

Leukaemia Section

Short Communication

Nodular sclerosis classical Hodgkin lymphoma (NScHL)

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Abstract

Over the past 50 years, a relevant progress has been made toward our understanding of classical Hodgkin lymphoma pathology and cell biology. Histologic classification evolved through different systems to the 2008 World Health Organization classification, upgraded in 2016.

Nodular sclerosis is a subtype of classical Hodgkin lymphoma characterized by sclerosis, diagnostic Hodgkin and Reed-Sternberg cells and other tumour cells displaying a "lacunar" type morphology. The architectural pattern consists of grouped lacunar cells in lymphoid nodules surrounded by collagen bands. Nodular sclerosis classical Hodgkin lymphoma may have a cellular proliferation of fibroblasts, in addition to the sclerotic component. The amount of sclerosis varies markedly from case to case, from ample sclerosis (total sclerosis phase of nodular sclerosis) to a paucity of collagen associated with abundance of lacunar cells (cellular phase of nodular sclerosis).

Keywords

Nodular sclerosis subtype of Hodgkin Lymphoma; Hodgkin Lymphoma; classical Hodgkin lymphoma; microenvironment; clinics, pathology; genetics.

Identity

Other names

Nodular sclerosis classical Hodgkin lymphoma
Nodular sclerosis Hodgkin lymphoma

Nodular sclerosis classical Hodgkin disease
Nodular sclerosis Hodgkin disease

Clinics and pathology

Note

Most patients present with limited disease (Ann Arbor stage II disease) and B symptoms. Mediastinal involvement occurs in 80% of cases, usually with Bulky disease. Splenic and/or lung involvement, as well as bone and bone marrow involvement, are less frequent.

Disease

Based on the characteristics of the Hodgkin and Reed-Sternberg (HRS) tumour cells (lacunar cells, multinucleated giant cells, pseudosarcomatous cells) and of the reactive infiltrate, four histologic subtypes of classical Hodgkin lymphoma (cHL) have been distinguished: lymphocyte-rich cHL (LRcHL), nodular sclerosis (NS) cHL, mixed cellularity (MC) cHL, and lymphocyte depletion (LD) cHL. Most cHL can be classified as NS or MC subtypes.

NS is a subtype of cHL characterized by sclerosis, diagnostic HRS cells and other tumour cells displaying a "lacunar" type morphology. The architectural pattern consists of grouped lacunar cells in lymphoid nodules surrounded by collagen bands. NScHL may have a cellular proliferation of fibroblasts, in addition to the sclerotic component. The amount of sclerosis varies markedly from case to case, from ample sclerosis (total sclerosis phase of

NS) to a paucity of collagen associated with abundance of lacunar cells (cellular phase of NS).

Phenotype/cell stem origin

Cell origin

Like Hodgkin and Reed-Sternberg (HRS) cells of other cHL subtypes, the tumour cells of NScHL derive from preapoptotic crippled Germinal Center (GC) B cells. They are derived from GC B cells that have acquired disadvantageous immunoglobulin variable chain gene mutations (Küppers et al., 2012), have lost the expression of most B-cell genes and acquired expression of genes that are typical for other types of hematopoietic and lymphoid cells (Greaves and Gribben 2012; Steidl et al. 2012; Tiacci et al., 2012).

Phenotype

Phenotypically, tumour cells of NScHL are CD30 and CD15 positive (Stein et al., 2008), and exhibit additional expression of the following markers:

- Plasma cell markers (MUM1/IRF4) usually positive.
- Molecules involved in Ag presentation (MHC class II, CD40, CD80, CD86) consistently positive.

Cellular components of the cHL microenvironment

express molecules involved in cancer cell growth and survival (such as CD30L or CD40L), and in immune escape (programmed death 1 (PD-1)). A fraction of infiltrating CD4+ T cells are regulatory T (Treg) cells. Treg cells and PD-1+ T cells also interact with HRS cells (Aldinucci et al., 2010; Liu et al., 2014; Carbone et al., 2015).

Epidemiology

Classical Hodgkin lymphoma is a distinct neoplastic entity with heterogeneous epidemiological features. It accounts for approximately 10% of all malignant lymphomas (Stein et al., 2008). Classical HL is the most common cancer in patients under 20 years (adolescents and younger adults). The first peak of incidence can be observed in patients under 35 years of age, whereas a second incidence peak can be observed in the elderly (Hjalgrim et al, 2008; Stein et al., 2008).

NScHL accounts for approximately 70% of cHL in Europe and USA and is more common in resource rich than in resource poor areas. The incidence of NScHL is similar in males and females and peaks at ages 15-34 years.

