Ewing sarcomas of the sino-nasal tract and maxillary bone

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Abstract  Ewing's sarcoma is a malignant tumor belonging to the group of small round cells tumors. Histologically similar to soft tissue neoplasms originally described as primitive neuro-ectodermal tumors (PNET), in the WHO classification, Ewing's sarcoma and PNET are labeled together under the rubric of EWS/PNET. Rarely located in the nasal cavity and the para-nasal sinuses, we report three cases of Ewing's sarcoma of maxillary bone and sinus. Our patients, 2 males and one female, were aged 20, 16 and 13 years respectively. The chief complaint was a painful face swelling. The diagnosis was retained on histologic and immuno-histochemical results. In two cases, surgery was performed as primary treatment modality followed by chemo-radiotherapy, which was the only therapeutic modality in the remaining case. After a follow-up of 2, 3 and 8 years (for each patient), we did not report local or distant failures.

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1. Introduction

Ewing’s sarcomas are malignant round cell neoplasms. They are the second most common malignant bone tumor in children after osteosarcoma.\(^1,2\) Most cases arise in the long bones of the limbs or the pelvis. Primary location in head and neck region is uncommon and accounts for 1–4% of all Ewing’s sarcomas.\(^3\) Primary sino-nasal location is even rarer. The mandible and the skull base are the two most common primary sites in this particular area.\(^2\) Most sino-nasal Ewing’s sarcomas previously described in the literature consist of sporadic case reports that predominantly lack molecular confirmation or long-term follow-up, excepting the 14 cases reported by Hafezi et al.\(^4\) Compared to other soft tissue and bone sites, diagnosis is often challenging. The differential diagnosis is, in fact, broader and includes specific tumors for this site and the other round cell neoplasms.\(^4\) The histologic and immunophenotypic diversity of Ewing’s sarcomas makes further difficulty particularly in small biopsies. Through three cases, we attempted to make a review of the literature to determine clinico-pathologic features, treatment strategies and prognostic factors.

2. Methods

It is a retrospective review of 3 patients followed for Ewing’s sarcoma of maxillary bone and sinus in Salah Azaiez Institute of Oncology. They were still alive till the date of data collection, which made the access to their medical records relatively easy.

Diagnosis was based on histologic and immuno-histochemical findings and only one patient of the three had a molecular confirmation showing the EWS-FLI1 fusion transcript.

Local extension was assessed based on clinical and diagnostic imaging findings including head and neck computed tomography (CT) in all cases and magnetic resonance (MRI) in one case. Distant extension evaluation was performed using thoracic and abdominal CT, bone marrow biopsy and bone scintigraphy.

Tumor stage was retrospectively re-evaluated using the American Joint Committee on Cancer (AJCC) staging manual sixth edition.

Chemotherapy regimen was that of the Euro-EWING-99 study using six cycles VIDE (Vincristine–Ifosfamide–Doxorubicin–Etoposide) as initial chemotherapy for all patients with VAI (vincristine, dactinomycin, and ifosfamide) as continuing chemotherapy for patients with good responses to VIDE.

Additional radiation therapy was done for all patients. Fractionation was classic (1.8-2 GY/session; 5 days/week) with a total dose varying between 52 and 70 Gy on the initial or the postoperative residual tumor volume.

Assessment of chemotherapy response was performed using cervical CT after the 6 VIDE cycle. Follow-up was endoscopic at each consultation. Additional imaging associated CT 8 weeks after the end of radiation therapy, then yearly or if suspicious clinic and endoscopic changes. MRI was performed in case of CT doubt on a local failure.

3. Results

3.1. Patients and clinical findings

Three patients, 2 males and 1 female were included. Ages at presentation were 13, 16 and 20 years (mean age: 16.3 years). Neither pathological personal history nor family history of cancer was noted. The chief complaint was a painful face swelling. Other functional complaints could be summarized as follows:

- Spontaneous tooth mobility and exophthalmos were noted in one case, which wandered the diagnosis before the histological results.
- General complaints were limited to weight loss reported by one patient.

