www.jmscr.igmpublication.org Impact Factor 3.79
ISSN (e)-2347-176x

Journal Of Medical Science And Clinical Research
IGM Publication An Official Publication Of IGM Publication

Extra skeletal Ewing's Sarcoma

Authors

Dr. Ketan Vagholkar[1] MS, DNB, MRCS (Eng & Glasg), FACS
Dr. Mahendra Bendre[2] (MS)

[1, 2]Professor, Department of Surgery Dr.D.Y.Patil Medical College, Navi Mumbai 400706, MS, India
Corresponding Author
Dr.Ketan Vagholkar.
Annapurna Niwas, 229 Ghantali Road. Thane 400602. MS. India
E mail: *kvagholkar@yahoo.com*

ABSTRACT

Extra skeletal Ewing's sarcoma is an uncommon tumour belonging to the Ewing's sarcoma family of tumours. The biological behaviour of the tumour is different from the osseous Ewing's sarcoma. Relevant articles on the topic from PubMed were identified and reviewed. A brief review of the pathology, clinical features, diagnosis and management is presented.

Key Words: *Extra skeletal Ewing's Sarcoma*

INTRODUCTION

Ewing's sarcoma is a highly malignant round cell tumour arising from the bone. It was first described by James Ewing in 1921 as "diffuse endothelioma of bone". [1] An extra skeletal soft tissue tumour histologically indistinguishable from Ewing's sarcoma was described by Tefft et al.[2] Subsequently a number of case reports and a few case series were published describing the extra skeletal soft tissue variant of Ewing's sarcoma.[3]

Ewing's sarcoma family of tumours (ESFT) and their cytogenetic characteristics

As more such cases were reported it was observed that a spectrum of tumours had similar histological and cytogenetic characteristics. [4, 5]They were classified as Ewing's sarcoma family of tumours. [6, 7] This group includes

1. Ewing's sarcoma
2. Extra osseous Ewing's sarcoma (EES)
3. Primitive neuroectodermal tumour.
4. Peripheral neuroepithelioma

5. Askin's tumour(Ewing's sarcoma involving the chest wall)
6. Atypical Ewing's sarcoma.

Translocation t (11; 22) is found in the Ewing's sarcoma family of tumours more so in the extra skeletal variant. [5, 6, 7] The gene from chromosome 22 which encodes the Ewing's sarcoma gene (EWS) and the gene from chromosome 11(FLI-1) are involved to create the new fused gene (EWS-FLI-1) in the translocation t (11; 22). This newly formed variant encodes an altered fusion protein which regulates other genes giving rise to ESFT's. [7]

PATHOLOGY

Ewing's sarcoma accounts for 6-15% of primary malignant tumours of the bone. [8] Extra skeletal Ewing's sarcoma (EES) usually is seen in young adults rather than children. It accounts for 1-2% of all malignant soft tissue tumours. [7, 8] Grossly EES are bulky tumours. The tumour assumes a large size over a period of time. It is tan white in colour exhibiting areas of haemorrhage and necrosis.

Histologically the tumours are composed of sheets of uniform round cells slightly larger than lymphocytes. The stroma is scanty but necrosis is prominent. Electron microscopic studies have revealed two types of malignant round cells.[9] One group called the chief cells which exhibit larger cell size with a thin rim, pale cytoplasm, less hyper chromatic nuclei, nucleoli and diffusely dispersed chromatin nuclear details. The second group called dark cells are smaller in size, are darker in colour with hyper chromatic and smudged nuclei. [9]

Immunohistochemistry of ESS reveals significant intracytoplasmic glycogen, positive vimentin and HBA-71 immunostaining. [9, 10]

These tumours are extremely aggressive and spread predominantly to the lungs followed by bones and lymph nodes.

CLINICAL FEATURES

EES occurs mostly in young adults. However tumours have been reported in advanced age groups as well. [11] It is more commonly seen in males. It has predilection for the paravertebral region, lower limbs and chest wall with a few cases arising in the pelvis, retroperitoneal region, upper limb head and neck. EES has also been reported at rare sites such as posterior mediastinum. [12] Adult EES are large masses which invade adjacent organs and frequently metastasize. The tumour presents as a painful expanding soft tissue mass. The mass is usually deep-seated to start with but may latter fungate giving rise to a grotesque soft tissue tumour. (Figure 1) Increased warmth locally and tenderness are common. The tumour surface becomes irregular and assumes a variegated consistency. Regional lymphadenopathy is a common accompaniment. This may either be due to metastases or secondary infection of the fungating mass. Tumours situated in the paravertebral region may become manifest by neurologic symptoms. Chest wall tumours may give rise to pain or pulmonary symptoms.

