Ewing's Sarcoma of Mandible: A Very Rare Disease and Review of Indian Literature

Deependra Kumar Sinha • N. K. Jha •
Sanjay Kumar Yadav • Jitin Yadav • Rishav Sinha

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Introduction

James Ewing was the first to describe Ewing's sarcoma, which was named after him in 1921. Ewing's sarcoma, a primary malignant tumor affecting the skeletal system, is now thought to arise from immature reticulum cells or primitive mesenchymal cells of the bone marrow [1]. It accounts for 4 to 10 % of all types of bone cancer, with most common locations being long bones and pelvis. It affects mainly adolescents and young adults and is rarely seen before the age of 5 and after the age of 30. Males are affected more commonly than females and it is more common in white population. Clinically, this tumor has an aggressive behavior characterized by rapid growth and high probability of micrometastasis at the time of diagnosis [2].

Ewing sarcoma rarely presents as lower jaw swelling, as it is being reported in this case.

Case Summary

A 18 years old female patient presented in surgery OPD with complaints of swelling of left side of lower jaw, associated with pain and fever of 2 months duration. On examination there was a left mandibular swelling of size 7 × 4 cm [2], firm to hard in consistency with few places of cystic consistency,

local temp. was raised and swelling was tender. Overlying skin appeared normal and upon intraoral examination mucosa was erythematous and non ulcerated. There was no lymphadenopathy. Patient was sent for FNAC and other routine investigations. FNAC was suggestive of reactive lymphadenitis. CECT head and neck was inconclusive (adamantinoma or osteogenic sarcoma arising from left mandible) (CT). Other routine investigations were within normal limits. Under general anaesthesia segmental mandibulectomy was done. Tissue (Fig. 1) was sent for histopathological examination which showed solid sheets of small round cells separated into small masses by fibrous tissue containing bony trabecula. The tumor cells show small round nuclei with hyperchromasia and indistinct nucleoli and brisk mitosis. Psuedorosettes around blood vessel and focal areas of necrosis are also seen (Figs. 2 and 3). On immunohistochemistry cytoplasmic membrane staining for CD99 was seen (Fig. 4), hence confirming the diagnosis of ES. Patient has received 2 cycles of chemotherapy with cyclophosphamide, doxorubicin and vincristine and is doing well. She is under regular follow up for remaining cycles of chemotherapy.

Discussion

In 1921, James ewing observed radiosensitivity in a subgroup of bone tumors and termed it as 'diffuse endothelioma of bone' and thought it to be from endothelial derivation. Ewing's sarcoma is the second most common primary malignant tumor of bone among children and adolescent. [3] Swelling, pain, parasthesia, and loose teeth are frequent symptoms. Radiographically, it is most often seen as destructive expansile, mottled radiolucent lesion, which may produce a laminated periosteal reaction. [4] Some authors point out that radiographic appearance of "onion skinning" is a characteristic sign of Ewing's lesion of the bone. In the jaw, an osteolytic

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D. K. Sinha • N. K. Jha • S. K. Yadav (✉) • J. Yadav
Department of General Surgery, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand 834009, India
e-mail: sky1508@gmail.com

R. Sinha
Department of DTMH, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand 834009, India

Fig. 1 Cut section of the tumor showing gross appearance

radiolucent area with cortical destruction was seen in most reported cases. With respect to teeth, some radiological features were noted, which include periodontal space widening, loss of lamina dura, root resorption, displacement or more commonly destruction of unerupted tooth follicles [1].

Angervall and Enzinger in 1975 reported the first case of extraskeletal ES. The ultra structural characteristics of the cells of this tumor studied by Gillespie and his associates proved that these cells are identical to those of the typical Ewing's cells [5].

Fig. 2 HPE (H&E) showing sheets of small round cells separated by bony trabeculae with Pseudorosettes around blood vessels

Fig. 3 H&E high resolution showing round cells with uniform hyperchromatic nuclei and more abundant, at some places vacuolated cytoplasm

Histopathologically, this tumor must be differentiated from other small, round cell tumors, including small cell osteosarcoma and malignant neoplasms like mesenchymal chondrosarcoma, rhabdomyosarcoma, malignant lymphoma, eosinophilic granuloma, neuroectodermal tumors, and metastatic neuroblastoma [6].

Of these, eosinophilic granuloma, malignant lymphoma, and metastatic neuroblastoma are most easily mistaken histologically for Ewing's sarcoma. Eosinophilic granuloma can be distinguished because of the presence of "histiocytic" features, that is, abundant, indistinct eosinophilic cytoplasm with oval or indented nucleus. Multinucleated cells may be present. Malignant lymphoma contains lymphoid cells, intermixed with round cell components of varying size and cytoplasmic contents. The nuclei of these cells are round or oval with a

