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The Breast Enriched HER2 Molecular Subtype-Like Salivary Duct Carcinoma: A Good Response to Novel Targeted Therapy in Two Advanced Disease Cases

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Abstract

Background: Salivary duct carcinoma (SDC) is one of the most aggressive malignant salivary gland tumors resembling high-grade mammary ductal carcinoma, with frequent local recurrence and regional lymph node and distant metastasis. SDC is often the absence of estrogen receptor and progesterone receptor, and Her2/neu overexpression. Treatment with molecular targeted therapy correlated well with long-term survival and therapeutic response in SDC patients. **Purpose:** We presented the clinicopathologic entity and treatment response of the two cases in Vietnam, firstly and compared it with the related literature to raise awareness of this tumor. **Methods:** The clinicopathological characteristics of two SDCs were recorded. Immunohistochemical staining was performed on ER, PR, HER2, and some markers. All SDC patients' treatment responses and survival were accessed. **Results and Conclusion:** Two men with salivary carcinoma were classified into the breast enriched HER2 molecular subtype-like salivary duct carcinoma in an advanced stage, who have got the molecular targeted therapy as anti-HER2 combined with chemotherapy. They displayed a good response to novel targeted therapy.

Subject Areas

Oncology

Keywords

SDC, Targeted Therapy, HER2 Subtype

1. Introduction

Salivary duct carcinoma (SDC) is an aggressive epithelial malignancy resembling high-grade mammary ductal carcinoma. SDC is one of the most aggressive malignant salivary gland tumors, with frequent local recurrence and regional lymph node and distant metastasis [1]. Estrogen receptor and progesterone receptor expressions are negative. High ERBB2 (also called HER2/neu overexpression) has been identified in approximately 25% - 90% of SDCs and is associated with a poor prognosis [1]-[7]. So, this immunophenotype of SDC should be classified into the HER2 molecular subtype as the molecular classification of breast cancer and these 2 patients. The patient can get benefited from anti-HER2 therapy. In addition to surgical resection followed by radiotherapy and conventional chemotherapy, recent advances in molecular-targeted therapy have broadened the therapeutic strategies. NCCN (National Comprehensive Cancer Network) guidelines today recommend the same with the use of trastuzumab for HER2+ disease. Her2/neu positivity and treatment with trastuzumab correlated well with long-term survival and therapeutic response in SDC patients [8]. Here, we presented the clinicopathologic entity and treatment response of the two SDC cases of enriched HER2 molecular subtype in Vietnam, firstly and compared with the related literature to raise awareness of this tumor.

2. Case Presentation

2.1. Case 1

The first 57-year-old male presented with the left parotid mass in September 2021. He complained of pain and a dry cough. The patient had a history of diabetes and chronic HBV (Hepatitis B Virus) infection. On admission, cirrhosis score was assessed as Child-Pugh A, and the patient had grade-I thrombocytopenia without haemorrhage. Bone marrow biopsy showed a decreased formation of megakaryocytes in the marrow. The patient was hospitalized for further examination, and his finding of ultrasound and magnetic resonance imaging (MRI) showed a mass with a diameter of 43 × 27 mm on the left parotid with left enlarged cervical lymph nodes (13 mm). A computed tomography (CT) scan result showed both multiple pulmonary metastases. The histopathological diagnosis of core needle biopsy of the left parotid mass confirmed a salivary duct carcinoma, and immunohistochemistry results were positive for the expression of mammaglobin, CK7, Her2/neu (2 plus), GCDFP-15 but negative for that of ER (estrogen receptor), PR (progesterone receptor) and CK20. The fluorescence in situ hybridization (FISH) test showed a HER2 genetic amplification. Based on the CT scan findings, pathological and molecular results, the patient has confirmed the HER2-positive lung metastatic salivary duct carcinoma, stage IVC (cT3N1M1). The patient was initially treated with first-line chemotherapy of paclitaxel/carboplatin plus trastuzumab. After one cycle of chemotherapy, the patient developed thrombocytopenia with blood platelets of 65 G/L, and no complication was reported. We then decided to change the chemotherapy regimen to docetaxel plus trastuzumab.

