

LARGE CELL UNDIFFERENTIATED CARCINOMA OF PAROTID GLAND: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Large cell undifferentiated carcinoma of parotid gland is a rare disease of salivary gland cancer accounting about 1%, however, it has high malignancy and very poor prognosis. We report a clinical case with symptoms of left parotid gland tumor, rapid growth, invasive skin and superficial ulceration. The differential diagnosis is difficult between parotid adenocarcinoma and skin cancer or metastatic cervical lymphoma. The patient underwent extensive surgical resection of the lesion, radical cervical lymphadenectomy, and reconstruction with local flaps. The definitive diagnosis after surgery: large cell undifferentiated carcinoma of the left parotid gland stage IV (pT4aN0M0). The patient did not receive early radiation therapy, therefore local recurrence and distal metastasis, and death 6 months after surgery.

Keywords: *large cell undifferentiated carcinoma, LCUC, salivary cancer...*

I. INTRODUCTION

Large cell undifferentiated carcinoma (LCUC) is a rare form of salivary gland cancer. According to the World Health Organization classification, LCUC is a subtype of undifferentiated carcinoma of the salivary gland, which includes: small-cell undifferentiated carcinoma, large-cell undifferentiated carcinoma, and lymphoepithelial carcinoma. LCUC is rare,

accounting for about 1%, but has a high malignancy and a poor prognosis [1]. Because this disease is rare and only reports with a few cases are available, our understanding of the epidemiology, lesion characteristics as well as prognosis and treatment is limited. Diagnosis of LCUC is based on clinical signs and symptoms as well as subclinical results, but final diagnosis must need histopathological results. Radical surgery and postoperative adjuvant radiotherapy are the main treatment methods. However, LCUC has a poor prognosis and its 5-year survival rate is only about 36%.

We introduce a severe case of large cell undifferentiated carcinoma of parotid gland with relatively typical clinical signs and symptoms, which progresses very rapidly. So, we can get experience in diagnosis, treatment and prognosis for this rare disease.

II. THE CASE STUDY

P.X.T, a 64-year-old man with history of hypertension, appeared an ulcerative lesion behind posterior and inferior region of the left ear. At lower-level hospital, he was diagnosed with parotid abscess and received medical treatment with antibiotics and anti-inflammatory medications. After treatment, the disease progressed rapidly and was more severely. His ulcerative lesion had a size of about 2x3cm, infiltrated to the skin and subcutaneous tissues of the parotid region and the earlobe, pushed out the left external auditory canal, and was accompanied by pain. The patient had no signs of dysfunction

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of facial nerve branches. He was biopsied and the result showed suspicion of malignant lesions. Then, he was transferred to the Craniofacial and Plastic Surgery Center of

108 Military Central Hospital on June 2021. Here, he received biopsy of the lesion again, and the histopathological result was a differentiated squamous cell carcinoma.

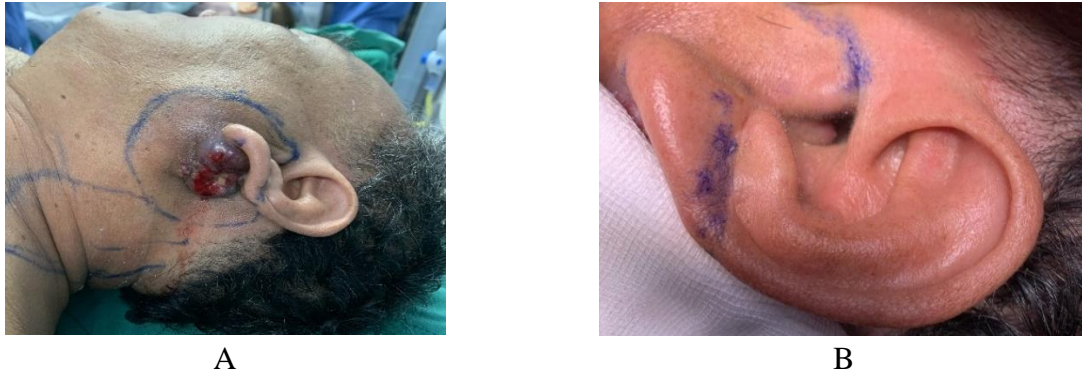


Figure 1: A, Ulcerative lesion and skin infiltrates in the left parotid gland, B, The lesion pushed out the left external auditory canal (patient P.X.T).