Fig. 4 Diffuse cytoplasmic membrane staining for CD 99

Table 1 List of ewing's sarcoma cases involving jaw among indian population

Age (Year)/Sex/Site	Author	Clinical features	Radiological features	Duration	Remarks
6-20/M>F/ Mandible>Maxilla	Potdar G.G./1970	Bony hard swelling in the affected site	Osteolytic mottled destruction of bone	6 week- 1 year	Largest series (9 cases)
17/F/Body of the mandible	Sidhu S.S. et al./1976	Swelling in the lower third of right side of face	III-defined radiolucency with root resorption	6 months	Clinically appeared to be a cyst
15/M/Zygoma	Narasimhan A et al./1993	Hemispherical swelling over zygoma	III-defined radiolucency in zygoma and infratemporal fossa	4 months	Intracranial extension
20/F/Ramus of mandible	Singh et al./2003	Painless swelling over right half	Lytic destruction of ramus	Not given	Plain radiogram, CT, MRI, IHC done
15/M/Mandible and maxilla	Sharada P et al./2006	Painful swelling from Ala tragus line to right angle of mandline, crossing the midline	III-defined lytic lesion, floating teeth	6 months	Both the jaws involved
M/18/Maxilla	Prasad V et al./2008	painful hard swelling, lobulated, proptosis	Mixed lesion involving naso-maxillary complex	6 months	History of trauma
F/15/Zygoma	Deshingkar et al./2009	Painless immobile mass in right zygoma extending upto lateral canthus,	III-defined lytic lesion in right zygomatic and lateral wall of orbit	1 month	2nd reported case involving zygoma
M/30/Maxilla	Gupta et al./2009	Firm to hard pedunculated mass on posterior palate crossing midline, surface necrosis.	Lobulated ill-defined radiolucency in the naso-maxillary complex	3 months	Oldest in age in Indian literature.
M/12/Maxilla	Dadhe et al./2010	Painful nonulcerated swelling in maxillary tuberosity, decreased eye opening, reduced right nasal airway	Mixed lesion in naso-maxillary complex, displaced teeth	4 months	Well-defined lesion
F/11/Mandibular ramus	Rao et al.2011	Painless hard swelling, expansion of buccal cortical plate, mobility of teeth	III-defined radiolucency in the ramus, thinning and erosion of buccal cortex	6 months	Bone scan done
F/16/Maxilla	Pampori et al./2011	Painless hard swelling, restricted eye opening, mobility of teeth.	III-defined radiolucency, regional teeth mobile	6 months	Chemotherapy done, no surgery
F/8/Anterior mandible	Present Case	Smooth surfaced, hard swelling in the mandibular alveolar ridge, expansion of buccal/lingual plates	III-defined mixed lesion in mandibular alveolar ridge. sunburst appearance	7 months	Site-Anterior mandible CD 99 positive

distinct nuclear membrane, which is sometimes smooth or cleaved. The PAS stain is usually negative, and reticulin stain is often positive [6].

Ewing's Sarcoma HPE shows small, poorly differentiated cells with medium-size, round or oval nuclei exhibiting a fine chromatin pattern, small nucleoli and scanty cytoplasm [7]. The Intracytoplasmic glycogen may be demonstrated by PAS stain in 75 % of the cases. Tumor cells are positive for vimentin and CD99 and negative for neural, skeletal, vascular and lymphoid cell markers [8]. Regarding Mic-2 antigen, recently published data have confirmed the high sensitivity of the Mic-2 gene product (CD99) for all ES family tumors with over 95 % of the cases showing positivity for this marker. In fact the expression of CD99 protein is not conclusive to ES because other round cell tumors, such as Merkel cell carcinoma, small cell osteosarcoma T-lymphoblastic lymphoma poorly differentiated synovial sarcoma may express this marker [9].

Treatment of ewing sarcoma includes multimodality approach consisting surgery, chemotherapy and radiotherapy. This approach has improved 5 year survival rate among ES patients. Radiotherapy only should be restricted to non-resectable tumors, otherwise wide surgical excision with chemotherapy should be done [10]. Radiotherapy in doses greater than 4,000 cGy has been effective in short-term control of tumor growth in about 86 % of cases. The chemotherapeutic agents most commonly used are Vincristine, Doxorubicine, Cyclophosphamide, Ifosfamide and Actinomycin-D. The use of chemotherapy has greatly improved survival rates for patients with localised ES, from about 10 % to 70–80 %. The first North American randomised study (Intergroup Ewing's Sarcoma Study [IESS-I]; 1973–78) showed that VAC (Vincristine-Actinomycin-cyclophosphamide) plus doxorubicin was better than VAC plus chest irradiation, which in turn was better than VAC alone for patients with localised, non-pelvic primary tumours [11]. In the second IESS study (IESS-II, 1978–82) higher doses of doxorubicin earlier in therapy improved on the IESS-I regimen (overall survival 77 % vs 56 %) [12]. Children's Cancer Group-Pediatric Oncology Group (CCG-POG) cooperative study (INT-0091,1988–92) 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 (69 % Vs 54 %, $p=0.005$, and 72 % Vs 61 %, $p=0.01$, respectively) for patients with localised tumours [13]. The regimen of alternating VDC-IE every 2 weeks has become standard for North American patients with Ewing's sarcoma.

ES affecting jaws is uncommon among Indian population. Till date only 19 cases of ES involving jaws have been described in Indian literature. (Table 1) [14].

The prognosis of ES is poor because hematogenous spread and lung metastases occur within a few months after diagnosis, although the tumor burden is considered today as an important factor of prognosis [6].

Conclusion

Ewing's sarcoma is a rare malignancy of mandible but due to aggressive nature of the tumor, it warrants early diagnosis and multimodality therapeutic approach.

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