Int J Clin Exp Med 2018;11(12):13880-13886
www.ijcem.com /ISSN:1940-5901/IJCEM0078964

Case Report

Skeletal muscle and brain metastases arising from primary squamous cell carcinoma of the parotid gland: a case report and review of the literature

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Received May 4, 2018; Accepted October 30, 2018; Epub December 15, 2018; Published December 30, 2018

Abstract: Salivary gland tumors are less common in comparison to other head and neck tumors. Histological classifications of salivary gland tumor are diverse and complicated. Common malignant salivary gland tumors are mucoepidermoid carcinomas and adenoid cystic carcinomas. Although parotid gland carcinoma is the most common salivary gland tumor, primary squamous cell carcinoma (SCC) of the parotid gland was rarely reported with aggressive biology behavior and high rate of lymph node metastasis. Major metastatic sites of salivary tumors are lung, bone and liver. Skeletal muscle and brain metastases were rarely reported and indicated poor prognosis. Here, we report a case of primary squamous cell carcinoma of the parotid gland with metastases to skeletal muscle and brain after the wide local excision of the left parotid gland followed by adjuvant chemotherapy. According to our knowledge and searched literatures, this is the first report of primary SCC of the parotid gland with skeletal muscle metastases followed by multiple brain metastases.

Keywords: Parotid gland tumor, squamous cell carcinoma, skeletal muscle metastases, brain metastases

Introduction

Salivary gland tumors are infrequently found, accounting for 2%-3% of all head and neck tumors; 80% of tumors occur in the parotid glands, which 80% of them are benign [1]. Due to a relatively low incidence, salivary gland tumors are less commonly found in literatures with large samples than other tumors and its epidemiological data is currently not complete. Most parotid gland neoplasms originate from epithelial tissue. Diverse histological types may lead to different biological behaviors and clinical manifestations. Mucoepidermoid carcinomas and adenoid cystic carcinomas rank the first and the second commonly seen parotid gland neoplasms, which proved by relatively large amount of studies [2, 3]. SCC of the parotid gland is rarely reported with aggressive growth, metastasis patterns and disappointing prognosis. Cervical lymph node and facial nerve are commonly involved that results in local regional failure [4, 5]. There are some reported cases that parotid tumors metastases to lung, bone, liver and brain, however, based on our knowledge and searched literatures, this is the first report which showed SCC of the parotid gland metastasis to skeletal muscle and brain.

Case report

The patient was a 49-year-old man without any tumor histories. In August 2014, he complained of a moveable asymptomatic mass (about 1×1 cm) in left parotid gland region. Then the mass was resected as sebaceous cyst in a local hospital. One month later, there appeared a firm mass (the size of 4×3 cm) in former operative site with no pain or facial nerve numbness. Comprehensive physical examination found two firm 1×1 cm masses in abdomen and one hard 1.5×1.5 cm mass in the right side of the buttocks respectively. Subsequently, the wide excision of left parotid gland, cervical lymph nodes dissection with retaining the facial nerve and the extended local excision of mass in the right buttock were performed. The pathology

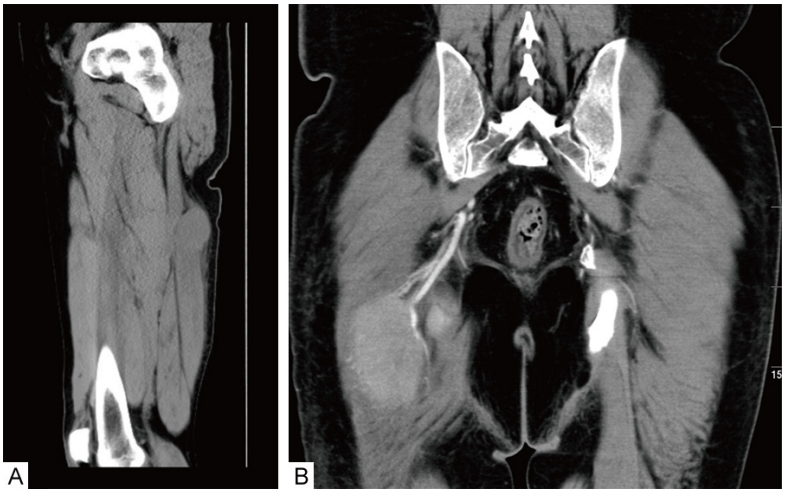

Figure 1. CT images of skeletal muscle metastases. CT scan of the right thigh shows oval mass with 3.2 cm in diameter (A); Pelvic CT shows the abnormal enhanced soft tissue mass in the right gluteus maximus (B).