The screening and staging tests for cancer showed that MRI's image of neck and face showed a left parotid tumor, located mainly in superficial lobe of the gland, with a size of about 38.7 x 36 x 37.8mm, irregular border, decreased signal on T1, increased signal on T2, and central necrosis. The tumor enhanced strongly and heterogeneously after injection of contrast agents, infiltrated to the skin behind posterior and inferior region of the left ear, pushed out left external auditory

canal and had possibility to invase buccal branches of the facial nerve. However, left cervical nodes in groups II and III did not change their morphology. Other tests including computed tomography for chest and abdomen, endoscopy for ear, nose, and throat, upper and lower GI endoscopies showed no abnormal lesions. Bone scans did not show suspicious lesions caused by Metastases.

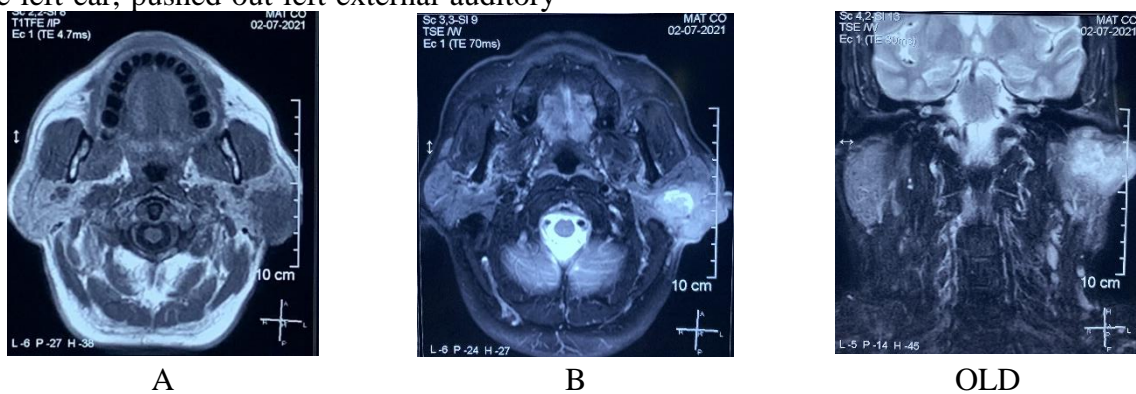


Figure 2: Lesions of left parotid gland on MRI.

A,B: On Axial slices, the tumor was located mainly in superficial lobe, and infiltrated to the skin
 C: On Coronal slices, the tumor pushed out left external auditory canal (patient P.X.T).

Consultation to confirm the initial diagnosis concluded that the patient got carcinoma of left parotid gland at stage IV (c T4 a N x M0), and he would receive extensive surgical removal of the cancerous lesion, removal of left entire parotid gland and invaded branches of facial nerve, radical dissection for cervical nodes, and defect reconstruction with local flaps. After surgery, he would receive adjuvant radiotherapy when stable.

The patient underwent surgical removal of the entire tumor with surrounding infiltrated skin region, removal of the entire parotid

gland with invaded buccal branches of the facial nerve, parts of the earlobe, the left external auditory canal, and dissection for left cervical nodes in groups I, II and III. The remaining areas, location of the nerve root and nodes in groups I, II and III were biopsied. The result showed no tumor cells remaining.

After removal of parotid gland, defect of soft tissue was covered by the ipsilateral sternocleidomastoid flap. The skin defect was covered by the left occipital region-neck-shoulder fasciocutaneous flap.