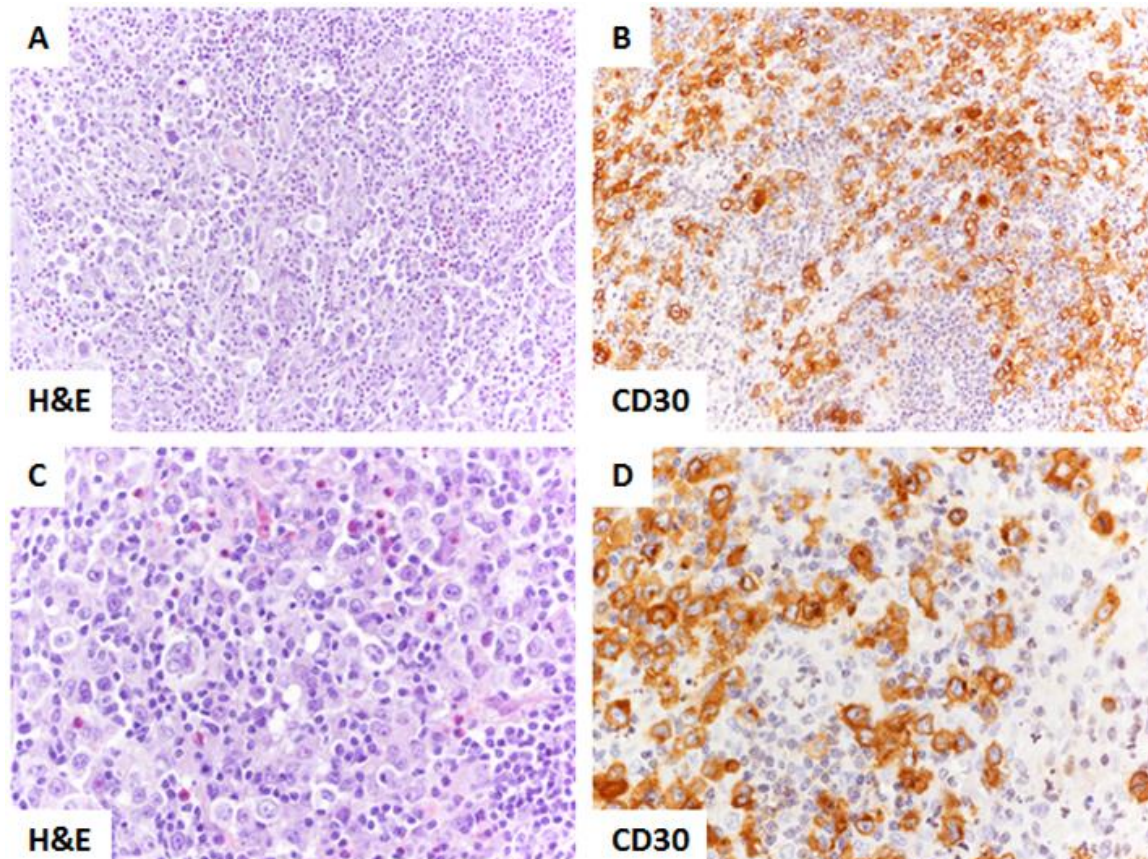


Figure 1. "cellular phase" of NScHL. (A) In this variant of NScHL the lacunar cells are numerous. Moreover, they differ morphologically. (B) Grouped lacunar cells show CD30 membranous localization. (C) At higher magnification most lacunar cells appear to be separated from the adjacent lymphoid cells by a clear space. (D) Several sheets of CD30+ lacunar cells with combined membranous and Golgian immunostain.

Cytology

The recognition of NScHL is based on the presence of HRS cells and lacunar cells, the specific tumour cells of NScHL. Binucleated and multinucleated HRS cells with bi- or multinucleation and huge nucleoli are pathognomonic for cHL identification. The lacunar cells tend to have more lobated nuclei with less prominent nucleoli and a large amount of cytoplasm than HRS cells in other subtypes of cHL. In formalin-fixed tissues the cytoplasm of the lacunar cells shows retraction so that the cells seem to be located in a lacuna. In the so called "syncytial variant", lacunar cells may be grouped, forming cellular islands which may be associated with necrosis.

Pathology

Involved tissues by NScHL exhibit a nodular growth pattern with tumour nodules surrounded by collagen bands. Broad bands of fibroblast-poor collagen may be scarce/absent (cellular phase of NS) or surround one nodule (early sclerosis of NS) or several nodules (classical nodular sclerosis). The fibrosing process may progress to reach a complete thickening of the nodules (total sclerosis of NS).

Lacunar cells usually resides in an inflammatory cell microenvironment. In NScHL, like in other cHL subtypes, microenvironmental cell types include T- and B-reactive lymphocytes,

eosinophils, granulocytes, histiocytes/macrophages, plasma cells, mast cells, and fibroblast-like cells (Aldinucci et al., 2010). The cellular background found in the nodules is variable. The nodules may be with lymphocyte predominance, mixed or with lymphocyte depletion. The cellular composition of the backgrounds of the nodules parallel those of non NS subtype of cHL

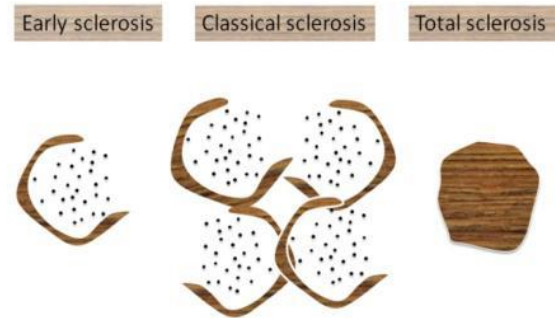


Figure 2. Schematic representation of NScHL with early sclerosis, classical sclerosis and total sclerosis.