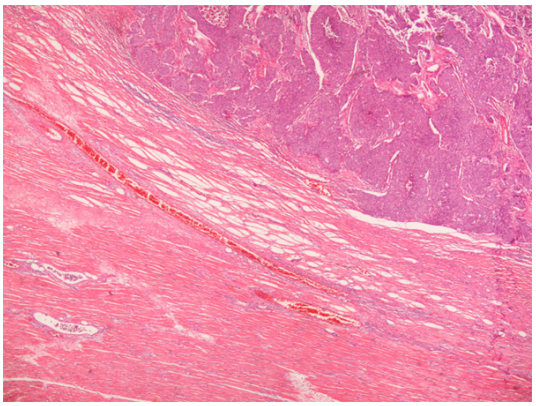

Figure 2. The metastasis of SCC invades the skeletal muscles. (H&E staining ×20).

results were epithelium-derived malignant tumors and metastatic 1/7 dissected lymph nodes. Nested cell clumps, heterocyst and tumor necrosis were seen under the microscope; immunohistochemistry (IHC) showed positive expression of 34BE12 (HCK), P63, Ki-67 and suspicious positive expression for LCK; immunohistochemistry markers including Act, CD117 and p16 were all negative results. Histopathology reported as poorly differentiated squamous cell carcinoma of left parotid gland.

In November 2014, two firm masses (about 1×1 cm in size respectively) in abdomen were found by physical examination. Chemotherapy with 8 cycles of TPLF program (docetaxel, cisplatin, calcium folinate, tegafur) was administered. After five cycles of chemotherapy, the masses in abdomen disappeared completely. Chest CT exhibited a mass located in hilum of left lung and multiple small high density nodules in lungs.

In October 2015, the patient complained a solitary mass on the right thigh. Imaging examination of the thigh CT revealed a mass in semitendinosus with soft tissue density and size about 3×3.2 cm (**Figure 1A**). The patient underwent intact excision of the thigh mass. The pathology examination exhibited an oval mass about 3×2.8×2.5 cm and the hoary tissues covered necrotic tissues; Tumor cells which invaded into skeletal muscle, heterocyst cells arranged in nets and tumor necrosis tissue were observed in pathological section with HE staining (**Figure 2**); Immunohistochemistry staining showed positive expression of epithelial membrane antigen (EMA), hemopoietic cell kinase (HCK), p63, cytokeratin 5/6 (**Figure 3**) and negative expression of CK7, CK20, SMA, Calponin, S100, GCDFP15. The pathological diagnosis was metastatic poorly differentiated squamous cell carcinoma of skeletal muscle tissue. Subsequently, he received radiotherapy with the total dose of 50 Gy (2 Gy per day, five days a week) for the right thigh tumor bed area.

In April 2016, the patient complained of low-grade fever lasting for one month and headache for a week. A pain firm mass with size of 6×7 cm was palpated on the right side of buttocks by physical examination. Brain CT exhibited multiple brain metastases lesions. Pelvic enhanced CT examination showed an abnormal enhanced soft tissue mass in right gluteus maximus (**Figure 1B**). It's not found that there are obvious changes of chest CT compared with former scans. Then, he received palliative chemoradiotherapy with temozolomide and radiation therapy (30 Gy in 15 fractions of 2 Gy each day, five days a week) for brain metastases.

Discussion

Primary SCC of the parotid gland is a very rare neoplasm which accounts for less than 1% of

