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Short Communication

Classical Hodgkin lymphoma

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Abstract

Hodgkin lymphoma (HL) was one of the earliest cancers to be cured with multiagent chemotherapy even before its biology was understood.
Over the past 50 years, a relevant progress has been made toward our understanding of HL pathology, cell biology and treatment options. Histologic classification of HL evolved through different systems, starting from the modern histologic classifications by Jackson and Parker in 1944 and Lukes and Collins in 1966, to the 2008 World Health Organization (WHO) classification. Classical HL involves a clonal expansion of neoplastic B lymphocytes, though a small subset of cases may derive from T cells. Cure rates approaching 80% have been achieved in patients undergoing chemo-radiotherapy, qualifying cHL as a chemosensitive disease.

Keywords: Hodgkin lymphoma; classical Hodgkin lymphoma; microenvironment; clinics, pathology; genetics; EBV infection

Identity

Other names: Hodgkin lymphoma, classical Hodgkin disease, Hodgkin disease

Clinics and pathology

Disease

Hodgkin lymphoma(HL) has been classified into classical HL (cHL), which accounts for 95% of all HL cases, and the less common nodular lymphocyte predominant HL (NLPHL), which is considered to be a separate entity (Stein et al., 2008; Poppema et al., 2008).
Classical HL is a distinct neoplastic entity with typical clinical, epidemiological, pathological, genetic, and virological features. It accounts for approximately 10% of all malignant lymphomas.

Phenotype/cell stem origin

Cell origin: Hodgkin and Reed-Sternberg (HRS) cells, the tumour cells of cHL, derive from preapoptotic crippled germinal center (GC) B cells. In fact, molecular features of HRS cells in cHL demonstrate that they are derived from GC B cells that have acquired disadvantageous immunoglobulin variable chain gene mutations and normally would have undergone apoptosis (Kuppers et al., 2012).
As shown in gene expression profiling (GEP) studies, HRS cells have lost the expression of most B-cell genes and acquired expression of genes that are typical for other types of immune cells (Greaves and Gribben 2012; Steidl et al. 2012; Tiacci et al., 2012).
Phenotype: Phenotypically, HRS cells of cHL are consistently positive for CD30, CD15, CD40, and IRF4/MUM1 (Stein et al., 2008).
Expression of molecular markers in cHL include (Younes et al., 2014)
- B-cell markers (CD20 and CD79) usually negative
- GC B-cell markers (BCL6 and AID) usually negative
- Plasma cell markers (MUM1/IRF4) usually positive

- Molecules involved in Ag presentation (MHC class II, CD40, CD80, CD86) positive

A surfaceoma study by TMA analysis indicated that gamma-glutamyltranspeptidase 1 is a potential additional marker for differential diagnosis of cHL versus non Hodgkin lymphoma (Hofmann et al., 2015).

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). For example, CD30L+ eosinophils and mast cells, and proliferation-inducing ligand (APRIL)+ neutrophils, are consistently admixed to HRS cells, whereas CD40L-expressing CD4+ T lymphocytes rosette HRS cells. 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 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).

Cytology

Binucleated and multinucleated HRS cells are giant cells wirh bi- or multinucleation and huge nucleoli. These cells and their mononuclear variant, the so-called Hodgkin cells, are pathognomonic for cHL identification.

Pathology

HRS cells reside in an inflammatory cell microenvironment.

Based on the characteristics of the HRS cells (lacunar cells, multinucleated giant cells, pseudosarcomatous cells) and of the reactive infiltrate, four histologic subtypes 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. The remaining LRCHL and LD subtypes are uncommon. LRCHL cases display histological and clinical features intermediate between those of cHL and NLPHL (Poppema et al., 2008; Stein et al., 2008; Swerdlow et al., 2016).

In cHL, microenvironmental cell types include T- and B-reactive lymphocytes, eosinophils, granulocytes, histiocytes/macrophages, plasma cells, mast cells. In addition, a great number of fibroblast-like cells and fibrosis are frequently found (Aldinucci et al., 2010).