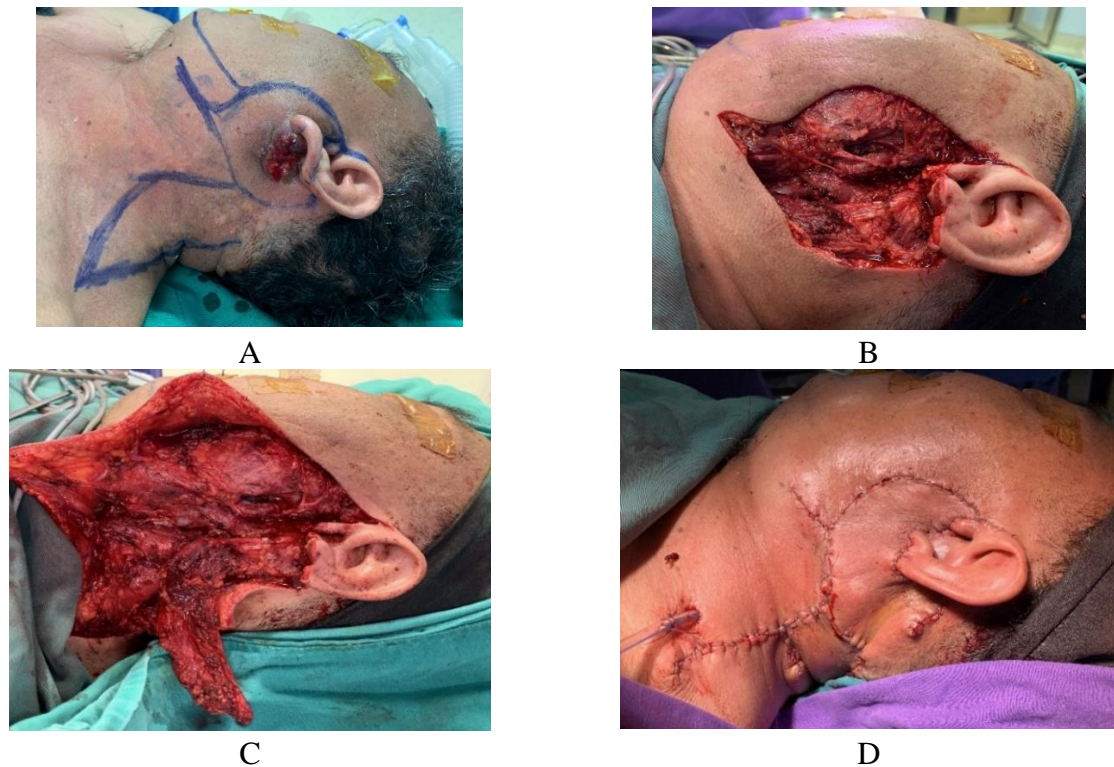
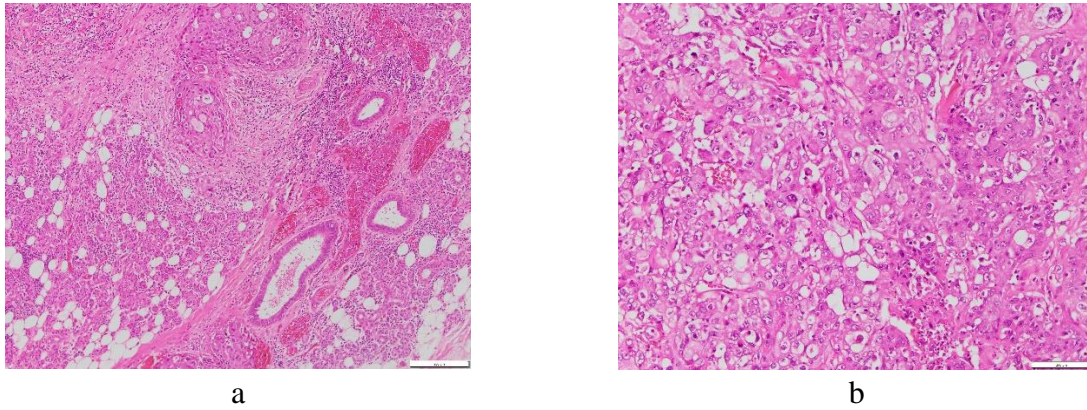


Figure 3: A, Design of the incision for removal of the lesion - skin flap. B, Defect of soft tissue after extensive removal of the lesion. C, Removal of the occipital region-neck-shoulder fasciocutaneous flap. D, Postoperative outcome (patient P.X.T).