Tumours situated on the extremities usually give rise to large masses accompanied by neuromuscular symptoms. [8]

Systemic symptoms are seen in advanced cases which include fever malaise, anaemia and lassitude. [13]

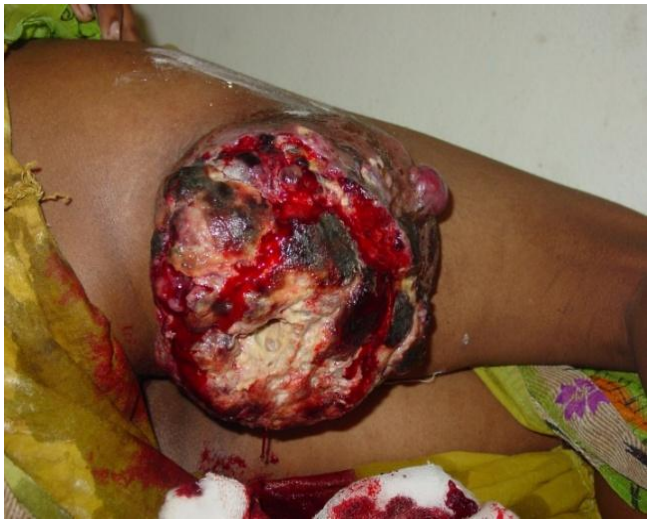

Figure 1 Extra skeletal Ewing's sarcoma over the lower extremity.

INVESTIGATIONS

A systematic investigative protocol needs to be followed in order to determine the best therapeutic algorithm for the patient.

Haematological investigations usually will reveal anaemia especially in an advanced presentation. Neutrophil leucocytosis may be present in cases of secondarily infected fungating masses arising from the extremities.

X ray of the local parts will reveal a soft tissue mass devoid of the classical onion peel appearance seen classically in the osseous Ewing's sarcoma. Soft tissue calcification may be seen in less than 10% of cases. [14]

FNAC may help in the diagnosis but detailed structural characteristics will not be revealed. Hence biopsy still remains the mainstay of diagnosis. A good open biopsy for fungating lesions or a core biopsy is essential. Biopsy will help in establishing the tissue diagnosis as well as confirming the tumour variant based on immunohistochemistry of the tumour tissue. [8, 9, 10, 14]

Immunohistochemistry and electron microscopy helps in establishing the biological nature of the lesion. Positive vimentin, CD 99 and negative S 100 are typically seen in EES. Chromosomal karyotyping will also aid in diagnosing the translocation (11; 22).

Imaging methods like CT and MRI are of great relevance in staging the disease once the tissue diagnosis has been made. For tumours arising in the extremities or in the paravertebral region, an MRI will be of great help. It will reveal the exact extent of the growth, involvement of neurovascular structures and the extent of compartmental involvement. CT scan is of immense help in tumours situated in the pelvic cavity, chest wall or retroperitoneal regions. CT will also help in diagnosis of metastatic spread. Many a time both MRI and CT need to be done to achieve a more accurate staging of the tumour. [10, 15]

PET scan is only helpful in follow up of cases for recurrence of tumours. Bone scan may have to be done in cases with suspected osseous metastasis. [16]

TREATMENT

EES is a complex tumour to treat. A multimodality approach is essential. [11, 12, 13, 17] Deciding the combination of treatment needs to be based on the staging of the tumour both locally and systemically. Chemotherapy, surgery and radiotherapy are the three modalities of treatment. [18]

Aggressive induction chemotherapy has found to yield good results. The standard chemotherapeutic agents are cyclophosphamide, adriamycin, vincristine, ifosfamide and etoposide.[17,18] The rationale for administering chemotherapy before surgical intervention is based on the assumption that micro metastases will already be present even in localized lesions. It also leads to shrinkage of the growth rendering it more amenable for a complete surgical resection. Therefore a dose intensive combination therapy will be of great help in controlling the disease. This will also have an advantage of reducing the duration of therapy. Adjuvant completion chemotherapy should follow either surgery or radiotherapy. [18, 19]

Surgical intervention comprises of wide local resection of the tumour mass ensuring tumour negative margins confirmed intraoperatively by frozen section.[18] If bone is significantly involved then an amputation may be required. In the extremities compartmental excision may be done if the staging of the tumour permits. Results in such cases may not always be promising.

Radiotherapy is indicated in situations wherein complete surgical resection could not be achieved leaving behind residual tumour or the margins are positive for the tumour or in cases of either local or lymph node recurrence.[16,17,18] Daily radiation of 45-50 Gy to the primary site is administered over a period of 6 weeks in case of localized disease.

PROGNOSIS

The overall 5 year survival rate is 61% and the disease free survival rate is 54%. [13,19]ESS has a better overall prognosis as compared to osseous Ewing's sarcoma.[7] Higher age of the patient, surgical treatment, high haemoglobin, low lactate dehydrogenase, use of combination chemotherapy and response to chemotherapy are the most significant positive prognostic factors associated with improved survival.[19,20,21]

CONCLUSION

The existence of an uncommon entity namely extra skeletal Ewing's sarcoma needs to be considered while diagnosing soft tissue malignancies.

Extra skeletal Ewing's sarcoma has a better prognosis as compared to osseous Ewing's sarcoma.

Accurate preoperative diagnosis and staging are important in determining the course of multimodality treatment.

ACKNOWLEDGEMENT

We would like to thank Mr Parth Ketan Vagholkar for his help in typesetting the manuscript.

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