

## Leukaemia Section

### Short Communication

# Mixed cellularity classical Hodgkin lymphoma (MCcHL)

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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.

Mixed cellularity is a subtype of classical Hodgkin lymphoma characterized by diagnostic Hodgkin-Reed Sternberg cells in a mixed inflammatory background without sclerosis. Mononuclear Hodgkin cells can be present. The mixed cellular background is considered the hallmark of the Mixed cellularity classical Hodgkin lymphoma subtype. In particular, heterogeneous constituents including admixed eosinophils plasma cells, histiocytes and small lymphocytes are usually found. The composition of this background varies greatly.

### Keywords

Mixed cellularity subtype of Hodgkin Lymphoma; Hodgkin Lymphoma; classical Hodgkin lymphoma; microenvironment; clinics, pathology; genetics

## Identity

### Other names

Classical Hodgkin lymphoma (HL): Mixed cellularity subtype  
Mixed cellularity Hodgkin lymphoma  
Mixed cellularity classical Hodgkin disease  
Mixed cellularity Hodgkin disease

## Clinics and pathology

### Note

Most patients affected by mixed cellularity (MC) classical Hodgkin lymphoma (cHL) present with B symptoms and in intermediate stages (II and III), compared with frequent stage II presentation in nodular sclerosis (NS) cHL. Peripheral lymph nodes are commonly involved. Splenic and liver involvement are frequent, whereas bone marrow and other organs 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 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.

MC is a subtype of cHL characterized by diagnostic HRS cells in a mixed inflammatory background without sclerosis.

Mononuclear Hodgkin cells can be present. The mixed cellular background is considered the hallmark of the MCcHL subtype. In particular, heterogeneous constituents including admixed eosinophils, plasma cells, histiocytes and small lymphocytes are usually found. The composition of this background varies greatly.

## Phenotype/cell stem origin

### Cell origin

Like HRS cells of other cHL subtypes, the tumour cells of MCcHL 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 (Kuppers 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 MCcHL 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

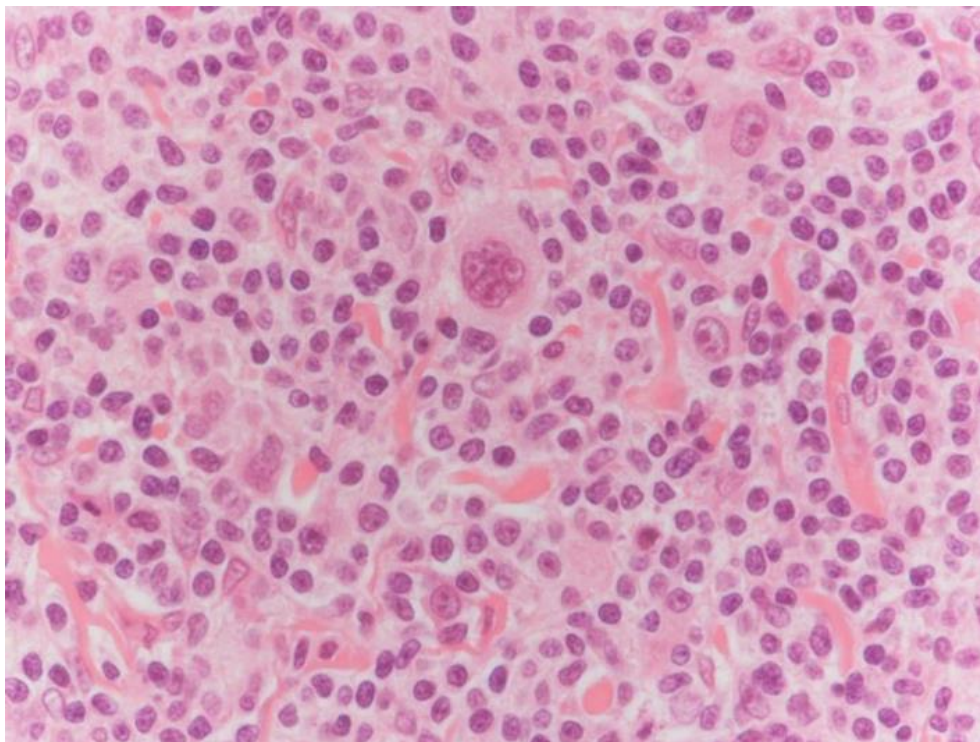
neoplastic entity with heterogeneous epidemiological features. It accounts for approximately 10% of all malignant lymphomas (Stein et al., 2008). Classical HL is the most common cancer in patients under 20 years (adolescents and younger adults). The first peak of incidence can be observed in patients under 35 years of age, whereas a second incidence peak can be observed in the elderly (Hjalgrim et al., 2008; Stein et al., 2008). MCcHL accounts for approximately 20-25% of cHL. MCcHL is more frequent in patients with HIV infection and in resource poor areas. The incidence of MCcHL is more frequent in male than in females and peaks at age 35-40 years.

### Cytology

The recognition of MCcHL is based on the presence of diagnostic HRS cells in a specific inflammatory background, the composition of which varies greatly and includes eosinophils, neutrophils, histiocytes and plasma cells. Binucleated and multinucleated HRS cells with bi- or multinucleation and huge nucleoli are pathognomonic for MCcHL identification.