Postoperative histopathological results of the tumor showed Large cell undifferentiated carcinoma (LCUC). Histopathological results of the left cervical nodes showed no tumor cells.



a. Tumor and salivary gland tissues b. Tumor cells with large nuclei, and wide cytoplasm

Figure 4: Histopathological images of patient P.X.T

After surgery, the patient received critical care, then his incision was healed in the first stage, and he was discharged 1 week after surgery. Diagnosis at discharge was Large cell undifferentiated carcinoma of parotid gland at stage IV (pT4 a N0M0). He was appointed for radiotherapy 1 month after surgery.

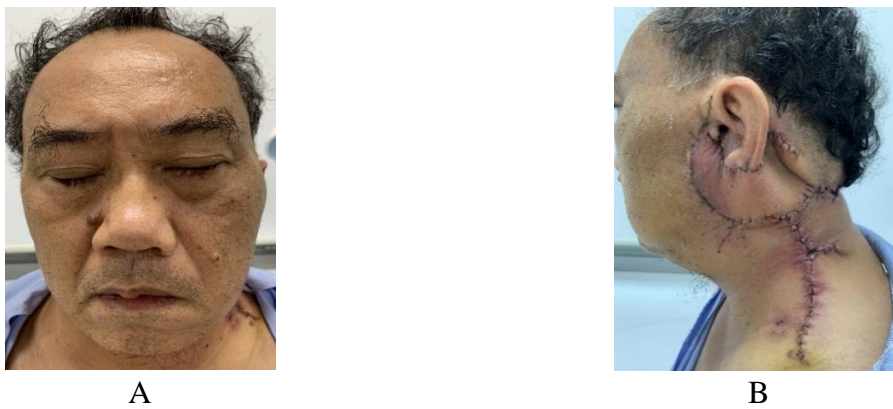


Figure 5: A, B the incision 1 week after surgery (anterior and lateral views) (patient P.X.T)

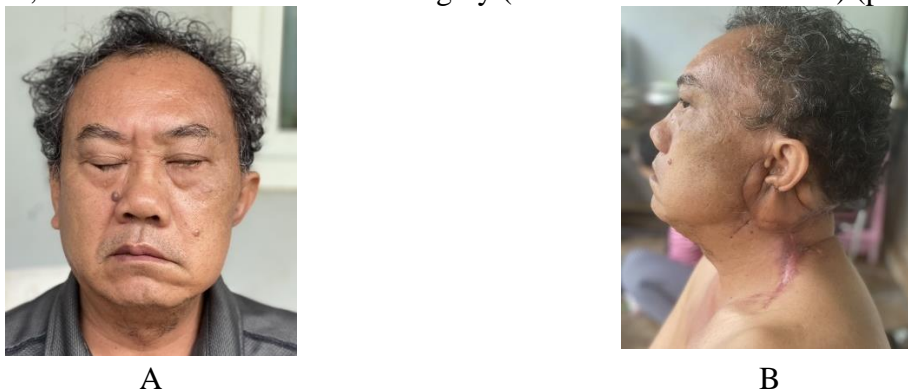
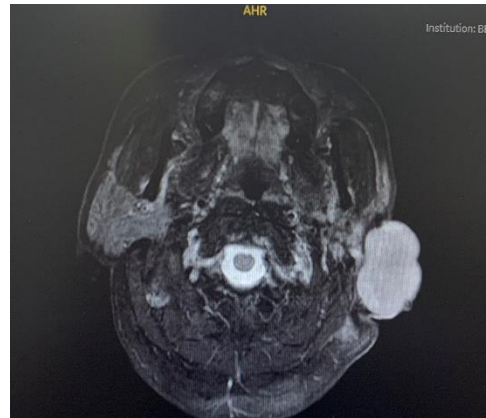


Figure 6: A, B incision 1 month after surgery (anterior and lateral views) (patient P.X.T)

Due to the impact of the Covid-19 pandemic, the patient did not receive early adjuvant radiotherapy. After 4 months of surgery, the lesion recurred locally, and metastasated to the lungs and thoracic spine. He received aggressive chemotherapy but had a poor response and died 6 months after surgery.



