

Leukaemia Section

Short Communication

Histiocytic Sarcoma

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Abstract

Histiocytic Sarcoma (HS) is a rare hematologic malignancy that belongs to the group of histiocytic and dendritic cell neoplasms. The causal etiology of HS is unknown. The clinical course is very aggressive.

Keywords

Histiocytic Sarcoma; Lymphoma malignant histiocytosis; Malignant histiocytosis.

Identity

Other names

Lymphoma malignant histiocytosis, Malignant histiocytosis

Clinics and pathology

Disease

Histiocytic Sarcoma (HS) is a rare hematologic malignancy that belongs to the group of histiocytic and dendritic cell neoplasms. The defining morphologic and phenotypic features of HS neoplastic cells are similar to mature tissue histiocytes (Pileri SA et al., 2002). The causal etiology of HS is unknown (no genetic or environmental factors are well described) HS could arise as a secondary malignancy, in the context of evolution from low-grade B-cell lymphoma. In these cases both disorders are clonally related (Feldman AL et al., 2004; Feldman AL et al., 2008; Wang E et al., 2010). An association with germ cell tumors has been reported (Song SY et al., 2005). The HS often develops solitary or multifocal extranodal tumors (gastrointestinal tract, soft tissue, skin or

other organ damage). The clinical course is very aggressive and overall survival (OS) of 2 years has been reported (Ansari J et al., 2016). There is no standard treatment; in disseminated forms systemic therapy (chemotherapy) has an important role, whereas surgical resection with or without adjuvant radiotherapy reaches better outcomes in localized masses (Facchetti F et al., 2017; Kommalapati A et al., 2018).

Phenotype/cell stem origin

PATHOGENESIS is poorly understood but in the last decade some advances had been made.

There is a clear association between various hematological neoplasms (especially those of B cell origin) and HS. To explain this evolution three mechanisms have been proposed (Wang E et al., 2010): transdifferentiation, where B cells change phenotypically but remains its genotypic features (Feldman AL et al., 2008), dedifferentiation where B cells regresses to early progenitors stage suffering afterward a new differentiation (not evidence in HS cases), and a common neoplastic progenitor (Feldman AL et al., 2004).

Transdifferentiation represents the most probably and well described pathway since some studies have demonstrated cases of HS (subsequent or concurrent with these neoplasms) showing clonal immunoglobulin heavy chain (IGH) and/or T-cell receptor (TCR) gene rearrangements, providing the evidence of a common clonal origin (Feldman AL et al., 2008; Wang E et al., 2010).

BRAF V600E mutation has also been observed in HS, being activation of RAS/RAF pathway another possible malignant transformation mechanism (Go H et al., 2014). Furthermore, alterations in KMT2D

(MLL2), also described in HS, have a role in its pathogenesis, in particular, in chromatin dysregulation (Hung YP et al., 2017).

Epidemiology

HS is a very rare disorder that affects people at any age with predominance in adults and male gender. Recent studies establish a median age at diagnosis of 63 years and lower incidence in African Americans than Caucasians (Kommalapati A et al., 2018).

Clinics

The vast majority of patients present with single or multifocal tumors, mostly affecting lymph nodes, skin, gastrointestinal tract, soft tissues, spleen, liver or bone (Takahashi E et al., 2013). Thus symptoms related to those targets organs (eg, intestinal obstruction, cytopenias or hepatosplenomegaly) could be presenting symptoms (Dalia S et al., 2014). Consequently, the clinical presentation of HS is diverse. Patients may have other systemic symptoms like fever, fatigue, weight loss or low blood counts (Ansari J et al., 2016; Takahashi E et al., 2013). Skin involvement can be seen in a variety manifestations, from a rash to tumors that can arise in extremities or the trunk.

Pathology

HS shows a diffuse growth pattern involving nodal or extranodal tissue; nevertheless sinusoidal or parenchymal pattern predominates if there is a lymph node, liver/spleen or bone marrow infiltration (Skala SL et al., 2018). Tumor cells are large and pleomorphic, with abundant eosinophilic cytoplasm that may enclose vacuoles. The nuclei, also pleomorphic, usually presents prominent nucleoli and in some cases multinucleation. A dense inflammatory background, confirmed by lymphocytes and neutrophils, is observed (Hung YP et al., 2017). Images of hemophagocytosis and necrosis have also been described.

