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Salivary Duct Carcinoma of Parotid Gland with Femur Metastasis: Case Report and Literature Review

SUMMARY

Background/Aim: *Histologically similar to both in situ and invasive ductal carcinoma of the breast, salivary duct carcinoma (SDC) is an uncommon and excessively aggressive subtype of primary salivary gland carcinoma. The salivary gland most frequently involved in cancer cases is the parotid. With an estimated frequency of 1 in 1,000,000 individuals, SDC is an incredibly rare cancer that is more common in men. Due of its early metastasis to distant areas and regional lymph nodes, it is frequently identified at an advanced stage.* ***Case report:*** *We present a case of SDC of the parotid gland with femur bone metastasis as well as a detailed literature review for SDC. According to the existing literature, this is the first reported case of salivary duct carcinoma of the parotid gland with femur metastasis. Currently the patient remains stable with no signs or symptoms of recurrence.* ***Conclusions:*** *It is crucial to note the possibility of femur metastasis from salivary duct carcinoma of the parotid gland for the most appropriate treatment plan determination, and a more comprehensive understanding of the disease's progression.*

Keywords: Salivary Duct Carcinoma, Femur, Metastasis

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Introduction

Salivary duct carcinoma (SDC) is a rare, highly aggressive form of cancer. It was reported by Kleinsasser and colleagues in 1968, and it was indicated that this lesion was dialectal between a salivary cancer and an in situ or invasive ductal carcinoma[1-7]. SDC is the least common cancer type among all salivary gland malignancies (5–10%) with the parotid gland being affected by 80% of all patients, followed by the submandibular gland (8-12%) and a smaller percentage of minor salivary glands (<10%)[1]. The frequency of the SDC vary between 1-1.2:1000000, being more common in men.

The most up to date classification by the World Health Organization[2,3] suggests that of the 21 subtypes of primary salivary gland cancer, SDC is believed to be the most invasive, commonly spreading to local and distal sites[4-6]. Since it is many times detected in advanced states[1,2], there might be a need for further research on its early detection and treatment. Whereas very few systematic studies have been conducted, and only on a limited basis, the main therapeutic modalities are radiation and surgery[7-9]. Regretfully, patients diagnosed with SDC often end up with approximately a 3 year life expectancy after diagnosis, which defines the disease low survival rates[7–10].

In spite of this, development of immuno-histochemical and molecular techniques, as well as the investigation in recent times involving several organizations, holds the key to better understanding of SDC. It is anticipated that these changes will be reflected in the diagnosis and treatment methods of the future. A thorough synopsis of current developments to raise awareness of SDC during cytological diagnosis is provided by this review and case report.

We present a case of salivary duct carcinoma of the parotid gland that locally spread to the temporal region and further metastasized to the femur 4 years post-primary surgery.

Case Report

A 73-year-old, female patient was referred to our institution after a biopsy that diagnosed a malignant salivary gland tumour of the type of salivary duct carcinoma. The patient presented with a complaint of pain and a growth on the left parotid area. The tumour was fixed and immovable on palpation, with approximately 3x2 cm size. Furthermore, facial palsy with inability to wrinkle the forehead and close the affected eyelid was noted on clinical examination. Based on the institutions protocol for tumour investigation the patient was referred for X-ray and MRI scans.

Head MRI showed an expansile ill-defined tumorous lesion of the anterosuperior aspect of the left parotid, measuring 3x15 cm (Figure 1). The most anterior tumour aspect overlying the masseter appeared to extend into the subcutaneous fat of the area. There was no evidence of infiltration of the masseter. Another suspect focal lesion was shown within the lower posterior aspect of the gland measuring 12 mm. In addition, there were multiple borderline or slightly enlarged longitudinal shaped lymph nodes of the submandibular area, angle of the jaw and anterior and posterior triangle bilaterally, compatible with chronic reactive lymphadenopathy.