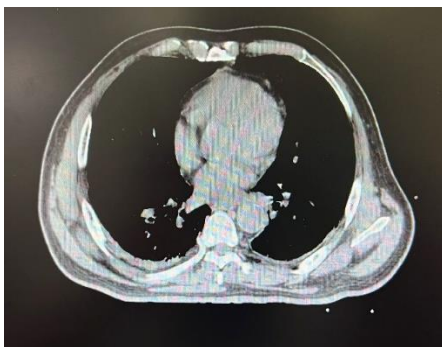
A



B

Figure 7: A, The lesion recurred locally 4 months after surgery

B, The tumor recurred in the left parotid region on the Axial slice of MRI image (patient P.X.T)



A



B

Figure 8: Chest CT image

A, Metastatic lesions in 2 lower lobes of the lungs on the Axial slice

B, Metastatic lesions in thoracic vertebrae T2, T3 on Sagittal slice (Patient P.X.T)

III. DISCUSSION

3.1. Diagnosis of large cell undifferentiated carcinoma:

P.Schrank, who studied on 36,224 patients with salivary gland cancer, finds that the LCUC rate accounts for 0.68%, mostly in parotid gland (89.5%), less common in the

submandibular gland (10.1%). LCUC is common between the ages of 60 and 65. Its male-to-female ratio is 2:1, and about 70% presents signs and symptoms at late stages with local invasion and regional node metastasis.

Wang et al. emphasizes that LCUC's main signs and symptoms are a rapidly growing mass (92%), pain in affected gland (33%), facial paralysis (8%) and cervical lymphadenopathy (58%) [2]

According to Robert L. et al., invasion of the skin and surrounding soft tissue is a very common symptom in LCUC [3].

P.X.T, a 64-year-old patient, presents with relatively typical symptoms of LCUC of parotid gland such as: a rapidly progressing lesion with pain in affected gland, causing skin ulceration and compression of the external auditory canal. MRI image shows that the lesion is located in superficial lobe of the gland, strongly enhances with contrast agent, infiltrates to the skin and the external auditory canal. Ipsilateral cervical nodes in groups II and III are seen, although not morphologically changed.

Because the disease is rare and experience in the diagnosis and treatment for it is limited, so when the patient was treated in lower-level hospital, doctors misdiagnosed a parotid abscess there, and treated with medical regimen but not effected. Only until the tumor are removed and biopsied for histopathology, we can have the final diagnosis as large cell undifferentiated carcinoma of salivary gland.

Thus, symptoms of a parotid tumor progress rapidly, causing pain with skin invasion. These help us oriente the diagnosis of LCUC, but the final diagnosis still has to be based on histopathology. MRI is very helpful in staging, which helps to assess the extent of invasion and metastasis of the tumor, thereby making a suitable treatment plan.

3. 2. Surgical treatment for large cell undifferentiated carcinoma of salivary gland:

Because preoperative diagnosis is carcinoma of salivary gland at stage IV (cT4aNxM0), i.e the tumor has passed beyond border of the gland's capsule, and invaded into adjacent tissues. In addition, there is no evidence to confirm cervical and distant metastases. So, we need to make a plan for how to remove the lesion, how to dissect cervical nodes so that no tumor tissue remains and recurrence rate is low.

Toshitaka Nagao, who reportes 2 cases of LCUC, emphasizes that this is a cancer type with very high malignancy and recurrence rate after surgery. He reportes a case with large tumor, local invasion and no node metastasis. This patient receives preoperative chemoradiotherapy, then undergoes surgical removal of the entire lesion with radical dissection of the cervical nodes. After surgery, this patient continues to receive adjuvant radiotherapy. However, the lesion recurs locally after only 4 months. Another case has a small lesion in superficial lobe of parotid gland, which has not metastasized to the cervical nodes. This patient receives extensive removal of the lesion, radical dissection of the cervical nodes and postoperative adjuvant radiotherapy. However, the lesion recurs in the ipsilateral cervical nodes after only 2 years [4].

The principle of radical surgery is extensive removal of the entire tumor tissue, ensuring that the remaining removal area is negative. According to the recommendations of the American Society of Clinical Oncology (ASCO) in 2020, removal of the lesion should at least perform that of superficial lobe of parotid gland and consideration of total glandectomy is necessary for late-stage patients, because parotid cancer with high malignancy and late

stages has a high risk of lymph node metastasis. [5].

