New Trends In Management Of Ewing Sarcoma

An Essay

Presented by

Mohamed Osman Ayoub
(M.B.,B.Ch)

In the partial fulfillment of master degree

In

"Orthopedic Surgery"

Under supervision of

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Introduction:

Ewing sarcoma, a highly malignant primary bone tumor of small round cells, was first described by James Ewing in 1921. Most frequently, it is observed in children and adolescents aged 4-15 years and rarely develops in adults older than 30 years. Ewing sarcoma is one half to one third as common as osteogenic sarcoma .but among patients less than 15 years of age, Ewing sarcoma is nearly as common as osteogenic sarcoma. [4] This reflects the fact that Ewing sarcoma has a sharper peak incidence in younger patients than osteogenic sarcoma and is rare beyond the third decade. The disease usually affects Caucasians and is distinctly uncommon in blacks and Asians. The male to female ratio is approximately 3:2. [6] The pelvis and femur are favored locations, but many other bones may be involved, including the humerus, tibia, and fibula.

The etiology is related to a chromosomal translocation. In over 90% of cases, there is a reciprocal t(11;22)(q24;q12) translocation that results in a fusion of the EWS gene to the Fli1 gene. In approximately 5% of cases there is a 21;22 translocation that fuses the EWS gene to the ERG gene, and in rare cases the EWS gene may be fused to other genes such as the E1A gene and the ETV1 gene. [8, 11]. It is believed that the fusion proteins activate and/or repress a set of genes which result in neoplastic transformation of the cell, but the critical target genes have yet to be identified.

Most patients complain of pain and swelling at the affected site. Growth of the tumor is rapid, and symptoms are typically present for only weeks to months. In most cases, a substantial firm mass is present, and its sudden appearance and enlargement may cause alarm in the patient. The presentation can simulate acute osteomyelitis, and some patients have constitutional symptoms of fever, malaise, and lethargy. Pathologic fractures occasionally occur

Ewing sarcoma has variable radiographic manifestations . The most well-known finding — onionskin formation — is not consistently present. Moreover, it is not a unique attribute and can be produced by numerous other diseases, including osteomyelitis, Langerhans cell granuloma, and osteogenic sarcoma. Onionskin formation is one form of reactive periosteal bone formation . Ewing sarcoma usually produces an ill-defined, lytic defect that permeates up and down the medullary canal, giving the bone a moth-eaten appearance. However, in approximately 10% of cases, the tumor may have a predominantly blastic appearance as a result of exuberant

reactive bone formation. This can cause it to be confused with osteogenic sarcoma, particularly the small cell variant. [12]

An important clue that suggests the possibility of Ewing sarcoma is the presence of a large soft tissue mass adjacent to the bone. This may be subtle and difficult to appreciate on plain radiographs but becomes apparent with CT or MRI scans. In certain bones such as the pelvis, periosteal reaction is often absent radiographically, and the soft tissue mass becomes more important to making the diagnosis.

Laboratory tests may show leukocytosis with a left shift, and the erythrocyte sedimentation rate may be elevated. These findings, along with the history, examination, and radiographs, can easily deceive the clinician into thinking that the diagnosis is osteomyelitis. The serum lactate dehydrogenase (LDH) is important to note since it is correlated to the disease burden, and it has prognostic importance.

Ewing sarcoma may be morphologically indistinguishable from other small round cell tumors, such as lymphoma of bone and metastatic neuroblastoma. Differentiation from these other entities has been facilitated in recent years by the development of the monoclonal antibodies HBA71 and O13 against Ewing sarcoma. [5] The development of reverse transcriptase-polymerase chain reaction (RT-PCR) has also aided the diagnosis of Ewing sarcoma by facilitating the detection of specific chromosomal translocations. [10]

Treatment will depend on a number of factors, including the size and position of the tumour, and may include chemotherapy, surgery and radiotherapy, or a combination of these.Recently high-dose chemotherapy with hematopoietic stem cell transplant (HSCT) as consolidation treatment, in an effort to improve outcome.[6 -9]

Aim of the study:

The aim of the study is to discuss the modern teqniques ,trends&methods in the management of Ewing`s sarcoma, comparing the standard treatment with a new or modified version of the standard treatment aiming to improve our understanding of the best way to treat the disease .