The average time to consult was 1.6 months (1–2 months) after the onset of the functional complaints.

Apart from face swelling which was left sided in 2 cases and right sided in 1 case, clinical examination did not reveal any associated cervical lymphadenopathies.

3.2. Imaging and distant extension evaluation findings

Limited lesion to the anterior wall of the maxillary sinus and its surrounded tissues was noted in one case (Fig. 1). In the other cases, this maxillary tumor extended to:

![Figure 1](image-url)  
CT coronal section: limited lesion to the anterior wall of the right maxillary sinus.
The left floor of the orbit, nasal fossa and cheek in the second case (Fig. 2).

The tumor extended farther to the sphenoid and ethmoid sinuses, the left pterygo-palatine fossa and the anterior cranial fossa in the third case (Fig. 3).

The diagnosis of Ewing’s sarcoma was based on histological analysis of tumor specimen. This specimen was a simple biopsy in two cases, which was done through maxillary vestibular approach. In the last case, diagnosis was posed on operative resected tumor, as the preoperative endoscopic biopsy was inconclusive.

Distant extension evaluation was negative in all three cases. Based on AJCC staging manual (sixth edition), tumor staging was T3N0M0, T3N0M0 and T4aN0M0 respectively.

4. Treatment

Two patients underwent first-line surgery before the diagnosis of Ewing’s sarcoma for 2 different reasons:

- In the first case, the lesion was inaccessible to biopsy under local anesthesia. Given its limited size, a complete excision was accomplished through maxillary vestibular approach.
- In the second case, the biopsy evoked the diagnosis of angio-fibroma. The patient has, even, had preoperative embolization of the left sphenopalatine artery, presumed to be the tumor-feeding artery. Extra-cranial portion of the tumor was, then, excised via lateral nasal approach (Moure’s technique modified by Weber-Fergusson).

Macroscopic appearance was that of a poorly defined and friable tumor. Definitive pathology report confirmed the diagnosis of a malignant tumor showing a proliferation of monomorphic small round cells arranged in diffuse layers.

![Figure 2](image-url) MRI axial and sagittal sections: extended tumor to the left floor of the orbit, nasal fossa and cheek.

![Figure 3](image-url) CT axial, coronal and sagittal sections: extension to the sphenoid and ethmoid sinuses, the left pterygo-palatine fossa and the anterior cranial fossa.

![Figure 4](image-url) CT coronal section: CT evaluation two months after completion of treatment of the patient shown in Fig. 3: endoscopy and biopsy were negative, despite the appearance of circumferential thickening of the surgical cavity.
and highlighted by a richly vascularized fine fibrous stroma. There was a large single cell necrosis with a filigree aspect. Immunohistochemistry was positive for CD99 and anti-FLI1 antibodies. Cells were poorly marked by neuron specific enolase (NSE). In contrast, epithelial markers: broad-spectrum cytokeratin and epithelial membrane antigen (EMA) were negative. One of these 2 patients had a molecular confirmation showing the EWS-FLI1 fusion transcript.

The remainder of the treatment for these two patients was chemotherapy as described above and external beam radiotherapy on the tumor bed at a dose of 52 Gy and 70 Gy respectively.

In the latter case, the biopsy was affirmative of the diagnosis of Ewing sarcoma. This patient was treated by neoadjuvant chemotherapy followed by 64 Gy external beam radiation therapy. This exclusive chemo-radiotherapy was decided given the young age (16 years) of the patient and even the refusal of the surgery by the patient and her family.

5. Clinical course and outcome

Chemotherapy and radiotherapy were well tolerated apart from a regressive febrile neutropenia noted in two patients. No major functional and esthetic consequences were noted after surgery. In fact, a patient with orbital invasion at diagnosis has developed permanent left blindness at the end of treatment. After a follow-up of 2, 3 and 8 years (for each patient), no local or distant relapses were reported (Fig. 4).

