed at their possible metastatic nature from a still undiscovered major salivary gland neoplasm. Nevertheless, repeated clinical and radiological investigations ruled out the existence of primary neoplastic foci within the major salivary glands or other sites, thus making it likely to interpret the bone lesions as the primary neoplasms. Although the occurrence of synchronous primary mandibular ACC cannot be excluded, we tend to believe, in consideration of its largest extension, that the tumour located in the right hemimandible could have been the original neoplasm from which subsequent haematogenous metastases to the contra-lateral hemi-mandible and lungs developed.

The clinical and radiological presentation of the current case as a bilateral radiolucent lesion surely was intriguing as to its correct interpretation. In fact, while benign odontogenic lesions, such as inflammatory or developmental cysts, including odontogenic keratocyst, which more frequently appear as multiple lesions, could be excluded due to absence of cystic components within the lesions, fibrous dysplasia of bone or ossifying fibroma were hard to consider in the differential diagnosis due to evident signs of malignancy (erosion of the cortical bone, interruption of the cortical plate and invasion of adjacent tissues) at radiological examination (Favia *et al*, 2000). For the same reasons, other jawbone lesions that may frequently show bilateral localizations, such as giant cell granuloma or cherubism were excluded and all the above lesions appeared even less probable following the detection of lung multinodularity attributable to metastatic disease (Brookstone and Huvos, 1992; Favia *et al*, 2000).

Ameloblastoma, ameloblastic carcinoma and odontogenic carcinoma seldom appear as bilateral neoplasms but it is very infrequent that these tumours display such aggressive behaviour as to manifest with rapid distant metastases to the lungs. In addition, these neoplasms usually exhibit mixed radiolucent/radiopaque appearance on radiographs, are frequently associated with impacted teeth and display more or less prominent intralesional calcifications.

Osteosarcoma of the mandible is another rare tumour that could have been considered in the differential diagnosis but its presentation as a bilateral lesion is exceptional while mandibular localizations of squamous cell carcinoma of the oral mucosa could be ruled out, based on the absence of even minimal alterations of the oral mucosa. Consequently, the hypotheses of primary intra-osseous carcinoma or metastatic tumour were the most reliable, based on the clinico-radiological signs and required histological confirmation to choose the best therapeutic intervention.

The histological features of the current case were rather unequivocal for ACC, based on its cyto-architectural characteristics and especially on the presence of the typical cribriform pattern. The latter should be extensively searched in multiple sections when the solid pattern predominates to achieve the correct diagnosis that may be facilitated by the demonstration of CD 117 immunoreactivity in the tumour cells (Holst *et al*, 1999).

In conclusion, this paper reports on a very unusual presentation of bilateral intra-osseous salivary gland type neoplasm that manifested in a very aggressive behaviour but is under acceptable control after chemo-radiotherapy. Such cases may prove difficult to diagnose, based on clinical and radiological investigations and may be interpreted as metastatic deposits from cancers of the major salivary glands or other sites until complete clinical and imaging work up exclude the existence of primary tumours outside the jawbones.

References

Billroth T (1859). Beobachtungen Uber Geschwulste der Speicheldrusen. *Arch Path Anat* **17:** 357–375.

Blanchard P, Faucqueur B, Auriol M *et al*. (1998). Intramandibular adenoid cystic carcinoma. *Rev Stomatol Chir Maxillofac* **98:** 343–348.

Brookstone MS, Huvos AG (1992). Central salivary gland tumors of the maxilla and mandible: a clinicopathologic study of 11 cases with an analysis of the literature. *J Oral Maxillofac Surg* **50:** 229–236.

Ellis GL, Auclair PL (1996). *Tumors of salivary glands. Atlas of tumor pathology*, 3rd series. Armed Forces Institute of Pathology: Bethesda, pp. 203–216.

Favia G, Maiorano E, Orsini G *et al*. (2000). Central (intraosseous) adenoid cystic carcinoma of the mandible: report of a case with periapical involvement. *J Endod* **26:** 760–763.

Holst VA, Marshall CE, Moskaluk CA, Frierson HF Jr (1999) KIT protein expression and analysis of c-kit gene mutation in adenoid cystic carcinoma. *Mod Pathol* **12:** 956–960.

Waldron CA, El-Mofty SK, Gnepp AR (1988). Tumors of the intraoral minor salivary glands: a demographic and histologic study of 426 cases. *Oral Surg Oral Med Oral Pathol* **66:** 323–333.