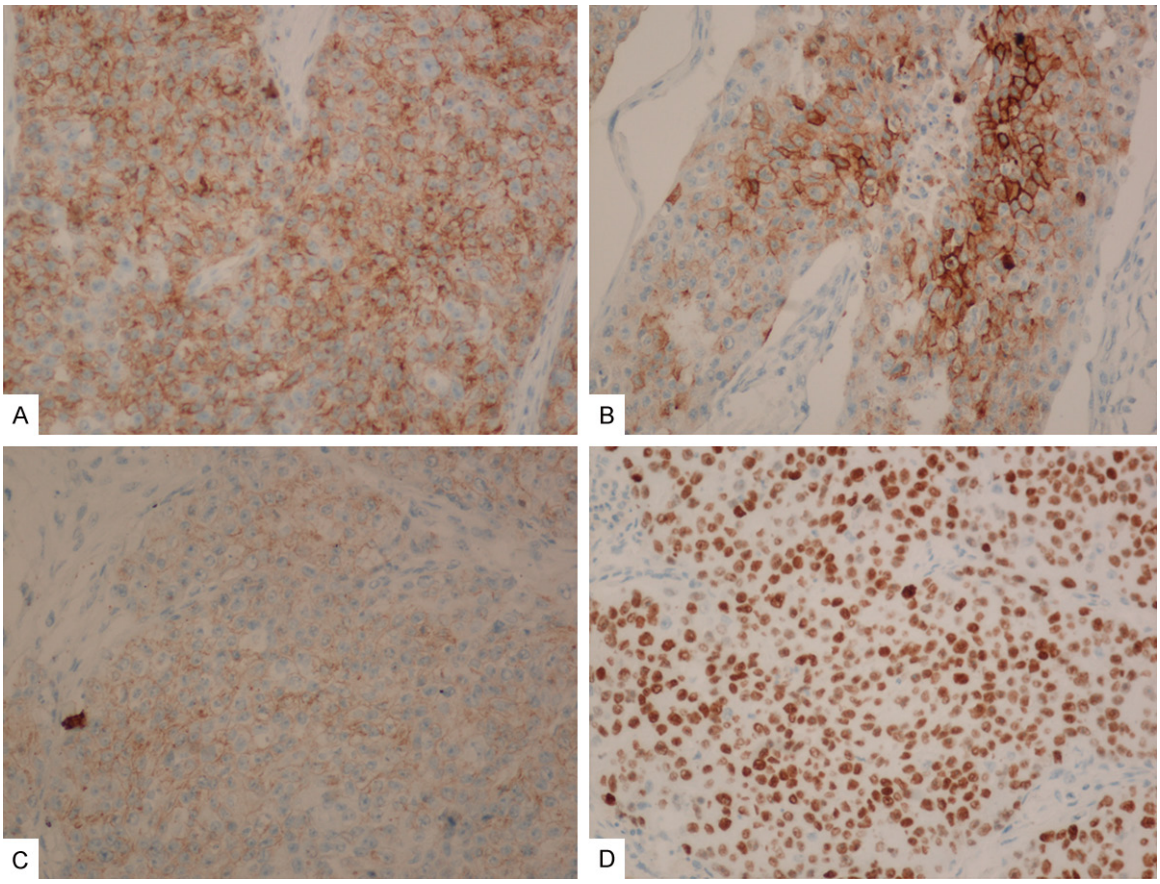

Figure 3. Immunohistochemistry. The position immunohistochemical staining for HCK, EMA, Ck5/6, P63 (A-D, respectively) in the metastatic tumor cells. (Immunohistochemistry ×200).

all salivary gland neoplasms [6]. This is an aggressive malignancy with poor prognosis, frequently presenting in advanced stage in which facial nerve involved or nodal metastases [4, 5]. To make final diagnosis, metastatic SCC to the parotid gland or high-grade mucoepidermoid carcinoma (MEC) should be excluded; Metastatic SCC usually originate from cutaneous malignancy of face and scalp; High-grade mucoepidermoid carcinoma was often confused with squamous cell carcinomas in which cases mucins stains was usually employed to distinguish them [4-6].

For this patient, there is no medical history of head and neck tumors, so the probability of metastatic SCC was ruled out. Additionally, the diagnosis of primary SCC of the parotid gland can be supported by the following immunohistochemistry markers. Firstly, immunohistochemistry of this salivary tumor specimen showed positive expression of HCK (34BE12), P63 and Ki-67, which manifested the diagnosis of SCC. In previous retrospective study which used IHC to identify SCC of head and neck, a high molecular weight cytokeratin called by 34BE12 was the most usually used antibody, and study showed that squamous epithelium was labeled by 34BE12 [7]. Over expression of P63 is helpful to identify SCC of head and neck and it also has its value in prognosis [8, 9].