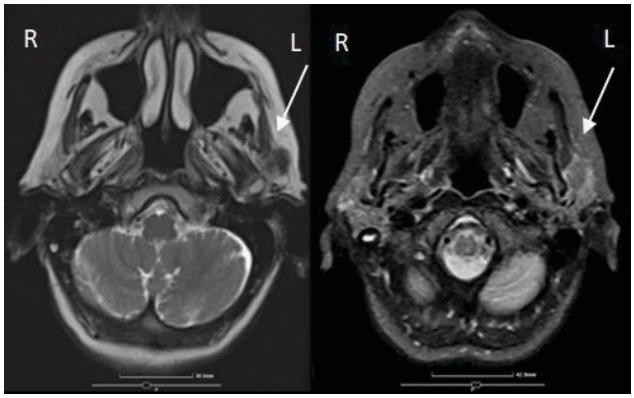

Figure 1: Head MRI without contrast showing an expansile 3x15 cm tumorous lesion of the anterosuperior aspect of the left parotid

A Fine Needle Aspiration (FNA) biopsy was performed confirming a malignant salivary gland tumour of salivary duct carcinoma type.

Subtotal left Parotidectomy with facial nerve preservation, was conducted under general anaesthesia (Figure 2A and 2B). Preservation of labial and buccal branches along with sacrifice of the frontal nerve that was involved in the tumour. Frontal nerve anastomosis with auricular nerve graft took place. Furthermore, left regional cervical lymph node removal was performed. A 3x2x1.5 cm mass was resected (Figure 2C). The histopathologic examination revealed SDC of the left parotid (Figure 3). The neoplasm was proximal to the resection margin, while infiltrating vessels and nerves and lymph nodes. The patient was referred for adjunctive radiotherapy and was yearly followed-up.

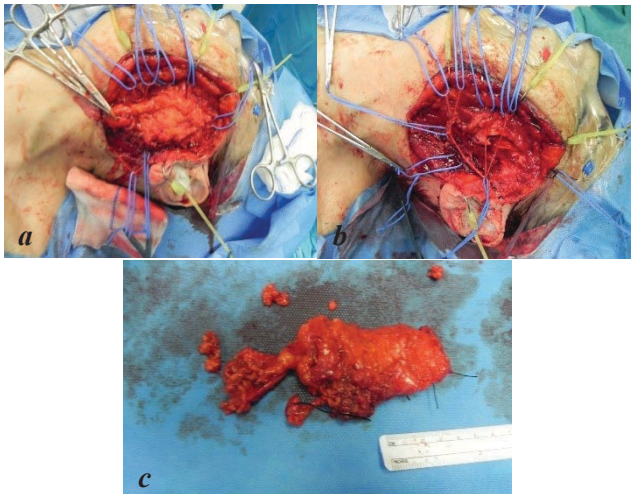

Figure 2: Intraoperative clinical pictures of surgical procedure for mass removal;
***a**: Intraoperative picture before mass excision, **b**: Intraoperative picture after mass excision; **c**: 3 x 15 cm mass excised from the neck.*

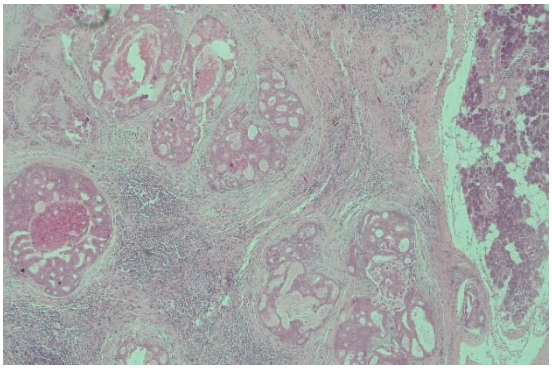

Figure 3: Salivary duct Carcinoma – parotid primary; H&E staining; magnification x40.

Four years later, the patient noticed a new growth under the area of the left zygomaticotemporal area, as well as an atypical skin lesion. FNA biopsy of the mass was performed, and recurrent malignancy was identified. A CT scan of the Head/Neck and Thorax was conducted showing thickening with contrast enhancement of the temporal left subcutaneous soft tissue in an area of approximately 34x11mm due to local recurrence of the disease. No obvious presence of lymph node swellings in the lateral cervical regions or presence of unevenness in the parapharyngeal areas. No other obvious metastatic disease was noted from these CT scans. Local surgical removal of the tumour in healthy clinical margins, as well as the involved skin was performed, for potential recurrency clearance. The histopathologic examination of the excised sample showed metastatic infiltration in the

dermis from salivary duct carcinoma with characteristics of high-grade transformation. Some areas of the borders showed infiltration from the SDC. The patient then underwent a new cycle of radiotherapy.

