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Clear cell carcinoma, not otherwise specified/hyalinising clear cell carcinoma of the salivary gland: The current nomenclature, clinical/pathological characteristics and management

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ABSTRACT

Clear cell carcinoma, not otherwise specified (NOS)/hyalinising clear cell carcinoma (HCCC) is a rare entity in salivary gland tumour. The aim of the research is to review the current concepts and characteristics of this carcinoma. The clinical and pathological data of the disease obtained from literature and two original cases were analysed. Overall, 152 cases were reviewed up to the year 2014. The carcinomas were noted often in woman, in the seventh decade of life, located in oral cavity and as early-stages cancers. On pathological examination, they were characterized by tumour cells having clear cell morphology with hyalinised stroma. Immunohistochemical studies revealed that the carcinoma is positive for cytokeratin and negative for myoepithelial differentiation. *EWSR1-ATF1* fusion is specific for the carcinoma. Also, 9% of the reported cases had local nodal metastasis, with 6 cases demonstrating distant metastases at presentation. On follow-up, 22% of patients had recurrent or with persistent diseases after surgery. The time for the first recurrence could be as long as 24 years. Risk factors for recurrence include advanced stage at diagnosis and metastases at presentation. To conclude, HCCC is a low grade malignancy but have the potential for local metastases, recurrence, distant metastases and cancer-related death.

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1. Introduction

Clear cell carcinoma, not otherwise specified (NOS), is a rare form of salivary gland tumour. One hundred and fifty cases have been reported in the English literature (Chaudhry et al., 1983; Lattanzi et al., 1985; Uri et al., 1986; Hayashi et al., 1988; Ogawa et al., 1991; Newman and Funkhouser, 1993; Milchgrub et al., 1994; Orden et al., 1994; Rajab et al., 1994; Simpson et al., 1990; Tang et al., 1995; Okon et al., 1996; Urban et al., 1996; Triantafillidou et al., 1997; Berho and Huvos, 1999; Rinaldo et al., 1999; Rezende et al., 1999; Ereño et al., 2000; Milchgrub et al., 2000; Boccato et al., 2000; Grenevicki et al., 2001; Nayak et al., 2001; Balakrishnan et al., 2002; Browne and Holland, 2002; Félix et al., 2002; Manoharan et al., 2002; Moh'd Hadi et al., 2002; Wang et al., 2002; Sahasrabudhe et al., 2003; Chao et al., 2004; Fujita et al., 2004; O'Regan et al., 2004; Sun et al., 2005; Sicurella et al., 2004; Suzuki et al., 2006; Angiero and Stefani, 2007; Ponniah et al., 2007; Suzuki et al., 2007; Uzochukwu et al., 2007; Lai et al., 2008; Pujary et al., 2008; Yang et al., 2008; Cheng et al., 2008; O'Sullivan-Mejia et al., 2009; Solar et al., 2009; Yamashita et al., 2009; Barber et al., 2010; Antonescu et al., 2011; Kauzman et al., 2011; López-Quiles et al., 2011; Masilamani et al., 2011; Baghirath et al., 2011; Cashman and Woo, 2012; Hijjawi et al., 2012; Jin et al., 2012; Roby et al., 2012; Saleh et al., 2012; Adil et al., 2013; Gon et al., 2013; Shah et al., 2013; Kim et al., 2013; Fulciniti et al., 2014; Su et al., 2015; Arpaci et al., 2014; Ceballos Sáenz et al., 2014). The disease first appeared in German literature in 1968 as part of a heterogeneous group of oral malignancies demonstrating clear cell populations (Kleinsasser et al., 1968). Donath et al. (1972) described the carcinoma as a form of epithelial-myoepithelial carcinoma, originating from the intercalated ducts. Then, the carcinoma was defined by Chaudhry et al. (1983) who recognised that a subset of 'glycogen-rich' tumours were myoepithelium deficient. In 1994, Milchgrub et al. (1994) first isolated and characterized this unique subset of tumours, designating them as 'hyalinizing clear cell carcinomas'. This was based on the observation that the carcinoma has a prominent hyalinised stroma and a lack of myoepithelial differentiation. Also, Dardick and Leong (2009) proposed primary squamous differentiation of the tumour based on a review of morphological, immunohistochemical and ultrastructural features. In 2005, the World Health Organization (WHO) classified the tumour the as "clear cell carcinoma, not otherwise specified" (Ellis, 2005). The carcinoma is defined as a malignant epithelial neoplasm composed of monomorphous population of cells having clear cytoplasm.

In the recent decade, the identification of a specific translocation (*EWSR1-ATF1* (*Ewing sarcoma breakpoint region 1-activator transcription factor 1*) fusion-t(12; 22)(q13; q12)) in clear cell carcinoma, NOS indicates that this group of tumours belong to a distinct entity. Thus, the term "NOS" as a "wastebasket" qualifier is not appropriate anymore. Many authors recommended again using the term "hyalinising clear cell carcinoma" for this reason. Also, using the term "hyalinising" labelled the carcinoma as a separate class of salivary gland tumour as different from other clear cell malignancies of other origins (Gupta et al., 2015; Brandwein-Gensler and Wei, 2014).

