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Abstract

Ewing’s sarcoma are small round cell tumors belonging to Ewing’s family of tumors and the second most common bone tumor seen in children. The most common affected sites are long bones of extremities followed by pelvis and ribs. Primary arising in head and neck region is uncommon and maxillary Ewing’s sarcoma is rarely seen. Histologically it is one of many small round cell tumors found in children and therefore immunohistochemical and occasionally molecular studies are required to establish the diagnosis. Imaging features include aggressive bony destruction with periosteal reaction and associated soft tissue mass. Treatment of this tumor is a combination of induction chemotherapy followed by surgery and/or radiation with completion of chemotherapy due to aggressive nature and a high propensity for metastases. Our case is an 11-year-old boy diagnosed with primary non-metastatic Ewing’s sarcoma of left maxilla. The tumor was positive for CD 99 and FLI-1 and negative for CD 45 and Tdt on immunohistochemical examination. The patient was treated with induction chemotherapy comprising of alternating 3 weekly cycles of Vincristine, Adriamycin and Cyclophosphamide with Etoposide and Ifosfamide. This was followed by radical conformal radiation to a dose of 55.8Gy in 31 fractions with good response.

Keywords: Ewing’s sarcoma, maxilla, IHC, chemotherapy, radiation

Introduction

Ewing’s sarcoma are small round cell tumors showing a varying degree of neuroectodermal differentiation and belonging to Ewing’s family of tumors (EFT) affecting mainly children and young adults. [1] EFT accounts for 4 to 6% of all primary bone tumors with the long bones and the pelvis as the most common sites of involvement. [2] Primary EFT of head and neck is uncommon and occur in only 1–4% of all cases, mostly in the mandible and calvaria. [3] Paranasal sinus involvement is rare with sporadic case reports. [4] A rapidly enlarging, often painful mass is the most frequent clinical presentation. [5] Radiological imaging usually shows expansion and erosion of the cortical bones, with bone destruction, with or without periosteal thickening. [6] However, diagnosis is based on histopathological study, often in combination with immunohistochemical and molecular analysis. [7] Clinically, this tumor has an aggressive behavior characterized by rapid growth and high probability of micro metastasis at the time of diagnosis. [8] The current standard treatment of Ewing’s sarcoma is a multimodality approach with neoadjuvant chemotherapy to eradicate micro metastatic disease and facilitate effective local control measures with either surgery or radiotherapy followed by adjuvant chemotherapy. [9] Herein, we describe the clinicopathologic features, immunohistochemical profile and treatment of an 11-year-old boy with Primary Ewing’s sarcoma of left maxilla.

Case Presentation

An 11-year-old male child presented in our OPD with complaints of swelling over cheek, associated with mild pain of 2 months duration. On examination, there was a round and smooth swelling measuring 5 x 4 cm over left cheek region reaching up to left infra orbital region which was firm to hard in consistency. There was no lymphadenopathy and normal eye movements. A CT scan was done which showed a 5.3 x 3.2 x 3.2 cm destructive and homogenously enhancing mass lesion seen in the alveolus of maxilla on left side with sun burst pattern

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of bony fragments within. The mass was completely occupying the maxillary antrum and bulging into nasal cavity. There was erosion and destruction of superior and inferior wall of left maxillary sinus with intra orbital bulge. [Fig. 1 and 2] The overlying skin and subcutaneous fat appeared intact. A J needle biopsy was done which showed small round cell tumor. The cells were arranged in sheets and nests with high nuclear to cytoplasmic ratio and clumped chromatin pattern and scant, eosinophilic cytoplasm. [Fig. 3] This was followed by a panel of immunohistochemical tests. The biopsy specimen was positive for CD 99 and FLI–1; it was negative for Tdt and CD 45. [Fig. 4–7] These findings established the diagnosis of Ewing’s sarcoma. A PET CT scan was done for metastatic work-up. It showed an FDG avid (SUV max 6.83) heterogeneously enhancing soft tissue mass lesion arising from and destroying the left maxilla with an extensive sun–burst pattern of periosteal reaction. [Fig. 8] There was no other site of metastasis. Bone marrow examination was normal. It was finally diagnosed as a case of localized primary Ewing’s sarcoma of left maxilla. The patient was started on chemotherapy with VAC alternating with IE protocol. Vincristine 2 mg/m2, Adriamycin 75 mg/m2, and Cyclophosphamide 1200 mg/m2, were given on day one. This was alternated with Etoposide 100mg/m2 and Ifosfamide 1800mg/m2 with Mesna from day 1 to 5 every 3 weeks. After 4 cycles of this chemotherapy protocol, the patient was subjected to radical radiation therapy. A total dose of 55.8Gy/ 31# @ 1.8Gy per fraction was given to the left maxillary tumor with shrinking field technique by 3–dimensional conformal radiotherapy technique (3DCRT) on Varian linear accelerator. [Fig. 9] There was significant regression of the tumor following induction chemotherapy and radiation. The patient was further subjected to the same chemo cycle for a total of 17 weeks and is due for the first follow–up.