Five months later, the patient complained of worsening pain around the area of the left hip. An orthopaedic surgeon referred the patient for x-rays and a PET/CT scan in which a suspicious lytic lesion was identified. Specifically, scarcely hypermetabolic osteolysis of the left femoral diaphysis distally and moderately hypermetabolic osteolytic lesion of the same diaphysis proximally was found (Figure 4). Surgical removal of the lesion along with stabilization with an intramedullary nail due to high risk of impending fracture with suspicion of metastatic disease was performed at the femoral area (Figure 5). A histopathologic examination was performed and metastatic cancer with morphologic characteristics compatible with SDC was diagnosed based on the patients' medical history (Figure 6). Specifically, glandular forming structural formations of cuboidal moderately pleomorphic eosinophilic cells, exhibiting nuclear hyperchromasia and rare mitotic figures were identified in the sample. The patient underwent radiotherapy treatment. As a follow-up, the patient undergone abdominal MRI and CT scan of the head, neck, and thorax areas every 6 months. A year after the hip treatment, the patient is still without recurrence.

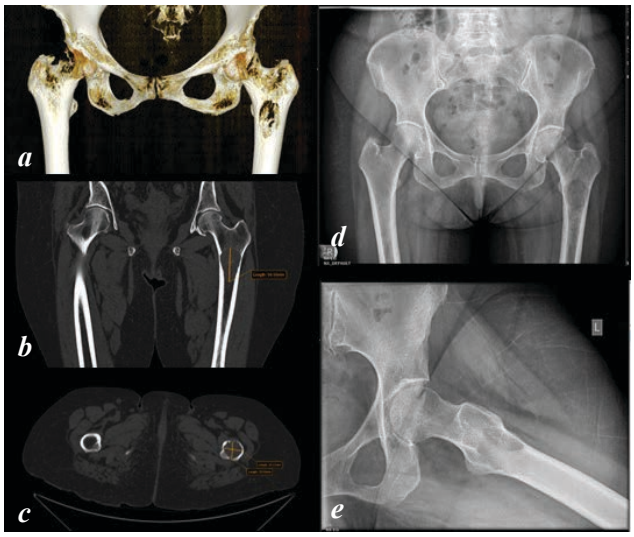

Figure 4: CT scan & Xray of femoral region with bone lytic lesion.
a: 3D CT view of femur with hypermetabolic osteolysis of the left femoral diaphysis distally and proximally.
b: Coronal plane view with a 5 cm osteolytic lesion of the left femur.
c: Axial plane view with a 2,8 x 3 cm osteolytic lesion of the left femur.
d: Anteroposterior radiographs of pelvic & femoral region with osteolytic lesion on left femur
e: Plain radiograph of left femur showed a localized lytic bone lesion.

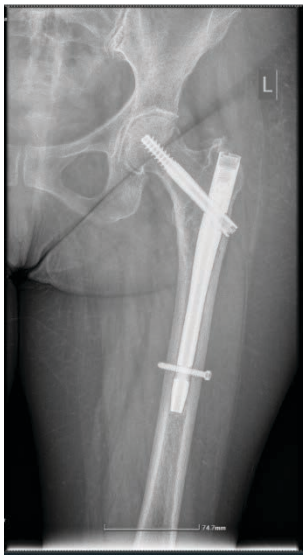

Figure 5: Post surgery radiographic image of lesion stabilization with intramedullary nail.

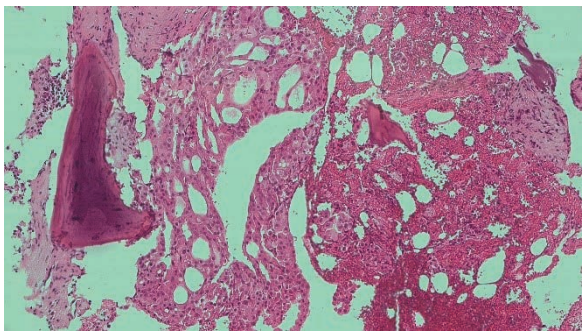

Figure 6: Salivary duct Carcinoma – bone metastasis; H&E staining; magnification x100.