As clear cell carcinoma, NOS/hyalinising clear cell carcinoma of the salivary gland is very uncommon, the majority of cases were reported in scattered case reports. There is a lack of comprehensive understanding of the clinical characteristics of the disease and subsequent treatment regimens. In addition to this, the finding of the specific translocation in the tumour and the proposed change in terminology led us to review the current concepts of the disease entity. In the current review, we analysed the clinical and pathologic characteristics of all the reported cases of clear cell carcinoma, NOS/hyalinising clear cell carcinoma in a systemic manner, in order to identify risk factors for recurrent disease and subsequent treatment recommendations.

2. Method

The literature between 1981 and 2014 recorded in PubMed was searched for the key-words included "clear cell"; "carcinoma"; "tumour"; "tumor"; "hyalinizing" "hyalinising" and "salivary gland". Only original publications in English were reviewed. One hundred and fifty cases of clear cell carcinoma; NOS/hyalinising clear cell carcinoma of salivary gland were identified in the literature (Chaudhry et al., 1983; Lattanzi et al., 1985; Uri et al., 1986; Hayashi et al., 1988; Ogawa et al., 1991; Newman and Funkhouser, 1993; Milchgrub et al., 1994; Orden et al., 1994; Rajab et al., 1994; Simpson et al., 1990; Tang et al., 1995; Okon et al., 1996; Urban et al., 1996; Triantafillidou et al., 1997; Berho and Huvos, 1999; Rinaldo et al., 1999; Rezende et al., 1999; Ereño et al., 2000; Milchgrub et al., 2000; Boccato et al., 2000; Grenevicki et al., 2001; Nayak et al., 2001; Balakrishnan et al., 2002; Browne and Holland, 2002; Félix et al., 2002; Manoharan et al., 2002; Moh'd Hadi et al., 2002; Wang et al., 2002; Sahasrabudhe et al., 2003; Chao et al., 2004; Fujita et al., 2004; O'Regan et al., 2004; Sun et al., 2005; Sicurella et al., 2004; Suzuki et al., 2006; Angiero and Stefani, 2007; Ponniah et al., 2007; Suzuki et al., 2007; Uzochukwu et al., 2007; Lai et al., 2008; Pujary et al., 2008; Yang et al., 2008; Cheng et al., 2008; O'Sullivan-Mejia et al., 2009; Solar et al., 2009; Yamashita et al., 2009; Barber et al., 2010; Antonescu et al., 2011; Kauzman et al., 2011; López-Quiles et al., 2011; Masilamani et al., 2011; Baghirath et al., 2011; Cashman and Woo, 2012; Hijjawi et al., 2012; Jin et al., 2012; Roby et al., 2012; Saleh et al., 2012; Adil et al., 2013; Gon et al., 2013; Shah et al., 2013; Kim et al., 2013; Fulciniti et al., 2014; Su et al., 2015; Arpaci et al., 2014; Ceballos Sáenz et al., 2014). In addition; two cases were included from our institution (Table 1). Overall; 152 cases were examined. Demographic; pathological and clinical details were collected. If the same cases were reported more than once; only one entry was entered. The data were analysed with Statistical Package for Social Sciences version 22.0 (IBM SPSS Inc.; New York; USA). P values of <0.05 were considered statistically significant.

3. Results and discussion

3.1. Epidemiology and clinical features

The majority of reported cases of clear cell carcinoma, NOS/hyalinising clear cell carcinoma of salivary gland were from the United States of America (n = 101). Other cases were published in India (n = 8), Japan (n = 7), Italy (n = 5), China (n = 4), Scotland (n = 3), Portugal (n = 3), Malaysia (n = 3), Canada (n = 3), Australia (n = 2), Spain (n = 2), United Kingdom (n = 2), Taiwan (n = 2), Ireland (n = 1), Poland (n = 1), Hong Kong (n = 1), Greece (n = 1), South Korea (n = 1), Turkey (n = 1) and Mexico (n = 1).

Clear cell carcinoma, NOS/hyalinising clear cell carcinoma is more common in women (male to female ratio = 1 to 1.6). The disease presented at a mean age 56 years (range, 17 months to 81 years). It most commonly occurs in the seventh decade of life (26%), followed by occurrence in the sixth decade of life (20%) (Fig. 1). Two patients were diagnosed in the setting of human immunodeficiency virus (HIV) infection (López-Quiles et al., 2011). The two patients treated at our institution were a 52-year-old man (case 1) and a 48-year-old woman (case 2).

Clinical presentation was described in 98 patients (64%). Clear cell carcinoma, NOS/hyalinising clear cell carcinoma of salivary gland most commonly arises as painless lump (74.5%; 73/98). The patient may present with symptoms arising from the mass effect or degeneration of the tumour. These symptoms included oral