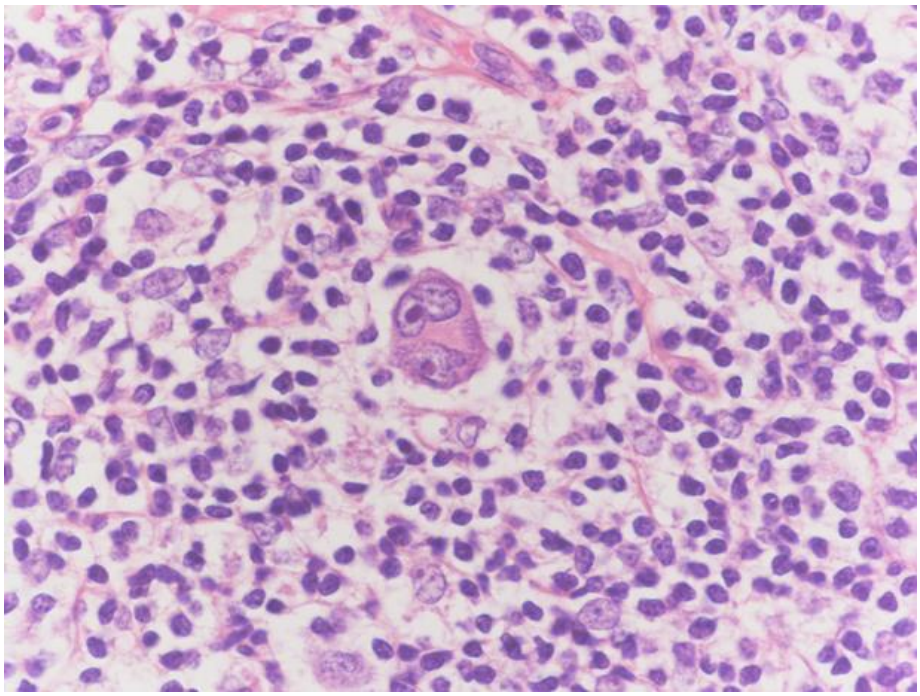

Figure 1. A multinucleated giant cell, the so called Reed-Sternberg cell.