Secondly, we use the CK7/CK20 to discern SCC from MEC. In Meer's study, twenty-one cases of mucoepidermoid carcinomas all showed CK7+/CK20- immunoexpression profile, and four cases of SCC of salivary gland showed negative CK7/20, which suggested that CK7-/CK20- immunoexpression profil may be helpful to differentiate SCC of the salivary gland from high-grade mucoepidermoid carcinomas [10]. In Nikitakis's study, CK7+/CK20- was found in 24 out of 26 mucoepidermoid carcinomas, which suggested that CK7/20 immunoprofile may facilitate identification of SCC and mucoepidermoid carcinomas of salivary gland tumors [11].

In the survey of 435 epithelial neoplasms, 9 salivary gland tumors (mixed tumors including Warthin's tumors, mucoepidermoid carcinomas) all expressed CK7+/CK20-, and this study indicated that most of SCC with various origins are CK7-/CK20- except cervical squamous cell carcinoma [12]. All of the mucoepidermoid carcinomas in their study showed CK7 positive expression. The CK7-/CK20- immunoexpression profile in skeletal muscle metastasis of this patient excluded the diagnosis possibility of high-mucoepidermoid carcinomas.

Primary SCC of the parotid gland is so rare that limited data is available to allow us understanding its metastatic characteristics. In a systematic review of patients with carcinoma of salivary glands, the incidence of distant metastasis is 24-61% [13]. The incidence of distant metastases is associated with the pathological characters of the primary tumor. For instance, distant metastases are more commonly seen in primary tumors including adenoid cystic carcinoma, high-grade mucoepidermoid carcinoma, salivary duct carcinoma and primary tumors located in the submandibular gland, posterior tongue and pharyngeal; Most common site of distant metastases is the lung; Other sites such as bone, liver and brain were also reported in some literatures [13, 14]. Skeletal muscles is distributed in all parts of the body, accounting for approximately 50% of the body mass, but primary malignant tumor metastases to skeletal muscles are extremely rare. There are few summative literatures about skeletal muscle metastases. Tuoheti Y et al. reported only 12 patients who had been confirmed as skeletal muscle metastases since January 1994 to October 2003, and the lung was found to be the most common primary source [15]. In Herring et al.' study, they recorded 15 patients with skeletal metastases at the authors' institution from January 1979 to 1998; The majority of the primary tumors also were lung cancer [16]. Yurut-Caloglu et al. reported a rare case with multiple metastatic sites such as lung, bone, skeletal muscles, cutaneous metastases from adenoid cystic carcinoma (ACC) of the parotid [17]. The common manifestation in most other reports was painful mass which occurred in lower extremity and most of them originated from lung adenocarcinoma, renal cell carcinoma, gastric carcinoma or melanoma [15, 16, 18]. According to our knowledge, this is the first report which shows skeletal muscle metastases arising from SCC of the parotid gland.

The rarity of metastases to skeletal muscles is not fully understood. Some factors may have the relevance for this rarity, such as lactic acid production by skeletal muscle, the variable blood flow, local temperature, pH and oxygenation, β-adrenergic stimulation and varied tissue pressure [16, 19]. Some researches considered that a new molecular weight factor released by muscle cells inhibits the proliferation of tumor cells [20]. Multiple skeletal muscle metastases in different parts of the body most likely indicated the high possibility of other metastases existence. Mechanism of skeletal muscle metastases needs to be further studied.

Skeletal muscle metastases manifest similarly as many soft tissue sarcomas. In Leinung's study, the final histopathological results of 597 isolated soft tissue tumors which were firstly suspected as soft tissue sarcoma finally confirmed that 318 cases were soft tissue sarcoma, 98 cases were metastatic carcinoma and 124 cases were benign tumor respectively, therefore, greater consideration should be given to the differential diagnosis [21]. It is essential to distinguish soft tissue sarcomas from metastasis tumor, because they need different treatment and have different prognosis. Plain radiograph and CT hardly help the differential diagnosis. Enhancement MR imaging may be helpful.

Some immunohistochemical indexes are helpful in the differential diagnosis of soft tissue tumors. Jose Antonio Plaze et al. recommend that epithelial markers (including cytokeratin and EMA), muscle markers (including SMA and Calponin), neural or melanocytic markers (including S 100 protein and HMB-45), vascular endothelial markers (including CD31 and CD34), which can be used as routine workup to differentiate soft tissue tumors [18]. In this case, positive expression of epithelial markers (including EMA, HCK, p63, CK5/6), negative expression of muscle markers (including SMA, Calponin) and melanocytic markers (including S 100 protein) can exclude the diagnosis of myoepithelial carcinoma and melanomas. Combined with his medical history and the results of immunohistochemical staining, we can con-

firm that the metastatic mass of thigh is from SCC of the parotid gland. Furthermore, pelvic CT examination showed an abnormal enhanced soft tissue mass in right gluteus maximus, and we also consider the lesion is skeletal metastasis.