IMMUNOPHENOTYPE It provides an important role, both to confirm the histiocytic nature of neoplasms cells and to dismiss other not well-differentiated tumors. Cells typically express CD68, CD4, lysozyme, and CD163 as specific markers of histiocytic differentiation (Dalia S et al., 2014). However, lysozyme and CD68 can be expressed in some other tumors like non-Hodgkin lymphomas and melanomas/carcinomas, respectively. Therefore, CD163 (membranous and cytoplasmatic pattern) is a more specific marker for the diagnosis of HS (Hung YP et al., 2017; Skala SL et al., 2018). It remains crucial the exclusion of poorly differentiated neoplasms as carcinomas, melanomas, hematological disorders (not specific B, T and myeloid cell markers either Langerhans and dendritic cell markers) (Hung YP et al., 2017). The Ki-67 index is usually between 5-50% (Skala SL et al., 2018). Recent studies have reported the

expression of the programmed death ligand 1 (PD-L1) in cases of HS, and its potential therapeutic target (Facchetti F et al., 2017).

Genes

There have not been reported characteristic molecular alterations specific for HS. Despite, there is a subset of HS that share molecular aberrations with other primary hematopoietic malignancies (being IGH and TCR gene rearrangements a case in point). Moreover, clonal IGH gene rearrangements have been described in sporadic HS (Chen W et al., 2009).

Application of Next Generation Sequencing (NGS) has improved the landscape of molecular features in HS.

Using NGS, recurrent alterations in KMT2D (MLL2), on chromosome 12q13.2, have been characterized.

This gene is involved in chromatin regulation and had also been reported in other hematologic malignancies (Hung YP et al., 2017).

Nevertheless, further studies are necessary to confirm those results and shed light on this matter.

Treatment

DIAGNOSIS Due to its low incidence and the possibility of overlapping of morphological and immunophenotypical features with other disorders, the diagnosis of HS is difficult. It is made based upon the evaluation of a biopsy specimen from the site of involvement.

The diagnostic key lies in the cytologic features and the advances in the recognition of histiocytic cell markers (CD 68, CD163 and lysozyme), mentioned above (Ansari J et al., 2016; Facchetti F et al., 2017). Certainly, clinical context also has an important relevance.

Imaging studies, as computed tomography or combined positron emission tomography, and bone marrow biopsy, could be useful to determinate the extension of the disease and the end organ damage (Dalia S et al., 2014).

The differential diagnosis must include: non-Hodgkin lymphomas, Langerhans cell histiocytosis, others histiocytic and dendritic cell neoplasms, carcinomas, melanomas, sarcomas

There is no standardized treatment for HS and the extent of the disease usually determines the therapeutic option among systemic chemotherapy, surgery and/or radiotherapy (Facchetti F et al., 2017; Kommalapati A et al., 2018). Traditionally, in cases of unifocal disease surgical resection with or without radiotherapy is employed; whereas systemic chemotherapy is the choice in multifocal disease. Regimens like CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), ICE (ifosfamide, cisplatin, etoposide) or ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)

are often used (Facchetti F et al., 2017; Kommalapati A et al., 2018). The role of adjuvant radiation therapy can be considered since it can reduce recurrence rates (Dalia S et al., 2014).

In a study using the National Cancer Database (NCDB) 330 cases of HS were reviewed (Kommalapati A et al., 2018). It was reported an improved OS in those HS cases where localized therapy (surgery either alone or with radiotherapy) was performed compared to systemic therapy. It has also been observed poorer outcomes (in terms of OS) when the hematopoietic or reticuloendothelial system was involved, despite the use of chemotherapy regimens (Kommalapati A et al., 2018).

The development of new therapies in this disease is necessary, new-targeted treatments are being used, like inhibitors of PD-L1 in those cases when it is expressed (Facchetti F et al., 2017) or tyrosine kinase inhibitors (as vemurafenib) if BRAF mutations are presented (Ansari J et al., 2016).

Prognosis

HS is an aggressive entity with an OS (in treated cases) that frequently does not get prolonged further than 2 years (Ansari J et al., 2016; Skala SL et al., 2018). Without treatment, survival is measured in months. Kommalapati A et al., in his studio of 330 HS cases, reported an OS of 6 months for the entire cohort, and described some possible prognostic factors: age, site of presentation, comorbidities, and therapy received (Kommalapati A et al., 2018).

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