Contents:-

References:

1. Bacci G, Ferrari S, Bertoni F: Prognostic factors in nonmetastatic Ewing's sarcoma of bone treated with adjuvant chemotherapy: analysis of 359 patients at the Istituto Ortopedico Rizzoli. J Clin Oncol 2000 Jan; 18(1): 4-11[Medline].
2. Ewing J: Diffuse endothelioma of bone. Proc N Y Pathol Soc 1921; 21: 17-24.
3. Fellinger EJ, Garin-Chesa P, Glasser DB, Huvos AG, Rettig WJ: Comparison of cell surface antigen HBA71 (p30/32MIC2), neuron-specific enolase, and vimentin in the immunohistochemical analysis of Ewing's sarcoma of bone. *American Journal of Surgical Pathology* 1999;16:746-755.
4. Gurney JG, Davis S, Severson RK, Fang JY, Ross JA, Robison LL: Trends in cancer incidence among children in the U.S. *Cancer* 1999;78:532-541.
5. Hamilton G, Fellinger EJ, Schratter I, Fritsch A: Characterization of a human endocrine tissue and tumor-associated Ewing's sarcoma antigen. *Cancer Research* 2000;48:6127-6131.
6. Hawkins D, Barnett T, Bensinger W, et al.: Busulfan, melphalan, and thiotepa with or without total marrow irradiation with hematopoietic stem cell rescue for poor-risk Ewing-Sarcoma-Family tumors. Med Pediatr Oncol 34 (5): 328-37, 2000. [PUBMED Abstract]
7. Huvos AG: *Bone Tumors*, Philadelphia, W.B. Saunders; 1999:
8. Jeon IS, Davis JN, Braun BS, et al: A variant Ewing's sarcoma translocation (7;22) fuses the EWS gene to the ETS gene ETV1. *Oncogene*2000;10:1229-1234.
9. Kushner BH, Meyers PA: How effective is dose-intensive/myeloablative therapy against Ewing's sarcoma/primitive neuroectodermal tumor metastatic to bone or bone marrow? The Memorial Sloan-Kettering experience and a literature review. J Clin Oncol 19 (3): 870-80, 2001. [PUBMED Abstract
10. MacEwen EG, Kurzman ID, Rosenthal RC, et al: Therapy for osteosarcoma in dogs with intravenous injection of liposome-encapsulated muramyl tripeptide. *Journal of the National Cancer Institute* 1999;81:935-938
11. Urano F, Umezawa A, Hong W, Kikuchi H, Hata J: A novel chimera gene between EWS and E1A-F, encoding the adenovirus E1A enhancer-binding protein, in extraosseous Ewing's sarcoma. *Biochemical & Biophysical Research Communications* 1999;219:608-612

12. Zelazny A, Reinus WR, Wilson AJ: Quantitative analysis of the plain radiographic appearance of Ewing's sarcoma of bone. *Investigative Radiology* 1999;32:59-65.

List of abbreviations

AAOS	American Academy of Orthopaedic Surgeons
AJCC	American Joint Committee on Cancer
CESS	Cooperative Ewing's Sarcoma Study
DXR	doxorubicin
ESFT	Ewing sarcoma family of tumors
EWs	Ewing sarcoma
FDG	Fluorodeoxyglucose
Fli1	friend leukemia virus integration site 1
GD-DTPA	Gadolinium-diethylenetriaminepentaacetic acid
IESS	Intergroup Ewing's Sarcoma Study
IFM	Ifosfamide
PET	positron emission tomography
PNETs	Primitive neuroectodermal tumors
POG–CCG	Pediatric Oncology Group–Children's Cancer Group
STIR	short-tau (τ) inversion recovery
VAC	vincristine, actinomycin-D, cyclophsphamide
VACD	vincristine, actinomycin-D, cyclophsphamide and doxorubicin

List of figures

Introduction

Ewing sarcoma (EWs), a highly malignant primary bone tumor that is derived from red bone marrow, was first described by James Ewing in 1921 [1]. This tumor is most frequently observed in children and adolescents aged 4-15 years and rarely develops in adults older than 30 years [2]

Ewing sarcoma accounts for approximately 5% of biopsy-analyzed bone tumors and approximately 33% of primary bone tumors.This disease is the second most common malignant bone tumor in young patients and it is the most lethal bone tumor[3].