In the entire process of disease, he didn't complain of cough, sputum, chest pain and emaciation. During the sequential treatment, the follow-up chest CT examination showed similar performances such as the mass located in hilum of left lung, calcified lymph nodes, multiple pulmonary nodules and pleural calcification. CT imaging suggested metastatic tumors or obsolete pulmonary tuberculosis. It's necessary to make histopathology of masses in lungs, unfortunately, the patient refused the further examination. The diagnosis of pulmonary metastases is more likely based on symptoms, the history of disease progression and CT examination.

The occurrence of brain metastases indicate the tumor has turned into widespread dissemination and the mortality of the patients is increased. Brain metastases may be derived from any primary systemic tumors, but some special primary tumors such as lung cancer, breast cancer, malignant melanoma are common origin of brain metastases [22]. Brain metastases from salivary gland tumor are relatively rare. In Venteicher's report, three patients with brain metastases from salivary gland tumors were identified from a database of 4117 elective craniotomies, and management of them was essentially the same as other brain metastases from other sites [23]. This diagnosis of brain metastases can be demonstrated by the history of salivary gland tumor, the new occurrence of acute headache symptoms and obvious multiple lesions in images.

At present, the main treatment ways of parotid gland neoplasms include surgery, radiotherapy and chemotherapy according to different situations. For relatively lower rate of incidence and complicated histological types, it's difficult to proceed randomized, controlled and prospective clinical trials to demonstrate which way is more suitable. Anatomical location of salivary gland adjacent to blood vessels and nerves limits the completely clearance of tumor through surgery, therefore, postoperative radiotherapy is important, especially for those with high risk of local recurrence and distant metastasis such as high-grade neoplasms, invasive tumor, positive surgical margin and node metastasis. In the literatures, studies suggest that surgery followed by adjuvant radiotherapy predominant in the treatment of salivary gland tumors with high-grade, high-T stage, nerve involvement or node metastasis, from which patients benefit the most [24, 25]. Palliative chemotherapy can be considered as one of comprehensive treatments. Rizk S et al. analyzed 205 patients with salivary gland tumor, then they suggested that platinum-based palliative chemotherapy can be a better choice because platinum is independent factor in survival [26]. This patient underwent parotidectomy followed by postoperative chemotherapy. Unfortunately, later on, he developed multiple skeletal muscles and brain metastases.

The prognosis of parotid gland tumor was associated with staging of tumor, pathological type, neck nodal status, treatment methods and so on. Koul et al. suggest that tumor size, local invasion, distant metastasis, tumor differentiation were important predictors for survival, in addition to, they consider adjuvant radiotherapy can reduce the risk of death [27]. Bhattacharyya N support nodal metastasis is the critical predictive factor in survival; the pathological type (especially SCC or adenocarcinoma), facial nerve involvement, staging and grade of tumor are related with nodal disease [28]. The prognosis of this patient is not optimistic for initial misdiagnosis, nodal metastasis but adjuvant radiation was not offered, skeletal muscle metastases and brain metastases.

In conclusion, the case with skeletal muscle metastases and multiple brain metastases from primary SCC of the parotid gland is the first report according to our knowledge. It's a challenge for oncologists, radiologists and pathologists. Some asymptomatic masses may be the signal of malignant tumors especially for those patients without tumor history. IHC play a crucial role in differential diagnosis. Comprehensive treatment should be considered to improve the effect.

Acknowledgements

This manuscript is supported by the National Natural Science Foundations of China (Juan

Ren, 31201060/C0709; Juan Ren, 30973175/H1621; Juan Ren, 81772793/H1621; and Juan Ren, 81172490/H1621); Supported by Program for New Century Excellent Talents in University (Juan Ren, NCET-12-0440); Scientific and Technological Research Foundation of Shaanxi Province (Juan Ren, 2012K13-01-06); Research Foundation of Health Department of Shaan'xi Province (Juan Ren, 2010D41); Qing Nian Jiao Shi Gen Zong Ji Hua of Xi'an Jiaotong University ("The Fundamental Research Funds for the Central Universities") (Juan Ren, 2012).

Disclosure of conflict of interest

None.

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