Discussion

In 1991, the World Health Organisation (WHO) identified SDC as a unique malignancy with 0.5-3% prevalence, being one of the most rare salivary gland cancers[1]. The majority of tumours arise de novo; however, 20% of incidents are secondary to benign pleomorphic adenoma, which is known as carcinoma ex pleomorphic adenoma[1,11]. A painless lump in the neck is the most common early symptom. In more advanced cases, facial nerve damage may even result in facial weakness[1,12]. Patients with SDC are males in majority and are usually diagnosed between 34-83 years, with a mean diagnosis age of 62 years old[1,3,10].

Metastasis

The SDC is an extremely fluctuating high-grade salivary carcinoma with an early upsurge of lymphogenic and hematogenic metastasis. High-grade recurrence is the main problem in subsequent treatment and the percentage

of regional metastases (20 to 73%) is higher than reported distant metastases (25-80%)[13]. Between 20 and 40 percent of distant failures occur, with high-grade tumours having a higher probability of failure[14]. The detailed examination of the initial histological type was found to be the single most reliable prognostic indicator of the time elapsed before the distant metastases occurred. Early metastatic dissemination is well acknowledged to be a sign of aggressive biology in many cancers and is associated with a decreased chance of survival[14].

The most common sites of distant metastasis are the lung, bone, brain, and liver[1,14,15]. Although rare cases of adrenal gland, Sinonasal Tract, cutaneous, vaginal, breast, small bowel, internal auditory canal, gingival, facial canal, distant lymph nodes, bone marrow, gastric, mediastinum and axilla metastasis have been also found in the literature 16-36.

Regarding bone metastasis, to our knowledge, the ribs, pelvis, spine, and cranium were mentioned in the literature and this is the first case reporting SDC with metastasis to the femur bone.

Because the long bones are important for walking and weight bearing, metastases to them can seriously impair a patient's ability to function. Severe pain, loss of function, pathological fractures, bone marrow aplasia, spinal cord compression, and hypercalcemia are examples of skeletal-related events that significantly worsen quality of life. Non-specific symptoms like malaise, appetite loss, and weight loss may also accompany skeletal-related events. Since treatment for bone metastasis is multimodal, rarely curative, and mostly focused on symptom palliation and prevention of disease progression, it is regarded as a chronic condition.

Histology and Prognosis

SDC has a cribriform pattern of spread and a high proliferation rate, closely resembling that of high-grade mammary ductal carcinoma[3,6]. Many individuals have morphologic signs of apocrine differentiation, such as apocrine snouts and secretions; however this evidence may only be localised. Apocrine differentiation results in abundant eosinophilic, granular, vacuolated, or foamy cytoplasm in nearly all individuals. Even in invasive cases, SDCs frequently exhibit well-defined nests with cribriform architecture, structures resembling Roman bridges, and comedo-type necrosis that mimics the look of breast ductal carcinoma in situ (DCIS)[6].

Perineural (PNI) and lymphovascular invasion (LVI), which are observed in 28-85% and 20-71% of patients, respectively, are frequently linked to SDC[1,6,7,10]. PNI and LVI were reported by Cheng et al. to be often prevalent in roughly 57-69% and 61-70% of individuals, respectively. In 58% of patients, there was extranodal invasion[1]. Large pleomorphic nuclei with noticeable nucleoli, coarse chromatin, and an abundance of eosinophilic cytoplasm are all present in the cancer cells[3,6]. Although more uniform nuclear enlargement can often make it difficult to identify, this major nuclear enlargement, nuclear pleomorphism is often marked[6]. Moreover, big "cherry-red nucleoli" are frequently seen. Typically, there is prominent mitotic activity and unusual mitotic figures[6].