Discussion

The Ewing’s sarcoma family of tumors (EFT) includes ES of bone (ESB), extra osseous ES (EES), peripheral primitive neuroectodermal tumor of bone (pPNET) and malignant small cell tumor of the chest wall (Askin’s tumor). It was first described by James Ewing in 1921 as a tumor of neuroectodermal origin. [10] It is the second most common tumor in childhood and classically arises from the diaphysis region of long bones, followed by pelvic bones and ribs. [11] However, Ewing’s sarcoma of the sino–nasal tract and particularly maxilla is rare with only few case reports are available. [3]

Our patient was an 11year–old boy presenting with a swelling over left cheek associated with pain for a duration of 2 months. As reported the most common age of diagnosis is the second decade of life with a slight male preponderance. Similarly, locoregional pain of varying intensity and swelling with or without fever is the most common presenting feature of localized Ewing’s sarcoma. [12] Being a high–grade tumor, it has a high propensity for metastases. Lung, bone and bone marrow are the most
common sites of metastases and when present the patient may present with related symptoms like cough, chest pain, bone pain, features of bone marrow suppression etc. [11]

The CT scan showed a 5.3 x 3.2 x 3.2 cm destructive and homogenously enhancing mass lesion seen in the alveolus of maxilla on left side with sun burst pattern. The imaging characteristic of Ewing’s tumor include
bone destruction with a moth–eaten pattern and a wide zone of transition. Cortical destruction with an associated soft–tissue mass is also common. Periosteal reaction is frequent and usually aggressive in appearance, either lamellated (onion skin) or spiculated (sunburst or hair–on–end). The radiographic differential diagnosis includes osteosarcoma, osteomyelitis, eosinophilic granuloma, primary lymphoma of the bone, or rarely a metastasis. [12]

The systemic workup should include blood studies, CT scan of the chest, bone scan, and bone marrow biopsy. However, recently Fluorine–18 fluorodeoxyglucose positron emission tomography (FDG–PET) has proved to be a highly sensitive screening method for the detection of lung, bone and bone marrow metastases in Ewing’s sarcoma. [13] The FDG–PET scan done in our patient showed no distant metastases.

Histologically, Ewing’s sarcoma is a prototype of the “small round cell” tumor group comprising of sheets of small cells with scanty and eosinophilic cytoplasm. Immunohistochemistry analysis is essential as the family of small round cell tumors is rather large and differentials include non–Hodgkin lymphoma, neuroblastoma, rhabdomyosarcoma, mesenchymal chondrosarcoma, retinoblastoma, desmoplastic small round cell tumor, osteosarcoma, synovial sarcoma and malignant peripheral nerve sheath tumor. Our patient was positive for CD 99 and FLI–1 and was negative for Tdt and CD 45. This confirmed the diagnosis of Ewing’s sarcoma as the membranous expression of CD 99 or MIC 2 and antibody against FLI–1 centered in the nucleus of the tumor cells has been found to be specific for EFT. Further negative tests for CD 45 and Tdt ruled out differentials like lymphoid cell tumors as they also stain positive for CD 99. [14]

In addition to histochemical analysis, molecular testing can be used to identify signature translocations involving the EWS gene (balanced translocation involving chromosomes 11 and 22). Molecular testing can be done with both reverse transcriptase polymerase chain reaction (RT–PCR) and fluorescence in situ hybridization (FISH) method in formalin fixed, paraffin–embedded tissue. [14] Molecular analysis was not done in our patient.

Despite being a radiosensitive tumor, fewer than 10% of patients with Ewing’s sarcoma survived for more than 2 years before the era of chemotherapy. Distant metastases being the most common cause of death in these patients led to the use of systemic treatment. The use of adjuvant chemotherapy in EFT began in the early 1970s and has dramatically improved the outcome. However, those with metastases have poorer outcomes. [15] Our patient was treated with a five–drug combination chemotherapy and radical radiotherapy. The chemotherapeutic agents most commonly used are Vincristine, Doxorubicin, Cyclophosphamide, Ifosfamide and Actinomycin–D. Multiple large North American randomized study known as Intergroup Ewing’s Sarcoma Study [IESS] have been conducted since 1970s to develop the best chemotherapy regimen for EFT. [16] One of the recent study, the Children’s Cancer Group Pediatric Oncology Group (CCG–POG) cooperative study (INT–0091) showed that Ifosfamide and etoposide (IE), alternating with the standard regimen of vincristine, doxorubicin, cyclophosphamide (VAC), and dactinomycin markedly improved both overall and event–free survival (69 % Vs 54 %, p=0·005, and 72 % Vs 61 %, p=0·01, respectively) for patients with localized Ewing’s sarcoma. [16] Based on these studies, NCCN recommends alternating VAC/IE every 3 weeks as the preferred regimen for patients with localized Ewing’s sarcoma. Both surgery and radiotherapy have been used either alone or in combination as the local treatment modality. [15] Though historical results favor surgery for local treatment in operable cases, these data are confounded by the fact of selection bias. Because of the functional and cosmetic side effects of surgery for tumors in the sino nasal tracts, radiotherapy is commonly used for local therapy. [15] For gross disease, the standard radiation treatment is to deliver a total dose of 55.8Gy at 1.8Gy per day in 31 fractions, with a field reduction after 45Gy. Local control rates of 53% to 93% have been reported with these doses. [19]

With the current protocol the 5–year survival rates have been reported to be up to 70% in various large studies. [20] However, regular intensive follow–up is required keeping in view the aggressive histology and propensity for both local and distant relapse.

**Conclusion**

Ewing’s Sarcoma is an aggressive tumor that rarely affects the maxilla. The location and the clinico–pathological features of the tumor presents a diagnostic challenge in view of large number of differentials. Treatment with induction chemotherapy followed by radiation therapy leads to a favorable outcome avoiding the morbidity of surgery.

**References**