6. Discussion

Primary bone tumors account for 5% of all child and adolescent cancers, and Ewing sarcomas are the second most common primary bone tumors. They are more common in white populations, and have a slight male predominance. About a quarter of Ewing sarcomas arise in soft tissues rather than bone. Primary Ewing sarcoma of the head and neck is uncommon. This location accounts for 3.8% of cases in a large mon primary bone tumors. They are more common in white populations, and have a slight male predominance. About 3% of all locations and up to 18% in children. Primary Ewing sarcoma of the head and neck has been reported to present from 1% to 7% of all locations and up to 18% in children. Primary sino-nasal location is rarer as a subgroup of these head and neck cancers. The exact percentage is unknown as most studies have not focused specifically on the sino-nasal region as a particular location among head and neck Ewing sarcomas.

Otherwise, tumors arising in the nasal cavities and paranasal sinuses present with non-specific symptoms such as nasal obstruction, rhinorrhea and epistaxis. Therefore, tumors are locally advanced or even metastatic at the time of diagnosis. Face swelling was the chief complaint in our cases with a relatively early clinical presentation.

The histologic and immuno-phenotypic diversity of Ewing sarcomas, including occasional keratin and neuroendocrine marker positivity, makes the diagnosis quite challenging particularly in small biopsies, as was reported in one of our patients who was diagnosed as angio-fibroma. Herein, we describe the immuno-histo-chemical profile and molecular characteristics of Ewing sarcomas according to the literature review. In fact, the immuno-histo-chemical profile of Ewing sarcomas can be summarized as follows: Pan-cytokeratin −/+ , Vimentin +/− , NSE −/+ ,Synaptophysin −, CD117 −/+ , CD56 −, CD99 +, WT-1 −, Fli-1 +/−.

These histological and differential diagnoses are summarized in Table 1.

The diagnosis of Ewing sarcoma becomes more complicated since we know that there are different types of Ewing sarcomas (ES). Even more, close tumors to this latter group were described and celled Ewing-like sarcoma (ELS). Three histological subtypes of ES were distinguished: conventional/classic ES, PNET and the atypical variant. The first two can be easily recognized by microscopical examination and a specific IHC profile. However, the diagnosis of the atypical histological variant, which shares some histological and IHC similarities with ELS, requires molecular studies to retain the diagnosis. In short, conventional ES (and PNET) subtypes are characterized by a monotonous small round cell proliferation. The atypical variant can display large and clear cells, which can mislead the diagnosis. The IHC study usually reveals strong membranous CD99 and FLI1 nuclear positivity in most of ES. An atypical morphology associated with poor or negative CD99 expression should exclude other tumors, especially those that belong to the ELS group. Genetic confirmation shows reciprocal translocations between EWSR1 and a gene of the ETS family (rarely between EWSR1 and non-ETS gene family) members of translocation factors. A small group of ESFT shows the FUS instead of the EWSR1 rearrangement with a gene of the ETS family. Unfortunately, these gene fusions are rarely found. Hence, the diagnosis of classic ES or PNET with a common clinical and immune-phenotypic profile (unlike atypical histological variants) do not require molecular confirmation except for inclusion in clinical trials. ELS were recently described by studying molecular alterations in EWSR1/FUS-negative unclassified/undifferentiated small round cell sarcomas (SRCS). Nevertheless, the clinical features of this emerging group of sarcoma are still somewhat unclear. So as not to complicate this work, we invite you to consult the article written by Isidro Machado et al.

Even if Ewing sarcomas are considered radiation sensitive, the proportion of patients primarily treated with radiation alone has regularly declined over the last 30 years. This is because of advances in reconstructive surgery and the awareness of the late effects of radiation, such as secondary malignancies and growth disturbances, particularly in head and neck locations. Patients whose primary tumors are excised might survive more often, although the prognosis is, also, influenced by tumor’s size and site. Actual treatment plan for Ewing sarcomas includes surgical excision and chemoradiotherapy.

When the diagnosis is made on biopsy, neo-adjuvant chemotherapy reduces tumor size and clears micro-metastases, which are presumed to be present in 80% of cases, all locations inclusive.

