Case Report
Proximal-type epithelioid sarcoma in the maxillary sinus: an unusual presentation

Weijin Gao, Jincai Xue, Chunyue Ma, Jingzhou Hu

Abstract: Epithelioid sarcoma (ES) is a rare histological type of soft tissue sarcoma presenting as a subcutaneous or deep dermal mass in the distal extremities of young adults. Recently, a more aggressive, so called ‘proximal-type’ ES has been described. The literature is limited on the clinical features and management of ES originating in the head and neck area. We here report a case of 16-year-old female who initially presented with progressive swelling and pain in the left cheek. On physical and radiographic examination, a malignant neoplasm was found in the left maxillary sinus with bony invasion. The definite diagnosis of proximal-type ES was based on the pathological and immunohistochemical characteristics. A subtotal maxillectomy with wide margins was performed on this patient. The patient survived uneventfully for three years. This is the first report of a proximal-type ES found in the maxillary sinus.

Keywords: Epithelioid sarcoma, soft tissue sarcoma, proximal-type, maxillary sinus, surgery

Introduction

Epithelioid sarcoma (ES) is a rare soft-tissue sarcoma, first described as an independent malignant entity by Enzinger [1]. It mostly occurs in the deep dermal or subcutaneous areas of the distal portions of the extremities of young adults [2]. Histologically, ES is a mesenchymal tumor of unknown lineage with a predominantly epithelioid cytomorphology [3]. The clinical presentation of ES is varied and can lead to a delay in diagnosis. In addition, ES may frequently be misdiagnosed as a benign necrobiotic granuloma [4] or metastatic squamous cell carcinomas [5] due to the microscopic resemblance that shows an admixture of epithelioid cells and spindle cells arranged in nodular aggregates around a central necrosis. In its classical form, ES typically occurs in the extremities (mainly the hands and wrists) of young adults as a slow-growing, solitary, subcutaneous neoplasm with mild cellular atypia, accompanied by superficial ulceration, hemorrhage, and necrosis [2, 3]. Recently, a more aggressive, so-called ‘proximal type’ ES has been described. In contrast to the conventional-type ES, the proximal-type ES exhibits a high degree of cytologic atypia, sometimes displaying a rhabdoid morphology microscopically [2, 6, 7].

ES has a high risk for local recurrence and metastasis. This tumor frequently recurs locally after excision and extends along tendon sheaths and spreads through vascular channels [3]. Unlike other sarcomas, ES displays a unique propensity to mimic epithelial malignancies and to spread by way of the lymphatic system [4, 8]. Several reports have cited lymph node involvement in 30% of the patients [9]. The prognosis of such a disease is dismal with high mortality rates in the recurrent and metastatic cases [10].

Despite sporadic reports of metastatic ES [10-12], primary ES in the head and neck region has not been well studied. We report a hitherto undescribed case of proximal-type ES arising in the maxillary sinus. Knowledge regarding the radiographic, pathologic, and clinical features is discussed.
Case report

A 16-year-old female who presented with progressive swelling in the left cheek for two months was referred to the outpatient clinic of our department. There was no intraoral or intranasal discharge with the swelling, and a history of facial trauma was denied. We were informed that during the previous two weeks it was associated with local pain and numbness and became more apparent on palpation. She was prescribed antibiotics and analgesics by a dentist but without relief. All of her vital signs were within the normal ranges.

Extraorally on inspection, a hard, nontender swelling was observed on the left midface over the body of the maxilla measuring approximately 2.5 × 3 cm. The skin over the swelling was normal in appearance and stretchable. There was no restriction in the eye movement, visual acuity, or mouth opening, and the width of palpebral fissure remained unchanged compared with the contralateral side (Figure 1).

An intraoral examination revealed the non-fluctuant involvement of the left buccal vestibule of the maxilla extending from the first premolar to the second molar. A slight swelling was also seen on the palatal side of the gingiva extending from the second premolar to the second premolar region. There was grade-2 mobility of the second molar.