After three cycles, CT scan findings showed a partial response in the pulmonary metastases and parotid mass according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), the patient improved clinical symptoms and tolerated well the treatment with grade 1 thrombocytopenia. At the time, the patient was receiving docetaxel/trastuzumab chemotherapy for 9 months with good tolerance.

2.2. Case 2

The second 49-year-old man was hospitalized with a right submandibular mass in December 2021. The clinical examination, ultrasound, and positron emission tomography (PET) scan findings showed a mass with a diameter of 10 × 23 mm on the right submandibular gland accompanied withenlarged cervical nodes and mediastinal metastasis. Biopsy of the right submandibular mass and neck lymph node were performed, the histopathological diagnosis confirmed salivary duct carcinoma with a metastatic lymph node. Immunohistochemistry (IHC) results were positive for the expression of HER2/neu, CK7, GATA3, mammaglobin and GCDFP15, but tumor cells were negative for that of P40, CK20, CK5/6, ER, PR and p63. Based on subclinical results, the patient was diagnosed with salivary duct carcinoma staged IVC (T3N2bM1) according to the 8th edition of the American Joint Committee on Cancer (AJCC). Patient received chemotherapy of paclitaxel/carboplatin plus trastuzumab for 6 cycles then followed by trastuzumab as maintenance therapy. After 6 cycles of chemotherapy, there was a complete response according to RECIST v1.1 without report of grades 3 - 4 toxicities (**Figure 1(a)** and **Figure 1(b)**, **Figure 2(a)** and **Figure 2(b)**). At this time, the patient was stable for 7 months.

3. Discussion

SDC is one of the most aggressive malignant salivary gland tumors resembling high-grade mammary ductal carcinoma. The luminal epithelial cells of both salivary and breast glands have a similar immunoprofile, expressing lowmolecular-weight cytokeratins, ER, PR, and AR. These similarities in structure may

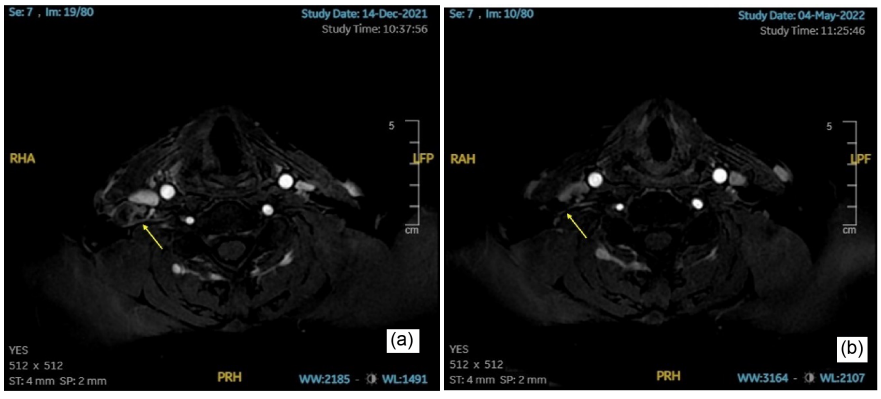

Figure 1. Illustrated pictures demonstrated a complete response of submandibular mass before (a) and after chemotherapy (b) on MRI (arrow).