Euro-EWING-99 study protocol recommends six cycles VIDE (Vincristine-Ifosfamide-Doxorubicin-Etoposide) as initial chemotherapy for all patients with VAI (vincristine, dactinomycin, and ifosfamide) or VAC (vincristine, actinomycin D, cyclophosphamide) as continuing chemotherapy for patients with good responses to VIDE. According to this protocol, chemotherapy is repeated every three weeks (1 cycle).

In case of insufficient bone marrow recovery (white blood cell count <2.0 × 10⁹/l or platelets <80 × 10⁹/l), the next cycle of chemotherapy is postponed and granulocyte-colony stimulating factor (G-CSF) is added to subsequent cycles.
motherapy is interrupted for surgery which includes wide excision of the tumor after the first six cycles of chemotherapy. If histological examination of a radically resected tumor reveals more than 10% of viable tumor cells, radiotherapy is also administered postoperatively. In this last case, considered as poor response, the authors of Euro-EWING-99 study propose an alternative myelo-ablative high-dose chemotherapy regimen associating Busulfan and Melphalan drugs, then rescue with marrow or peripheral hematopoietic stem cells. In case of initial surgery with a diagnosis based on definitive histology, the same radio-chemotherapy regimen could be followed. This chemo-radiotherapy regimen is the exclusive treatment for inoperable localized tumors or in case of refusal of surgery. Among our patients, one was treated by chemo-radiotherapy exclusively.

Other curative chemotherapy regimens have been proposed. It began with single-agent cyclophosphamide, dactinomycin, doxorubicin, vincristine, and carbustine, followed by single-arm multi-agent adjuvant chemotherapy trials using vincristine–actinomycin–cyclophosphamide (VAC) or VAC plus doxorubicin. Children’s Cancer Group-Pediatric Oncology Group (CCG-POG) cooperative study showed that ifosfamide and etoposide (IE), alternating with the standard regimen of vincristine, doxorubicin, cyclophosphamide (VDC), and dactinomycin markedly improved both overall and event-free survival owing to a marked decrease in local (rather than metastatic) relapse for patients with localized tumors.

### Table 1  Histological and differential diagnoses of Ewing sarcomas: particular focus on the maxillary bone and sinus location.

<table>
<thead>
<tr>
<th>Nesting pattern:</th>
<th>Confusion with:</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>Present in many cases of Ewing sarcoma at least focally</td>
<td>Carcinomas: particularly in those focally staining for keratin and synaptophysin</td>
<td>Carcinomas are generally diffusely positive for multiple keratins and rarely occur in young patients. Cases of Ewing sarcomas with a great degree of nesting and lack of keratin staining raise the possibility of ONB: ONB: S100 positive, sustentacular network, diffuse positivity for neuroendocrine markers and negativity for CD99. Ewing sarcomas: possible focal positivity for synaptophysin and other neuro-endocrine markers.</td>
</tr>
<tr>
<td>Can be described as lobulation</td>
<td>Olfactory neuroblastoma (ONB)</td>
<td></td>
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<tr>
<td>Cribiform pattern</td>
<td>Confusion with salivary tumors</td>
<td>The negativity for p63 ruled out salivary tumors showing a cribriform pattern.</td>
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<td>General myogenic markers: Desmin…; negatives in Ewing sarcomas</td>
<td>Rhabdomyosarcomas</td>
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<tr>
<td>Rhabdomyosarcoma markers: Myo D1; Myogenin (Myf-4).…: negatives in Ewing sarcomas</td>
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<tr>
<td>Melanoma markers: Melanosome (HMB 45); Melan (MART-1).…: negatives in Ewing sarcomas</td>
<td>Melanomas</td>
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<tr>
<td>Lymphoid markers: CD45 (LCA).…: negatives in Ewing sarcomas</td>
<td>Lymphomas</td>
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<tr>
<td>Diffuse positivity for CD99 (MIC 2) in Ewing sarcomas</td>
<td>Possible (exceptional) expression in endocrine and neuroendocrine tumors, melanoma, chondrosarcoma, rhabdomyosarcoma, meningal hemangiopericytoma…</td>
<td></td>
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<tr>
<td>Oncoproteins and tumor suppressor proteins:</td>
<td>A negative RT-PCR study possible in Ewing sarcomas: Alternative fusion gene partners for EWSR1: present in around 15% of Ewing sarcomas in other locations.</td>
<td></td>
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<tr>
<td>Cytogenetics and other molecular techniques (FISH and RT-PCR): EWSR1-FLI1 fusion transcript pathognomonic of Ewing sarcomas</td>
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In case of initial surgery with a diagnosis based on definitive histology, the same radio-chemotherapy regimen could be followed. This chemo-radiotherapy regimen is the exclusive treatment for inoperable localized tumors or in case of refusal of surgery. Among our patients, one was treated by chemoradiotherapy exclusively.
yelophosphamide–actinomycin), to VAIA (substituting ifosfamide for cyclophosphamide), to EVAIA (adding etoposide), to the current VIDE (omitting actinomycin). Several trials examined dose intensification by either increasing doses or decreasing the interval between these doses. Most of these trials demonstrated that these regimens were more toxic but no more effective excepting the Children’s Oncology Group (COG) study VDC–IE treatment every 2 weeks instead of 3 weeks interval for patients with localized disease, with 14 cycles and equal cumulative doses in each group. This interval compression provided a 25% increase in dose intensity of all agents without an increase in toxicity. Overall and event-free survivals were both improved in the interval-compressed group.