Biology of Ewing family of tumors

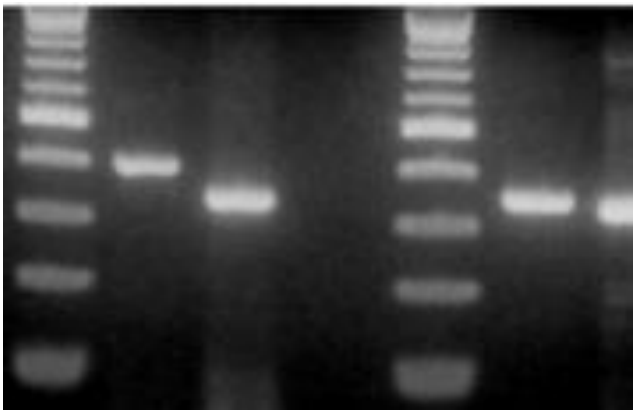
Ewing sarcoma family of tumors (ESFT) are tumors of neural crest derivation that differentiate along a neuroendocrine lineage and are described as "small round cell tumors." Although there are light microscopy variations between EWs and Primitive neuroectodermal tumors (PNETs), the finding that all ESFT tumors are characterized by a balanced chromosomal translocation between the 5' half of the EWS gene (22q12) and the 3' half of members of the ETS family of transcription factors has led to the understanding that the ESFT represents a single neoplastic entity.

The resulting fusion gene transcribes an oncogenic transcription factor that has been demonstrated to play a critical role in maintaining the malignant

phenotype in Ewing's tumor cells[4,5]. and may also act by modulating gene expression at the RNA level[6].In 85% of cases, the gene fusion is a result of a translocation between EWs and FLI1 (11q24)(figure-1)[7], It has been found that, within the gene fusions, there is marked heterogeneity resulting from translocation of different exons. For EWS-FLI1, there are two common fusions: type one, in which EWs exon 7 in-frame is fused with exon 6 of FLI1, and type 2, in which EWs exon 7 in-frame is fused with exon 5 of FLI1. Some studies have suggested that the type of fusion may have prognostic significance, with some studies, although not all showing a positive association between type 1 EWs-FLI1 fusions and longer survival[8,9].

Secondary non random chromosomal changes also occur commonly in ESFT, the most common being trisomies of chromosomes 8 or 12, seen in up to 50% of cases, and gains or losses in chromosome one,which are also common. Small retrospective studies have shown an association between these chromosomal changes and poorer outcome, although the data are conflicting [10,11].There is limited information regarding any relationship between age at diagnosis or clinical aplication and secondary chromosomal abnormalities[11].

Performed cytogenetic studies on tumor samples from 134 patients and compared results of these studies with the patients' clinical data. Trisomy of chromosome 8 was found in 52% of patients but was not predictive of outcome, whereas gain of 1q or loss of 16q were both associated with poorer outcome.



(figure-1)RT-PCR assay for the detection of *EWS–ETS* gene arrangements. *EWS–Fli*1 (left) and *EWS–ERG* fusion gene (right) transcripts were detected in the biopsy specimens of different patients with Ewing's sarcoma[9].

Both (1q) gain and (16q) loss correlated with age 15 years at diagnosis (34% vs. 13%, p = .005; and 31% vs. 15%, p = .035). Prospective studies are needed that compare these chromosomal changes (both primary and secondary) with factors including age, as well as more accurately define their role as prognostic variables. Until that time, the data are too limited to determine whether there is any evidence for age-associated differences in the biology of ESFT[11].

Origin

Ewing sarcoma and peripheral neuroepithelioma belong to the Ewing sarcoma family of tumors (ESFT) and are considered neural tumors. Ewing sarcoma represents a less differentiated form of the tumors, whereas neuroepithelioma represents a more differentiated form. Unlike neuroblastomas, these neural tumors are not derived from the sympathetic system, and

catecholamine metabolites are not excreted in the urine. In vitro, these tumors show neural differentiation and have neural features. Results with neuron-specific enolase and S-100 protein testing are positive. In addition, electron microscopy reveals neural structures such as neurites and dense-core granules. Glycogen granules are present, and alkaline phosphatase is absent[3,12].

Site

Most Ewing's sarcomas occur in bones. As opposed to osteosarcoma, flat bones of the axial skeleton are relatively more commonly affected, and in long bones, Ewing's sarcomas, unlike osteosarcomas, tends to arise from the diaphyseal rather than the metaphyseal portion.

The most common sites of primary Ewing's sarcoma are the pelvic bones ,the long bones of the lower extremities ,and the bones of the chest wall .Patients presenting with localized disease have an approximately two thirds chance of being cured . Those whose disease is initially metastatic have a much worse outcome . Ewing's sarcoma occurs less commonly at non-bone primary sites , a presentation that has historically been termed extraosseous Ewing's sarcoma[13].

Pathophysiology

Although the tumor is derived from bone marrow, Ewing sarcoma is histologically related to reticulum cell sarcoma. Most frequently, the tumor is