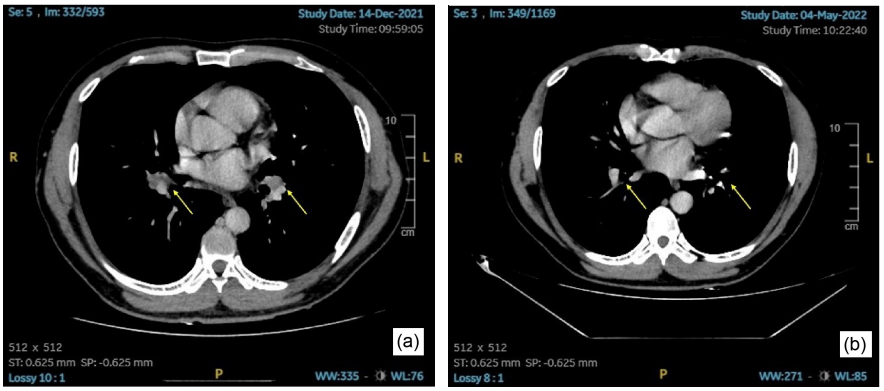

Figure 2. Photomicrographs of CT scan showed a complete response of bilateral mediastinal nodal metastases before and after chemotherapy ((a) and (b), respectively) (arrow).

result in the development of similar neoplastic lesions [9]. We used some breast cancer-specific markers for immunohistochemical staining of these two cases such as GCDFP-15, especially mammaglobin. It was interesting that both their tumor cells and benign epithelial cells were positive with these markers. Their expression is similarly with breast tissue. This exposure suggests that mammary and salivary gland, belonging to the exocrine glands, may share a primordial germ cell origin. If this is proven, it will be a good opportunity to apply adjuvant treatment regimens of breast cancer for salivary carcinoma, as well as evaluating prognostic factors such as molecular subtypes, risk stratification, and so on. As SDC has morphologic and molecular similarity to breast cancer, it is recommended that apart from regular histopathological examination, it keep to remind every pathologist's mind to perform the additional immunohistochemical staining including Her2/neu, Ki-67, ER, PR, androgen in order to provide the most important information for oncologists to make the exact adjuvant therapy decision.HER2/neu was overexpressed in 28.6 % to 31.0% in SDC [6, 7]. In the study of Jaehne *et al*., moderate and strong staining for erb-B2 were seen in 17.7% and 20.6% of patients, respectively [2]. Both of our patients were expressed HER2 2 plus. Their ISH (In situ hybridization) test showed HER2 gene amplification. Applying the molecular subtypes of breast cancer to these two cases, we identified their tumors as HER2 molecular type, which had a poor prognosis after the basal-like subtype as previous study of breast cancer in Vietnam [10].

SDC can occur de nova or as the outcome of a malignant component of carcinoma ex pleomorphic adenoma [1]. It has a distinct male predilection and generally affects elderly individuals, with peak incidence in the sixth and seventh decades of life [1]. Most tumors arise from the parotid gland [1]. The parotid gland was accounted in 83%, with the next most frequent site being the submandibular gland (12%) [7]. Both of our patients are male, one is 49 years old and the other is 56 years old. One tumor is located in the parotid gland and the other is belonged to the submandibular gland.

This tumor has a striking resemblance to high-grade ductal carcinoma of the

breast, including large ducts with comedo necrosis and cribriform and Roman bridge-like features. Both lymphavascular invasion (LVSI) and perineural invasion (PNI) are common. A hyalinized nodule suggestive of a pre-existing pleomorphic adenoma may be identified. SDC cells are typically apocrine, oncocytoid, and characterized by abundant cytoplasm and large pleomorphic nuclei with coarse chromatin and prominent nucleoli [1]. PNI was observed in 6/7 cases (85.8%), while LVSI was seen in 3/7 patients (42.9%). Lymph node involvement was observed in 3/7 cases (42.9%). Both of our patients displayed the positive lymph nodes and LVSI.