Considering the patient’s age and history and the clinical observations, a malignant tumor originating from the maxillary sinus was suspected, possibly an osteosarcoma or a squamous cell carcinoma. The following investigations were then carried out: an orthopantomogram (OPG), enhanced computed tomography (CT), and an incisional biopsy (Figure 2).
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Figure 2. Radiographs of the proximal-type ES in the maxillary sinus. A: A panoramic X-ray revealed a maxillary mass with blurred boundaries; B, C: Axial and coronal CT images showed the destructive properties of the lesion in the maxillary sinus. D: Cervical CT showed no evidence of lymphatic metastasis.
The diagnosis of "soft tissue sarcoma or poorly differentiated squamous cell carcinoma" was first rendered based on the hematoxylin and eosin (HE) staining microscopic findings of the biopsy tissues. A "proximal-type" ES was finally confirmed with special immunohistochemical (IHC) stainings (Figures 3, 4). The IHC results showed a strong positivity for AE1/AE3 and CD34, but INI1 and CD31 were negative.

As no evidence of cervical metastasis was found, after discussion with the patient and her...
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Relatives, the patient underwent left subtotal maxillectomy. The postoperative course was uneventful. A partial denture obturator was used for the rehabilitation. Observation, instead of adjuvant radiotherapy, was applied to this young patient and the follow-up so far has revealed no recurrence or metastasis for three years (Figure 5).

Discussion

The term “ES” was first coined by Franz Enzinger in 1970 as a distinct form of soft-tissue sarcoma comprising large polygonal cells resembling a squamous cell carcinoma or a necrotizing granuloma [6]. Based on Franz Enzinger’s findings, ES occurs most frequently in young adult males with a predilection for distal extremities. However, according to recent data, ES only accounts for less than 1% of all adult soft-tissue sarcomas, and for approximately 4% to 8% of pediatric non-rhabdomyosarcomatous sarcomas [6, 13]. The etiology of ES remains largely unknown. A conventional (classic)-type of ES usually involves the upper extremities (commonly the hands) and displays a characteristic granuloma-like pattern, with nodules of spindled and epithelioid cells surrounding the area of the central necrosis [2]. In contrast, a more aggressive proximal-type ES was described by Guillou in 1997 for its characteristic microscopic appearance of the large carcino-

Figure 5. Postoperative follow-up of the patient. A: Frontal view of the patient; B: PET-CT examination revealed no recurrence or metastasis; C, D: Intraoral views of the defect and the partial denture obturator.

ma-like epithelioid cells with “rhabdoid” traits while sharing the same immunophenotypic profile of classic ES. But unlike the conventional-type, it is more frequently seen in the deep-seated proximal regions, such as the pelvis, perineum, and genital tract [6, 7]. However, in terms of the head and neck area, there have been very few reports regarding proximal-type ESs (Table 1). This is the first case, to our knowledge, with a proximal-type ES found in the maxillary sinus. Other reports regarding head and neck ES are listed in Table 1.

Previous reports of the radiographic findings of histologically proven ESs differed little from those of the other typical soft tissue sarcomas. Diagnostic consideration of ES is essentially based on the pathological and immunohistochemical characteristics. Conventional-type ES consists of nodular arrays of relatively monomorphic epithelioid cells, with moderate amounts of eosinophilic cytoplasms, and occasional prominent central zonal necrosis [6, 14]. Spindled cells are often peripherally situated, merging with the epithelioid cells without clear demarcations. Compared with proximal-type ES, cellular atypia and mitoses of the conventional-type are relatively mild. Proximal-variant ES is composed of diffuse growth patterns of large polygonal cells with pleomorphic vesicular nuclei and prominent nucleoli, and a frequent rhabdoid cytomorphology. However, ES, with a seemingly epithelioid pathomorphologic appearance, is often misdiagnosed when first encountered [5, 7-10]. Therefore, immunohistochemical markers are used to distinguish ES from other similar neoplasms. In our case, the differential diagnoses included squamous cell carcinoma, rhabdomyosarcomas, synovial sarcomas, epithelioid angiosarcoma, extra-renal rhabdoid tumors, and also matrix-producing osteosarcoma. Squamous cell carcinomas usually present strong and diffuse cytoplasmic staining for cytokeratin (CK) 5/6, but ESs only show focal positive staining [15]. Also, there was no detectable expression of the SMARCB1/INI1 gene product in our ES case, but the infiltrating lymphocytes and entrapping nontumor tissue showed immunoreactivity to the SMARCB1/INI1 protein as a control. SMARCB1/INI1 deficiency is relevant to ESs or malignant rhabdoid tumors [14]. To distinguish ESs from primary and metastatic carcinomas as well as other sarcomas such as malignant rhabdoid tumors, CD34 reactivity helps in reaching the final diagnosis [6]. Synovial sarcomas display a similar epithelial immunophenotype to ESs with positivity for both CK and EMA. However, synovial sarcomas usually show, at least focally, biphasic patterns allowing a correct diagnosis, and they are consistently negative for CD34 [7]. Epithelioid angiosarcomas express CD34, and resemble ESs both morphologically and immunohistochemically. It is therefore important to look for other vascular markers such as CD31 and angiocomponents, which are generally absent in most ESs [2]. The possible diagnosis of rhabdomyosarcoma is ruled out due to a lack of desmin immunoreactivity [12]. Although osteosarcomas may show a wide variety of histologic appearances, they may not be expected to show diffuse CK or CD34 expressions [14].