While SDC and breast cancer have similar histological features, SDC demonstrates more pronounced cellular atypia and more mitoses[3]. Mucin-rich, sarcomatoid, invasive micropapillary, oncocytic, and rhabdoid are among the histologic variants of SDC that have been identified[3]. The prognosis for rhabdoid, invasive micropapillary, and sarcomatoid SDC is reportedly worse than that of ordinary SDC[3]. SDC is the most prevalent subtype of carcinoma ex PA because it results from preexisting pleomorphic adenoma (ex PA) in 20%-59% of cases[3]. While SDC is generally considered as a highly malignant tumour, it is important to note that several histologic characteristics can be independent prognosticators, in addition to the tumour TNM stage[3,10]. Clinical stage IV disease, nodal status, positive surgical margins, extranodal extension, and PNI are all strongly associated with decreased survival[3,6]. Generally, patients with poorly differentiated clusters, made up of >5 cells without gland formation and high numbers of tumour buds, as well as tumor cell clusters made up of up to 4 cells, have worse prognosis[3]. Besides, it was found out that the patients with involvement of parotid gland were supposed to have a higher cure rate than patients who demonstrated other salivary gland involvement[1].

FNA

Aspirates of SDC are easily recognised by fine-needle aspiration (FNA) as "malignant" in the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) due to the clear nuclear characteristics of high-grade carcinoma. When the sample is sufficient, the cytological diagnosis of malignancy is simple to make; nevertheless, it is not always possible to make a definite diagnosis of SDC based only on cytomorphologic features[3]. High-grade mucoepidermoid carcinoma, high-grade transformation of diverse primary salivary gland carcinomas, adenocarcinoma, not otherwise defined, and metastatic malignancies from other anatomic sites are among the differential diagnoses of SDC in FNA samples[3].

Immunohistochemistry

When combined with positive staining for GATA3 or GCDFP, immunohistochemically detected strong and diffuse AR expression is a useful tool in the diagnosis of SDC[3]. When separating mucoepidermoid carcinoma from SDC, which typically tests negative for p63, its expression is useful[3]. In contrast, 10% of cases of salivary gland tumours other than SDC, such as pleomorphic adenoma, adenoid cystic carcinoma, and acinic cell carcinoma, have been documented to express AR[3]. AR

immunohistochemistry should be used to support the morphologic characteristics that are the primary basis for the diagnosis of SDC[3]. SDC and invasive ductal breast cancer are physically similar by definition, and 85-100% of invasive ductal breast carcinoma cases express AR[3]. In certain situations, the absence of progesterone or oestrogen receptor expression in SDC may be beneficial to distinguish between SDC and metastatic carcinoma of breast origin.

In terms of correlation between prognosis and immunohistochemistry markers, it has been observed that individuals with AR who express forkhead box protein A1 (FOXA1) had a better prognosis[3]. Null or diffuse strong expression of p53, which indicates the existence of a TP53 point mutation, and CK5/6 staining are substantially related with a worse prognosis, even if HER2 status has no effect on patient survival[3]. Compared to other SDC cancers, "Apocrine A" type SDC (AR+, HER2-, Ki-67 low) on biomarker categorization demonstrated a superior prognosis[3].

Imaging Characteristics

Most SDCs show up on imaging to be advanced malignant tumours on a radiological level. When method-stated SDC is compared to the different subtypes of salivary gland tumours, SDC is more commonly seen to have indistinct border, invasion into neighbouring tissue, as well as necrosis on contrast-enhanced computed tomography scanning[3]. Clinicians may suspect SDC from any aggressive clinical features like palpable nodes or facial paralysis, as well as low- to intermediate-signalling intensity on T2-weighted MRIs, ill-defined borders, and invasion into surrounding structures[7]. PET/CT reveal SDC to be a highly metabolic tumour, and this imaging modality is helpful in identifying both local and distant metastases[7].

Differential Diagnosis

The finding of a high-grade primary salivary gland adenocarcinoma with apocrine differentiation represents the initial landmark for the diagnosis of this condition. In certain patients, segregation of varied morphology implies additional difficulties; therefore, analysing of a tumour sample with classic traits features may be necessary. Although there is a lot of morphologic match between high-grade Mucoepidermoid Carcinoma (MEC) and SDC, high-grade MEC is opposed by the lack of epidermoid and mucous cells, while SDC is supported by cribriform architecture[6]. According to immunohistochemistry, p63 is often negative in SDC and positive in MEC[6]. SDC's proliferating eosinophilic cytoplasm may potentially warrant a suspicion of oncocytic malignancy. Tumour cells with oncocytic carcinoma exhibit solid organoid to trabecular development, an abundance of finely granular cytoplasm due to many mitochondria, and the potential to display high-grade nuclear characteristics[6]. Comedo necrosis is uncommon, in contrast to SDC. The presence of apocrine differentiation in SDC is the primary characteristic that sets it apart from oncocytic carcinoma. In oncocytic variant of SDC, areas exhibiting apocrine differentiation could be difficult to be located, necessitating further histology testing[6].

