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Current thinking and scientific ideas on the pathology of Ewing's sarcoma and PNET

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ABSTRACT:-

Small round cell tumours that demonstrate varied degrees of neuroectodermal differentiation are what are known as Ewing's sarcoma and PNET, respectively. They are one of the most frequent tumours to develop in children and can take place in the bone or in the soft tissues. In the past, diagnosis could be accomplished through the use of light microscopy in conjunction with immunohistochemical stains. But nowadays, translocation analyses are being used not only for the diagnosis and classification of small round cell tumours, but also to determine the significance of their prognosis, detect micrometastasis, and monitor minimal residual disease, all of which have the potential to be treated with targeted therapies. In this essay, the author examines the clinical and therapeutic implications of the pathology, biology, and molecular features of Ewing's sarcoma and PNET.

Keywords: PNET, Ewing’s sarcoma, EWS-FLI1 translocation, pathology.

INTRODUCTION: -

In 1918, Arthur Purdy Stout identified a primitive neuroectodermal tumour in the ulnar nerve that was made up of tiny round cells with rosettes (PNET) [1]. Later, James Ewing characterised the Ewing sarcoma, a tumour of the long bones made up of radiosensitive undifferentiated cells [2]. These two tumours have been described as two separate entities over the years and in various locations. When Angervall and Enzinger (1975) described "an extraskeletal neoplasm resembling Ewing's sarcoma" and Jaffe et al. released an article on "the neuroectodermal cancer of bone" in 1984, the lines between these two tumours started to blur [3, 4]. As of now, we are aware that PNET and Ewing's sarcoma exhibit comparable translocations and are thought to lie at opposite extremities of the histological spectrum of the "Ewing's family of malignancies" (EFT). Our understanding of the molecular processes underlying the onset and advancement of EFT has significantly expanded over the last two decades. This improved knowledge of cell biology has been made possible by numerous technological advancements, which have also helped to illuminate the molecular processes that lead to malignant transformation. We may be able to better understand the biology of these lesions by analysing these tumours using a variety of molecular approaches. We may also be able to create more effective methods for diagnosing and maybe treating these lesions.

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DISCUSSION :-

Epidemiology

EFT is the second most frequent tumour in children, accounting from 5–10% of primary bone tumours [5]. It indicates a modest preference for men and is most common in children and young people. Although this is quite unusual because EFT is not a part of familial cancer syndromes, it has been described in siblings [6].

EFT typically develops in the metadiaphyseal or diaphysis region of long bones. It also comes from the ribs and pelvic bones. The vertebra, scapula, tiny bones in the hands and feet, and the skull bones are the other, less common and uncommon, places. Any location with soft tissue may be impacted. For a histological diagnosis of any bone malignancy, the radiographic results are crucial. The diaphysis of the bones are affected by Ewing's sarcoma, which manifests as a permeative pattern of involvement with periosteal response.

The most effective method of making a diagnosis is through a tumour biopsy. The majority of the time, a core biopsy is sufficient for making a histological diagnosis; an open biopsy is only necessary in cases when core biopsy attempts to collect enough tissue have repeatedly failed (technical difficulties, sclerotic bone, previously treated cases, etc.). A frozen section examination can be done to determine whether the biopsy is adequate if the representativeness of the sample is a problem.

Histology

A representative of the "small round cell" tumour subgroup is Ewing's sarcoma/PNET. Sheets of tiny cells with a high nuclear to cytoplasmic ratio make up its structure. The sparse, eosinophilic cytoplasm typically contains glycogen, which may be seen by periodic acid Schiff stain and can be broken down by diastase [7]. Rosette formation is also occasionally observed. There is no matrix created by EFT. The remaining surviving cells in this tumour typically have a "peritheliomatous" or perivascular distribution and frequently experience necrosis. Large EFT tumour cells with an uneven nuclear membrane and noticeable nucleoli are sporadic [8].

Aside from lymphoblastic lymphoma, rhabdomyosarcoma, synovial sarcoma, mesenchymal chondrosarcoma, the blastemal component of Wilms tumour, and occasionally DSRCT, CD99 can also be positive in other malignancies [9]. As a result, a panel of immunohistochemical stains is used to make a firm diagnosis. In ES/PNET, CD99, FLI1, and NSE would all be positive, as was already mentioned. Non-Hodgkin lymphomas would express the lymphoid markers CD45RB, CD3, CD20, and TdT; neuroblastomas would express synaptophysin and chromogranin, which are neuroendocrine markers; rhabdomyosarcomas would express desmin, myogenin, myo-D1, and myoglobin; and synovial sarcomas would also express pancytokeratins, EMA, B.