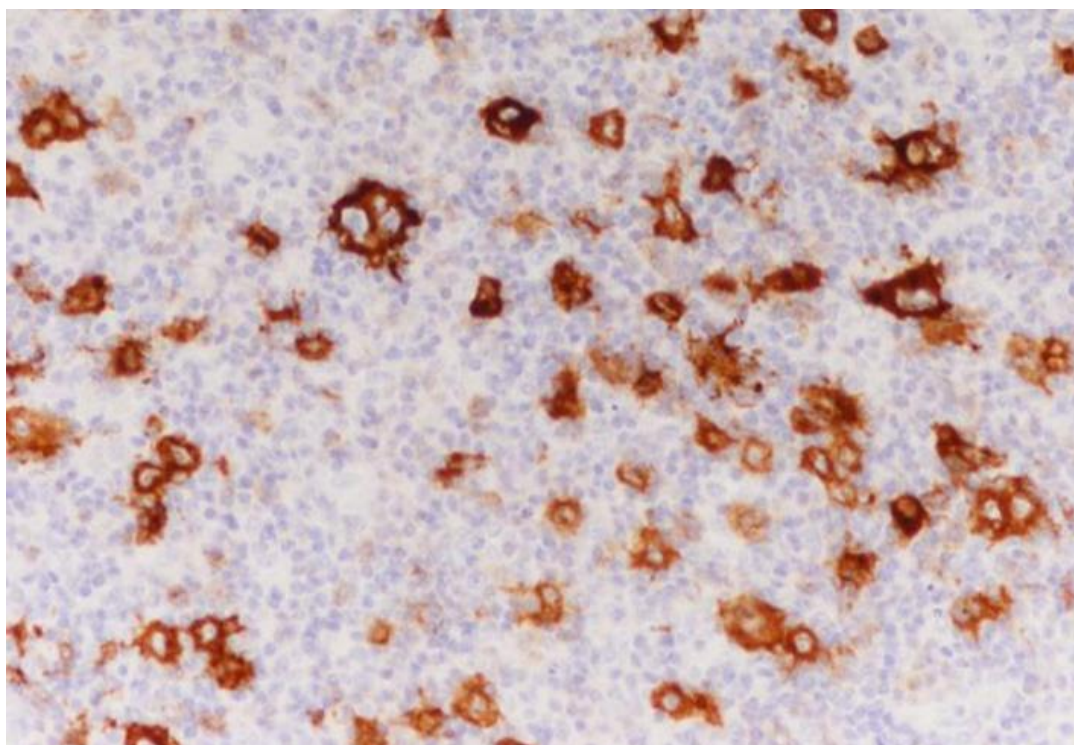
### Pathology

HRS cells reside in an inflammatory cell microenvironment. In MCcHL, like in other cHL subtypes, microenvironmental cell types include T- and B-reactive lymphocytes, eosinophils, granulocytes, histiocytes/macrophages, plasma cells, mast cells.

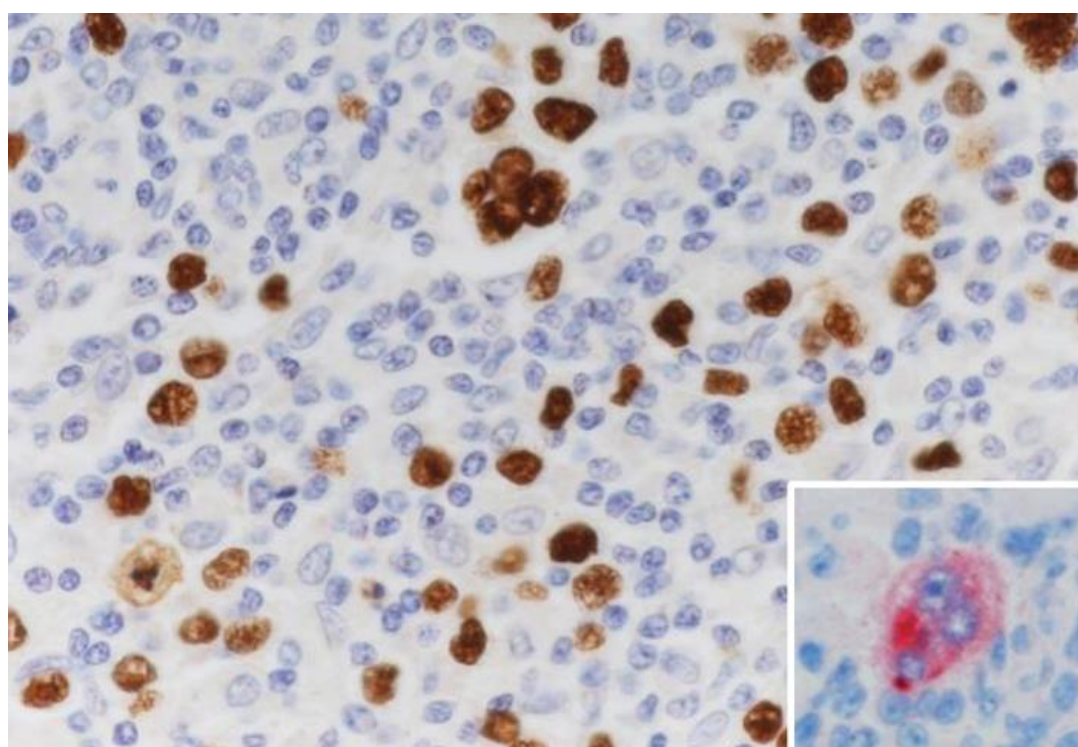


**Figure 1.** A typical multinucleated Hodgkin Reed-Sternberg cell is seen at the center.





**Figure 2.** The CD30 immunostaining highlights the presence of Hodgkin Reed-Sternberg cells and some mononucleated Hodgkin cells



**Figure 3.** EBV and EBV-encoded LMP1 (inset) are expressed by multinucleated Reed-Sternberg cells as nuclear and cytoplasmic staining, respectively

### **Other features**

#### **Virology**

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).

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

## 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

MCcHL exhibit a better prognosis than that of NScHL.

## Genetics

Recurrent genetic alterations have been identified in HRS cells of cHL (including MCcHL). These lesions affecting members of the NF-kappaB 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).

## 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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