Other features

EBV infection

EBV is found in HRS cells preferentially in cases of MC and LD cHL, and less frequently in NS and LRcHL. Notably, EBV is found in HRS cells in nearly all cases of cHL occurring in patients infected with HIV (IARC 2012; Younes et al., 2014; Dolcetti et al., 2016).

	Classical Hodgkin lymphoma subtype	EBV infection
cHL of the general population		
	cHL, nodular sclerosis	Usually absent *
	cHL, mixed cellularity	Usually present *
	Rare types	
	cHL, lymphocyte rich	Variably present
	cHL, lymphocyte depleted	Variably present
HIV-associated HL		
	cHL, lymphocyte depleted	Present
	cHL, mixed cellularity	Present
	Less frequent	
	cHL, lymphohistiocytoid	Present
	cHL, nodular sclerosis	Present
Post-transplant (cHL type PTLD)		
	Similar to other cHL	Present
Iatrogenic (methotrexate)		
	cHL, mixed cellularity	Variably present (usually present)

Table 1. Heterogeneity of classical Hodgkin lymphoma according to the morphologic and virologic characteristics.

Abbreviations. cHL, classical Hodgkin lymphoma; PTLD, post-transplant lymphoproliferative disorder

*Association with EBV is less frequent in ns (10-40%) than in mc cHL (approximately 75% of cases).

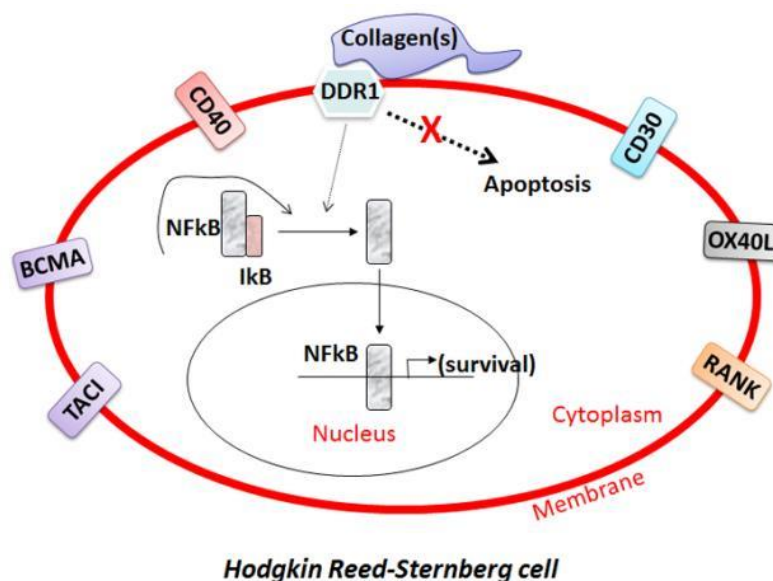


Figure 3. Schematic representation of the interaction of a tumour cell and its cell microenvironment: impact on NFκB signalling pathway. DDR1 pathway is likely to be an alternative or additional pathway to CD40 or CD30 signaling in the pathogenesis of Hodgkin lymphoma.

Treatment

Like in other cHL subtypes, cure rates approaching 80% have been achieved in patients undergoing chemo-radiotherapy, qualifying cHL as a chemosensitive disease (Santoro et al., 1987, Canellos et al., 2014).

Prognosis

NScHL exhibit a better prognosis than that of other subtypes of cHL.

Genetics

Note

Recurrent genetic alterations have been identified in HRS cells of cHL (including NScHL). These lesions affect members of the NF-κB or JAK/STAT signalling pathways (Küppers and Re, 2007; Hartmann et al., 2008; Steidl et al., 2010; Küppers 2011; Küppers et al., 2012; Pasqualucci and Dalla Favera, 2014). See also the pertinent section within the CARDS describing the general features of cHL (Küppers, 2011; Carbone and Gloghini, 2016).

Since NScHL microenvironment contains a collagen-rich ECM, and a large number of fibroblasts, defined HL-associated fibroblasts a lymphomagenetic role for discoidin domain receptor1 (DDR1), a receptor tyrosine kinase (RTK) (Xu et al., 2011; Valiathan et al., 2012), has been proposed. Interactions between HRS cells and HL-associated fibroblasts produce collagen-rich reticular fibers composed of collagen I, III and IV covered by the ECM. Importantly, collagen IV, which is recognized by DDR1 in turn induces DDR1 up-regulation and activation (Carbone and Gloghini, 2013).

After binding to collagen, DDR1 phosphorylation triggers the activation of downstream signaling pathways, including NF-κB (Das et al., 2006).

Cytogenetics

Cytogenetics morphological

See the pertinent sections within the CARDS describing the general features of cHL (Küppers, 2011; Carbone and Gloghini, 2016).

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