ES is generally considered a high-grade soft tissue sarcoma with an unfavorable prognosis [16]. Currently, the 5-year survival rate is around 50-70%, and the 10-year survival rate is 42-55%. Unfavorable prognostic factors for the overall survival of these patients have been reported to include a proximal location [2], tumor size [17], age, and gender [18]. Epithelioid sarcoma, especially the proximal-type, is also notorious for its high potential to recur when undertreated [16]. In Asano’s study, among the 33 ES patients who underwent curative wide resections (10 cases with amputation), local recurrences were still noted in 10 cases (about 30%). The tendency for an increased incidence of local recurrence was found to be significantly associated with the proximal-type ES relative to the classic-type [16]. In another consecutive series of 40 ES patients receiving multidisciplinary treatment, 26 patients still relapsed, among whom 19 died of their diseases and 2 presented relapsing diseases at their last follow-up [19]. Moreover, ES is also characterized by its high propensity to metastasize to regional lymph nodes and the lungs. Nodal involvement is a feature of ES that distinguishes it from most other types of soft tissue sarcomas [3]. Lymph node metastasis occurs in 2.6% of patients with the majority of soft tissue sarcomas. In contrast, lymphatic spread has been reported in 22% to 48% of patients with ESs [18]. Although there existed no statistics regarding whether ESs originating in the head and neck
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Table 1. Reports of ESs originating in the head and neck region

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient’s Age</th>
<th>Gender</th>
<th>Location</th>
<th>Subtype</th>
<th>Treatment</th>
<th>Neck dissection</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hagstrom J [22]</td>
<td>33</td>
<td>Male</td>
<td>Lower gingiva</td>
<td>Unknown</td>
<td>Surgery</td>
<td>Ipsilateral END</td>
<td>Unknown</td>
</tr>
<tr>
<td>Kao SY [26]</td>
<td>57</td>
<td>Male</td>
<td>Lower gingiva</td>
<td>Metastatic</td>
<td>Surgery+Chemotherapy</td>
<td>No</td>
<td>24 months</td>
</tr>
<tr>
<td>Leroy X [27]</td>
<td>35</td>
<td>Female</td>
<td>Tongue</td>
<td>Unknown</td>
<td>Surgery+Brachytherapy</td>
<td>Bilateral neck dissection</td>
<td>48 months*(died from distant metastasis)</td>
</tr>
<tr>
<td>Terada T [28]</td>
<td>77</td>
<td>Male</td>
<td>Pharynx</td>
<td>Proximal</td>
<td>Chemo-radiotherapy</td>
<td>No</td>
<td>24 months&amp;(died from distant metastasis)</td>
</tr>
<tr>
<td>Jameson CF [29]</td>
<td>20</td>
<td>Male</td>
<td>Hard palate</td>
<td>Unknown</td>
<td>Surgery</td>
<td>No</td>
<td>24 months</td>
</tr>
<tr>
<td>Nayak JV [30]</td>
<td>7</td>
<td>Male</td>
<td>External ear</td>
<td>Conventional</td>
<td>Surgery</td>
<td>Ipsilateral SND</td>
<td>12 months</td>
</tr>
<tr>
<td>Vadmal M [31]</td>
<td>51</td>
<td>Male</td>
<td>Pterygoid fossa</td>
<td>Unknown</td>
<td>Surgery+Radiotherapy</td>
<td>No</td>
<td>36 months</td>
</tr>
<tr>
<td>Frank R [32]</td>
<td>43</td>
<td>Male</td>
<td>Retro-orbital region</td>
<td>Proximal</td>
<td>Surgery+Chemotherapy</td>
<td>No</td>
<td>36 months</td>
</tr>
<tr>
<td>Frank R [32]</td>
<td>71</td>
<td>Female</td>
<td>Nasal cavity</td>
<td>Proximal</td>
<td>Surgery</td>
<td>Unknown</td>
<td>29 months</td>
</tr>
<tr>
<td>Frank R [32]</td>
<td>9</td>
<td>Female</td>
<td>Posterior neck</td>
<td>Proximal</td>
<td>Chemotherapy</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td>Rudzińska V [33]</td>
<td>20</td>
<td>Male</td>
<td>Neck</td>
<td>Unknown</td>
<td>Surgery+Brachytherapy+Radiotherapy</td>
<td>Ipsilateral SND</td>
<td>24 months</td>
</tr>
</tbody>
</table>