The histologic grading or risk stratification model is widely used to predict the prognosis in patients with various malignant tumors. In SDC, the application of the Nottingham histological grade was inappropriate because of the inability to stratify SDC cases as the previous studies, and a histological risk stratification model specific to this lesion has been warranted. In a recent study, Nakaguro *et al*. proposed a risk stratification model based on 4 histological features: prominent nuclear pleomorphism, mitoses, vascular invasion, and poorly differentiated clusters [11]. The evaluation criteria of nuclear size and pleomorphism, mitotic count, and tubule formation were primarily based on the Nottingham histological grade. The nuclear pleomorphism was defined that tumor cells had nuclei with marked variation in size and possessed prominent nucleoli. The mitotic count was determined in 10 fields with a ×40 objective lens (HPF). High mitotic counts were defined as ≥30 mitoses in 10 HPF (same field diameter). Vascular invasion was assessed by H&E staining. A poorly differentiated cluster (PDC) was evaluated as a cancer cell cluster composed of ≥5 cancer cells lacking a gland-like structure at the invasive margin. Patients were assigned to 3 risk groups according to the total number of positive factors (among these 4 factors), as follows: low risk (0 to 1 point); intermediate risk (2 to 3 points); and high risk (total 4 positive factors) [11]. According to these risk stratification criteria, both of our patients were in the high-risk group. The most patients with SDC were found in the advanced stage. In the previous study, 39% of SDCs were seen with T4 disease, and most patients had more than 2 positive lymph nodes (stage N2b), although 12% had no lymph nodes removed (stage Nx). Three patients were initially seen with distant metastasis [7]. Two the present cases were staged in IVC with distant metastasis.

The standard treatment for SDC is total salivarectomy, ipsilateral neck dissection followed by postoperative radiation therapy with or without concurrent chemotherapy. In addition to surgical resection followed by radiotherapy and conventional chemotherapy, recent advances in molecular-targeted therapy have broadened the therapeutic strategies, with approaches such as trastuzumab targeting the HER2 or combined androgen blockade targeting androgen receptor. However, molecular-targeted therapy has not yet been provided worldwide as a standard treatment option, and drug resistance is a perplexing problem that remains to be overcome [9]. Given the limited published data on the use of adju-

vant or maintenance Trastuzumab in SDC, it might also be useful to develop future Trastuzumab trials in SDC from Her2/neu positive breasts. As in breast cancer, patients with SDC, and HER2 overexpression derive benefits from anti-HER2 therapy. In a phase II study, 57 patients with advanced SDC received docetaxel and trastuzumab, with an objective response rate (ORR) of 70.2%. The median progression-free survival (PFS) was 8.9 months and overall survival (OS) was 39.7 months [12]. The use of double HER2 blockade with trastuzumab and pertuzumab was also evaluated in a basket study, which included five patients with advanced, refractory SDC, all with HER2 amplification/overexpression. Trastuzumab and pertuzumab, without chemotherapy, yielded a partial response in four out of five patients with HER2-positive SDC (ORR of 80%) [13]. In this report, after targeted therapy of anti-HER2 combined with chemotherapy, our 2 patients responded well to the treatment, especially the 2nd patient had yielded a complete response. Recent data has shown that Her2/neu overexpression and targeted therapy with Trastuzumab therapy are associated with improved DFS and OS rates [8]. AL-Qahtani*et al.* demonstrated that the poor prognostic factors for OS and DFS in SDC patients were age 50 years or above, tumor size, and lymph node involvement [6]. Their study showed median follow-up was 20.2 months (range: 11 - 48). Four patients (57.2%) were alive and disease free. The median time to survival was 15.8 months. The 4-year locoregional control, distant metastasis control, DFS and OS rates were 20.8%, 40%, 16.7% and 40%, respectively [6].

Taken together, interestingly, patients with salivary carcinoma displayed the molecular characteristics of breast cancer such as the enriched HER2 molecular subtype of SDC who are likely to benefit from the molecular targeted therapy as anti-HER2. The two current patients displayed a good response to this novel targeted therapy.

4. Conclusion

The present cases suggest that it is crucial for pathologists and oncologists to recognize this rare entity. It always keeps reminding every physician's mind to perform additional immunohistochemical staining including Her2/neu, Ki-67, estrogen receptors (ER), progesterone receptors (PR), and androgen receptors in order to make the exact adjuvant therapy decision.

Statement of Ethics

Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the patients for publication of details of their medical cases and any accompanying images.

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Conflict of Interest

The authors declare no conflicts of interest.

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