Because acinic cell carcinoma (aciCC) has an abundance of cytoplasm, it should also be taken into account while making a differential diagnosis in SDC. Necrosis, elevated mitotic activity, and nuclear pleomorphism that are often observed in SDC are absent in aciCC[6]. AciCC and other low-grade salivary gland neoplasms (myoepithelial carcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma) can exhibit high-grade transformation (HGT); nevertheless, in the majority of individuals, these areas of HGT have a basaloid look. Finding regions of the traditional lower-grade cancer that may benefit from IHC is beneficial in these individuals[6].

Metastatic carcinoma is another typical differential diagnosis to be taken into account. More specifically, intra- and periparotid lymph nodes can become the site of metastatic squamous cell carcinoma (SqCC) that originates in the head and neck, especially cutaneous sources. Nonkeratinizing SqCC has extensive eosinophilic cytoplasm that is similar to SDC's. IHC for p63/p40 and AR, however, can be useful[6]. Although it is uncommon, metastatic disease from locations more below the clavicles should be taken into account when a high-grade adenocarcinoma of the parotid gland, such as breast or prostatic carcinoma, is present[6].

Treatment

As of this moment, there are no National Comprehensive Cancer Network (NCCN) recommendations on the particular care of SDC. Because SDC is so uncommon, it has not been possible to undertake large-scale, definitive randomised trials that would define standard treatment techniques. According to reviews[3], the treatment options and trends available to patients with SDC are in line with the general NCCN guidelines that are advised for large salivary gland tumours. The first line of treatment for high-grade and T3/T4 salivary gland cancers is complete surgical excision of the lesions without nodal involvement (N0), with or without neck dissection.

In order to accomplish oncologically sound excision of the main site, facial nerve resection is frequently necessary (40-73%)[7]. For patients with node involvement (N+), neck dissection in addition to total surgical excision is advised. Furthermore, adjuvant radiotherapy is advised for tumours of high-risk characteristics, such as T3-4 tumours, neural/periineural invasion, lymph node metastases, near or positive margins, moderate or high grade, and lymphatic/vascular invasion. Regardless of the stage and margin status, postoperative irradiation

is a suitable therapeutic choice for SDC[1,3]. Excellent local control rates can be achieved with postoperative radiation therapy and complete surgical treatment. Smaller studies examine the efficacy of chemotherapy regimens that combine platinum and taxanes. There aren't many randomised clinical studies showing cytotoxic chemotherapy's advantages. Although smaller trials have demonstrated, there are no randomised trials that have determined the most effective cytotoxic treatment for recurring unresectable and/or metastatic SDC. Overall response rates to platinum (carboplatin) plus taxane (paclitaxel or docetaxel) treatment range from 39 to 50 percent for SDC. For different carcinoma subtypes, additional chemotherapeutic drugs such as taxanes, platinum, cyclophosphamide, doxorubicin, gemcitabine, vinorelbine, and eribulin have also been investigated[3].

Targeted therapy is the most common form of treatment for SDC. More than 90% of SDC cases exhibit androgen receptor expression, suggesting that androgen restriction therapy may be used to target the tumour[3]. Furthermore, in 15-40% of patients, HER2 expression is seen. Overall survival is increased when trastuzumab therapy is used for tumours overexpressing HER2[3].

Conclusions

The primary treatment goal for SDC patients is to achieve local control, preserve normal function, and prevent distant metastasis. Since metastasis can occur belatedly, a prolonged follow-up and a heightened level of suspicion are essential for early diagnosis, leading to a more favourable prognosis and improved quality of life. The rarity of the disease poses a challenge in pursuing further research and clinical trials to explore innovative approaches and novel therapies. Given the insidious clinical behaviour, poor prognosis, and aggressiveness of SDC, there should be increased interest in both laboratory and clinical studies to delve into the causes and progression of the condition which remains an unmet medical necessity.

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