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Perspective

Intrasinusoidal Hodgkin Lymphoma: Genetic Alterations and Therapeutic Approaches

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DESCRIPTION

Lymphomas are a heterogeneous group of malignancies arising from lymphoid tissues, characterized by abnormal proliferation of lymphocytes. Among the different subtypes, Hodgkin Lymphoma (HL) and Anaplastic Large Cell Lymphoma (ALCL) are distinct entities with unique morphological, immunophenotypic, and genetic features. However, there are rare cases where these lymphomas can show overlapping characteristics, posing a diagnostic challenge. This article aims to explore the intriguing entity of intrasinusoidal hodgkin lymphoma and its resemblance to anaplastic large cell lymphoma.

Understanding hodgkin lymphoma

Hodgkin lymphoma is characterized by the presence of Reed-Sternberg (RS) cells, which are large, multinucleated tumour cells derived from B-cells. The presence of RS cells in a background of reactive inflammatory cells is a hallmark of HL. The RS cells express CD30, CD15, and other B-cell antigens, making them distinguishable from other lymphomas. Classical HL subtypes include nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted.

Anaplastic large cell lymphoma

Anaplastic Large Cell Lymphoma (ALCL) is a T-cell lymphoma characterized by the presence of large anaplastic cells expressing CD30. These cells can exhibit varying degrees of pleomorphism and demonstrate strong and diffuse expression of CD30. ALCL can be subdivided into two major categories based on the expression of Anaplastic Lymphoma Kinase (ALK) protein: ALK-positive and ALK-negative ALCL. ALK-positive ALCL usually has a favorable prognosis, while ALK-negative ALCL is more aggressive.

Intrasinusoidal hodgkin lymphoma

Intrasinusoidal hodgkin lymphoma is an extremely rare variant of hodgkin lymphoma that closely resembles anaplastic large cell lymphoma. It is characterized by the presence of large atypical hodgkin/reed-sternberg-like cells located within the sinuses of lymph nodes, blood vessels, or other tissues. These cells show morphological similarities to ALCL, exhibiting anaplastic features, large nucleoli, and prominent nucleoli.

Clinical presentation

The clinical presentation of intrasinusoidal hodgkin lymphoma can be variable, with patients often presenting with generalized lymphadenopathy, B symptoms (fever, night sweats, weight loss), or extra nodal involvement. The disease is usually advanced at diagnosis, and the prognosis is generally poor, akin to ALCL.

Immunophenotypic features

Immunophenotypic analysis is significant for distinguishing intrasinusoidal hodgkin lymphoma from ALCL. In both entities, the tumour cells express CD30; however, they exhibit distinct patterns of CD15 expression. While ALCL is typically negative for CD15, intrasinusoidal hodgkin lymphoma often shows variable CD15 positivity. Additional immunohistochemical markers, such as ALK, PAX5, and T-cell markers, can aid in further differentiating between the two entities.

Genetic alterations

Genetic alterations can provide valuable insights into the pathogenesis and differentiation of intrasinusoidal hodgkin lymphoma and ALCL. *ALK* gene rearrangement is a hallmark of ALK-positive ALCL, leading to constitutive activation of the *ALK* kinase domain. In contrast, intrasinusoidal hodgkin lymphoma lacks *ALK* rearrangement and shows genetic

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alterations associated with classical HL subtypes, such as gains of 2p and 9p.

Diagnostic challenges

Distinguishing intrasinusoidal hodgkin lymphoma from ALCL can be challenging due to overlapping morphological and immunophenotypic features. Careful evaluation of the clinical presentation, histopathological features, and immunohistochemical profile is essential for accurate diagnosis. Molecular studies, such as Fluorescence *In Situ* Hybridization (FISH) or Polymerase Chain Reaction (PCR), may be necessary to confirm the diagnosis and exclude ALK rearrangement.

Treatment and prognosis

Intrasinusoidal hodgkin lymphoma is an aggressive disease with limited treatment options and a poor prognosis. The management approach often involves chemotherapy regimens used for classical HL, such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). However, the response to treatment is generally suboptimal, and patients may require additional therapies, such as stem cell transplantation or experimental agents targeting specific genetic alterations.

Intrasinusoidal hodgkin lymphoma is a rare variant of hodgkin lymphoma that shares morphological and immunophenotypic similarities with anaplastic large cell lymphoma. Its distinctive intrasinusoidal location and overlapping features with ALCL make it a challenging diagnostic entity. Accurate diagnosis relies on careful integration of clinical, morphological, immunohistochemical, and genetic findings. Further research is needed to elucidate the underlying molecular mechanisms and identify potential therapeutic targets for this aggressive lymphoma subtype.