Even in cases of macroscopic complete resection, radiation therapy, as local complementary control modality, is advocated by most authors. Radiation doses range from 45 to 60 Gy. Radiotherapy is, however, associated with numerous potentially devastating late effects that make its use problematic, including fibrosis, contractures, ankylosis of the tempo-mandibular joint, facial skeleton growth disorders and post-irradiation sarcomas, particularly in young children. For some authors, proton radiotherapy is an alternative equivalent choice to photon radiotherapy for disease control and is also well tolerated with few acute side effects and low rates of late side effects.

Prognosis begins with the attempt to classify patients in risk groups. There is, in fact, no recognized risk classification. In the Children’s Oncology Group studies in North America, there are three risk groups: patients with localized tumors, patients with lung metastases only, and patients with other or multiple metastases. The EuroEWING-99 study, cited above, considers resectability and histological response to initial chemotherapy (for resected tumors) to assign patients to treatments. In total, it divides the patients in six therapeutic and prognostic groups ranging from localized resectable tumors, lung and pleura metastatic tumors then those metastatic outside of latter locations.

Surprisingly, Ewing sarcomas showed a less aggressive course in this location despite the complexity of the anatomy of the primary site, the difficulty in achieving a negative-margin resection and late presentation. For some authors, initial response to chemotherapy is the only prognostic factor significantly affecting both disease free survival (DFS) and overall survival (OS). Yeshwanth includes age of the patient, stage, anatomic location and size of the tumor to prognostic factors. He stated that patients younger than 15 years, with axial and sino-nasal tract disease, have a better outcome. The five-year survival was 55% without metastases and it was reduced to 22% with it. In the study of Allam about 24 cases of head and neck Ewing’s sarcoma, the 5-year actuarial DFS as well as OS were 30% and 53%, respectively. OS in the Intergroup Ewing’s Sarcoma (IESS) study was 80% at 3 years.

7. Conclusion

Ewing sarcoma involves a wide histological spectrum. Sino-nasal location is rare. A multidisciplinary management, including surgery and chemo-radiotherapy is the only guarantee of healing and longer survival. Though our study deals with a series of patients, which cannot serve for statistical analysis, it asserts the effectiveness of EuroEWING-99 chemotherapy regimen in association with surgery and radiotherapy. Awaiting for more effective therapeutic targeting the EWS-FLI1 transcript expression, in particular, and inhibiting Ewing sarcomas cell lines growth, head and neck locations (including maxilla and sino-nasal tract) still have a better prognosis compared to other locations.

References