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Molecular Genetic

In 85% of cases, the EFT is linked to the translocation t(11;22) (q24;q12). A chimeric fusion transcript called EWS-FLI1 is created when the FLI1 gene on 11q24 and the EWS gene on 22q12 fuse [10]. The two types of typical translocation locations are type 1 (exon 7 of EWS to exon 6 of FLI1) and type 2 (exon 7 of EWS to exon 5 of FLI1). The translocation t(21;12)(22;12) resulting in EWS-ERG (Ets-related gene) fusion [11] is observed in an additional 10-15% of instances. The remaining 1–5% of instances display translocations, which result from the fusion of a EWS gene with a transcription factor belonging to the ETS family. The translocations that resulted are EWS and ETV1 (Ets variant 1) (t(2;22)(p22;q12)), EWS and E1AF (Ets variant 4 - ETV4/E1A enhancer binding protein),[12] and EWS and FEV (t(2;22)(q33;q12) [13]. There have also been reports of more sophisticated translocations.

The EWS gene

The TET gene family includes the EWS gene. TET proteins are believed to be involved in transcription and RNA processing based on their structure and capacity to bind RNA. EWS also controls splicing by interacting with splicing proteins [14].

The FLI1 gene

The Friend's murine leukaemia virus was found to insert itself into the FLI1 gene [15]. During embryonic development, FLI1 is expressed in neural crest-derived mesenchymal cells as well as hematopoietic and endothelial cells. The physiological function of FLI1 in hematopoiesis and vasculogenesis is significant [16].

The effect of EWS-FLI1 expression in tumor development

The expression of EWSFLI1 in murine NIH-3T3 cells led to rapid carcinogenesis and anchorage independent development in immunocompromised animals, with a tumour phenotype resembling human Ewing's sarcoma. These findings lend credence to the idea that EWS-FLI1 can promote oncogenesis and is mostly in charge of the histological traits connected to EFT.

Mechanism of action of EWS-FLI1

Ewing's sarcoma pathogenesis may be aided by EWS-FLI1 by promoting at least two sets of events that work in concert to advance the tumour, including cell proliferation and survival (by upregulating candidate genes such as PDGFC, IGF-1, MYC, CCND-1, and NKX2-2), and escape from apoptosis and growth inhibition (by downregulating candidate genes such as p21, p57kip, TGF-RI.

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Cell of origin

EFT is a poorly differentiated tumour with both mesenchymal and neuroectodermal histological and immunohistochemical characteristics; hence, it is difficult to determine whether this tumour originates from the mesenchyme or the neuroectoderm. EFT-like tumorigenesis was not observed despite numerous trials and the introduction of EWS-FLI1 into fibroblasts. Instead, it caused apoptosis and a growth stop. A retrovirus was used to introduce the EWS-FLI1 [17] fusion gene into murine cells with varied levels of differentiation potential, such as embryonic stem cells, primary mesenchymal progenitor cells, and embryonic fibroblasts. Embryonic fibroblasts and stem cells did not retain EWS-FLI1 expression at the protein level, while bone marrow-derived mesenchymal progenitor cells did. These cells created a tumour in mice that was made up of sheets of tiny spherical cells. Immunohistochemistry revealed that these tiny round cells expressed NSE and CD99, and that EFT-related genes were correspondingly up- and down-regulated in these cells [18].

Techniques for Detection of Translocation

Translocations are typically shown through chromosomal karyotyping. To make and interpret the karyotype, however, highly qualified individuals and a fresh tumour that needs to be cultivated are required. Cryptic translocations may be missed using this method.

Excision samples that are received after chemotherapy are carefully analysed, and the tumor's largest dimension is plotted into grids to gauge necrosis. Semi-quantitative grading of the histological response to treatment is performed.

Factors Associated with Prognosis

In EFT, a number of variables—including stage, original tumour site, size, age, and therapeutic response—have been thought to have prognostic significance. Radiological and radionuclear scans, together with bone marrow biopsy, are used to find metastases. The problem of occult- or micrometastasis, found by molecular techniques in the blood and bone marrow, has been the subject of numerous research. According to certain researchers, chimeric transcripts can be identified in the bone marrow of seemingly nonmetastatic EFT cases at presentation in up to 43% of cases, and this is linked to a poor prognosis [19]. Others, on the other hand, have not found a strong connection between diagnosis-time detection and the final result [4].

Therapeutic Targets

Finding a therapeutic drug is the main goal of all tumour research. No other normal cell in the body has the EWS-FLI1 fusion; it is only found in EFT cells. Therefore, EFT has a special protein produced by tumor-specific translocation that may be a molecular target, but nothing has made it to the clinic as of yet. This might be because EWS-FLI1 has a poor solubility, making it challenging to directly analyse in vitro [20].

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Monoclonal antibodies are being tested against this potential target because IGF-1 is connected to the growth of EFT [21]. Phospholipase D2 (PLD2) [22] and protein tyrosine phosphatase I (PTPL1) [23], both of which are highly expressed in EFT, are further potential possibilities.

CONCLUSION :-

In order to properly diagnose EFT, it is necessary to combine traditional or conventional methods such as histology and immunohistochemistry with more recent molecular technologies like as FISH and PCR. The purpose of these is to provide an accurate diagnosis as well as sufficient information regarding the tumour. This information should help in performing a more accurate risk assessment, enhancing clinical management, and increasing the patient's chances of survival.

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