*: Metastasis to the lung, scalp and brain. &: Metastasis to the brain and lymph nodes.
region carried a higher or lower rate of cervical lymph nodal metastasis, suspicion of possible nodal metastasis is still warranted, especially for the proximal-type, given their high regional lymphatic spread in other anatomic locations.

Surgical excision with wide and clear margins is the mainstay treatment of choice. To achieve a better locoregional control of head and neck ESs, it is worthwhile to examine the cervical lymph nodes after the primary diagnoses has been made. If the lymph node metastases are present, therapeutic neck dissection is indicated. However, when it comes to clinical negative lymph nodes, there is a substantial divergence of opinions of treatment recommendations. Baratti claimed that lymph node dissection was indicated for local control of the nodal basin only when positive lymph node involvement has occurred. Based on their data (29.6% nodal involvement), a policy of indiscriminate prophylactic nodal dissection would have implied roughly two-thirds of patients being unnecessarily subjected to the possible morbidity deriving from the procedure [20]. On the other hand, elective neck dissection (END) is routinely performed to treat squamous cell carcinoma (SCC) in the lower oral cavity when the risk of occult metastasis is considered higher than 20% [21]. As reported in an ES case of the lower gingiva, the occult metastatic cells were found in 2 lymph nodes after END performed in a radiological negative neck [22]. But as for maxillary or palatal SCC, the traditional surgical management in the absence of clinical suspicious lymph nodes is to closely “watch and wait”. However, more recent retrospective reports have recommended END instead of observation in NO neck as higher-than-expected rates (29%) of occult cervical metastases were found in their groups of patients [23]. There is still controversy in this field with a lack of more convincing multicentric prospective studies. Apart from the “observation or END” approaches, sentinel node biopsy was also recommended to head and neck ES patients where nodal metastasis was not evident [17]. This can be accomplished in combination with the ultrasound scanning, but the clinical value of reliably detecting occult nodal metastasis is largely unknown. Considering the young age of our patient and after a preoperative discussion with her relatives, the conservative decision based on the observation was eventually made.

The published experience with adjuvant chemo-radiotherapy in general ES is limited [8], let alone head and neck ES. This treatment modality was primarily used in the late course of the disease. Most series have reported anecdotal data demonstrating, in general, a variable response to therapy. Some authors claimed that wide local excision plus adjuvant radiotherapy was ideal to lower local recurrence [24]. Like other high-grade soft tissue sarcomas, adjuvant radiation was generally given in tumors with positive or close margins with the intention that it might be helpful in this histology. The studies by Livi [25] and de Visscher [17], however, did not confirm the therapeutic benefit. For ES patients, chemotherapy has often provided marginal results for reducing the tumor burdens. Wolf [8] reported the limited efficacy of chemotherapy on ES as 55% of his patients received anthracycline-based regimens as either neoadjuvant or adjuvant therapy around the time of their first surgical excisions. This, together with other clinical reports, argues for novel protocol-based chemotherapy or targeted therapy for head and neck ES. Due to the clear-margin resection of the primary lesion and the related-toxicity, adjuvant therapy was not administered to our patient.

Conclusion

ES is a rare type of soft-tissue sarcoma with aggressive biological characteristics. A proper radiographic and histological evaluation is crucial as it has many mimics. The proximal-type ES found in the maxillary sinus is exceedingly rare and a wide excision with clear-margins should be attained, as surgery is the best option so far. The rarity of such disease hampers the evaluation of the appropriateness of END for head and neck ES. Besides, more studies, including those with molecular analysis, would contribute to the optimum management of ES.

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University School of Medicine, China. The subject’s parents have given written informed consent to publish the case.

Disclosure of conflict of interest

None.

Abbreviations

ES, epithelial sarcoma; OPG, orthopantomogram; CT, computed tomography; HE, hematoxylin and eosin; IHC, immunohistochemical; CK, cytokeratin; END, elective neck dissection; SCC, squamous cell carcinoma.

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