Surgical dissection of the cervical nodes should be considered for all cancers with high malignancy and late stages (adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma, etc.) although there is no evidence of lymph node metastasis. Histopathological results for assessment of lymph node metastasis after surgery play an important role in prognosis as well as selection of adjuvant therapy [6] [5]. According to P.Schrank, about 28% patient with LCUC of parotid gland has cervical lymph node metastasis. Dissection of the cervical nodes helps limit recurrence and improve survival rate after surgery [8].

Our patient has a stage IV cancer. The tumor is large (38.7 x 36 x 37.8mm), located in the superficial lobe of the salivary gland, invading the skin behind his ear, parts of the earlobe and ipsilateral external auditory canal. Ipsilateral cervical nodes in groups II and III do not change their morphology. Therefore, he is suitable for extensively surgical removal of the lesion, radical dissection of the cervical nodes: removed skin area includes the entire ulcerative part and its surrounding infiltrates, about 1.5 cm from the edge of the lesion, and parts of the left earlobe and external auditory canal. Removal of entire left parotid gland with the buccal branch of the left facial nerve related to the tumor, and dissection of the left cervical nodes in groups I, II, III are done. Remaining removal area is biopsied in location of skin in front of the ear, behind the ear, neck, external auditory canal, earlobe, masseter muscle and next to the left facial nerve root. Cervical nodes in groups I, II, and III are collected for histopathology. The result shows no tumor cells.

3.3. Adjuvant treatment after surgery:

Our patient's final diagnosis after surgery is large cell undifferentiated carcinoma of parotid gland at stage IV (pT4aN0M0). This is a late stage cancer, which has high malignancy in histopathology. According to the ASCO recommendations, all these cases should receive adjuvant radiotherapy after surgery [5]. According to Hosni.A et al., adjuvant radiotherapy after surgery for salivary gland cancer helps improve the effectiveness of local lesion control and survival rate, especially for lesions with late stage, removal area which remains tumor cells, lymph node metastasis, vascular and neurological invasion as well as cancers with high malignancy [7].

Due to the impact of the Covid-19 pandemic, travel is restricted strictly, so the patient does not receive adjuvant radiotherapy early. Thus, he recurs the lesion locally and has metastases to lungs and thoracic spine. He receives aggressive chemotherapy but dies after 2 months of treatment.

3.4. Prognosis of large cell undifferentiated carcinoma of salivary glands:

LCUC is a rare disease. The prognosis plays a very important role, which helps the surgeon make a suitable treatment plan and explain to the patient and family properly about the disease. According to P.Schrank, 5-year- and 10-years survival rates are 50% and 31% for early stages (I and II), and are 35% and 18% for late ones (III and IV) respectively, in a case with negative removal area as 48% and 33%, while removal area which remains tumor cells as 31% and 9% respectively [1]. In the study of Wang et al., the survival rate of more than 2 years in LCUC patients with cervical node metastasis

is 14%, while that of LCUC patients without cervical node metastasis is 75% [2] . Toshitaka Nagao, who studied 2 cases of LCUC, emphasizes that patients have very poor prognosis despite of extensive surgery and combined treatment with many methods. 1 case dies after 5 months of surgery, the other dies after 4 years [4] . There is no specific report on the postoperative recurrence rate of LCUC, however, the overall postoperative recurrence rate for parotid gland cancer is about 10.1% according to Prekazi- Loxha [8] . Patient P.X.T came to us at a late stage and did not receive early radiotherapy, so relapsed and died 6 months after surgery.

IV. CONCLUSION

Through this case and medical literature, we find that large cell undifferentiated carcinoma of salivary gland is a rare disease with high malignancy, very poor prognosis, and common in parotid gland. Clinical signs and symptoms usually progress rapidly and accompany pain, infiltrates to the skin and soft tissues around the gland, so it is easy to be confused with other diseases. Final diagnosis mainly bases on histopathological results . Extensive surgical removal of the lesion and radical dissection of cervical nodes are main treatment for LCUC. After surgery, patients need adjuvant radiotherapy and periodic follow-up. However, its mortality rate is still very high despite of early detection and radical treatment.

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