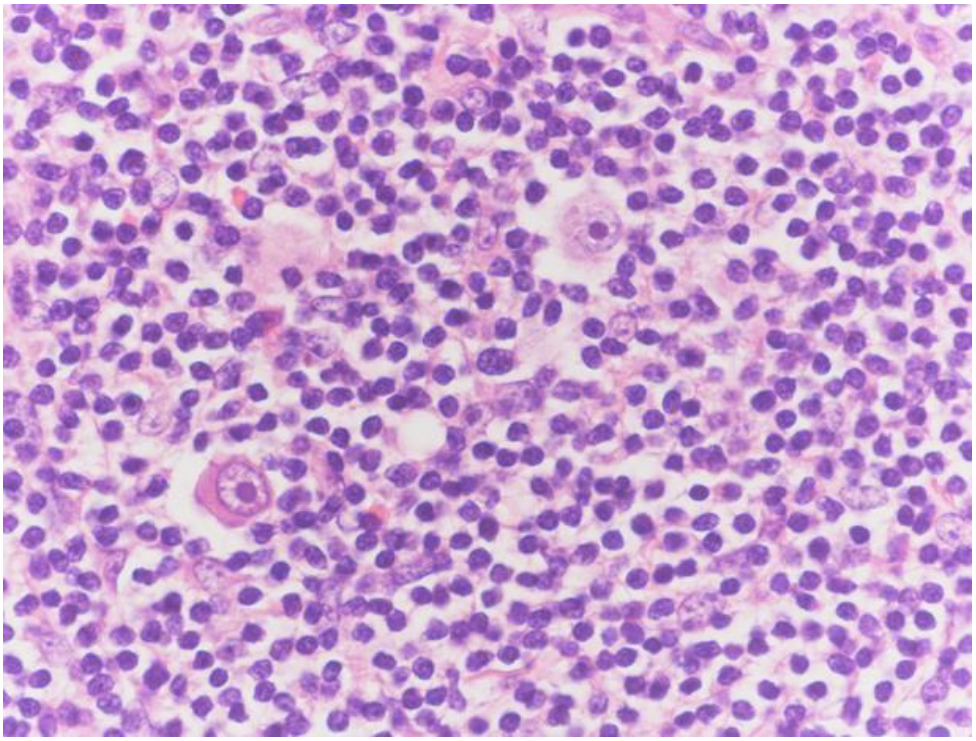

Figure 2. Mononucleated giant cells, the so called Hodgkin cells

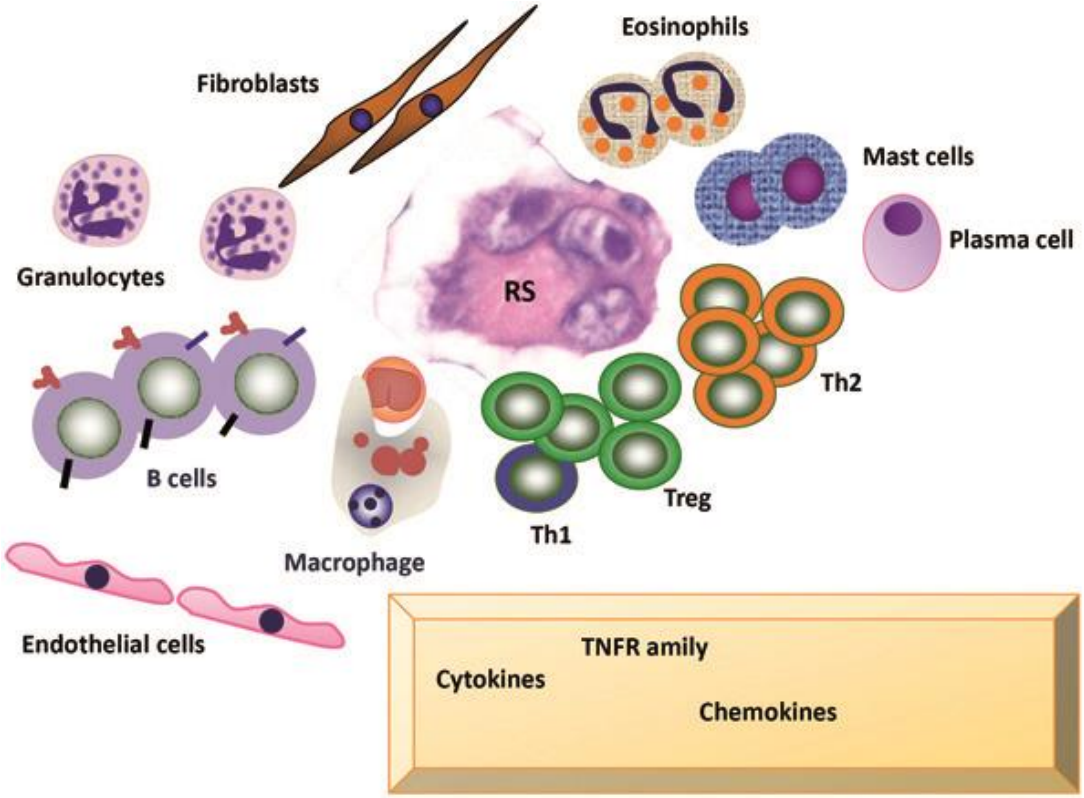

Figure 3. The schema shows a Reed-Sternberg within its cell microenvironment.

Other features

EBV infection

The immunophenotypic and genetic features of HRS cells are identical in the different histologic subtypes of cHL. Conversely, the association with EBV shows differences. 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 (Younes et al., 2014; Dolcetti et al., 2016).

The virologic characteristics of cHL vary according to the immunocompetence status of the host and cHL subtype (IARC, 2012) as follows:

cHL of the general population
- NS cHL, usually EBV negative
- MC cHL, usually EBV positive
- LRCHL, variably EBV positive
- LD cHL, variably EBV positive

Immunodeficiency-associated cHL
- HIV-associated cHL, EBV positive
- Post-transplant cHL, EBV positive
- Iatrogenic (methotrexate), variaby EBV positive

Treatment

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) . However, 25% to 30% of these patients show either primary refractoriness to chemotherapy, early disease relapse or late disease relapse (Canellos et al., 2014; Carbone et al., 2015).

Prognosis

The implementation of novel agents for the treatment of multi-relapsed cHL patients has improved the outcome of these patients and will significantly impact the history of multi-relapsed cHL in the near future when the results of combination studies become available. For example, the synergistic effect of Dehydroxymethylepoxyquinomicin (DHMEQ) with three chemotherapeutic drugs widely used in cHL treatment, doxorubicin, gemcitabine and cisplatin, has recently been demonstrated (Locatelli et al., 2014).

Genetics

Recurrent genetic alterations have been identified in HRS cells of cHL. These lesions affecting members of the NF-kappaB or JAK/STAT signalling pathways include inactivating mutation in NFKBIA (10-20% of cases), NFKBIE (10%), TNFAIP3 (40%), SOCS1 (40%), genomic gains of RELA (30%) and JAK2 (30%) and rare BCL3 translocations. TNFAIP3 mutations are found in Epstein-Barr virus-negative cases of cHL. Mutations have been found in the tumour suppressor genes FAS (CD95) and TP53.

Further genomic imbalances, identified by comparative genomic hybridization studies include gains of IKBKB, CD40 and MAP3K14 that are regulators of NF-kappaB signaling (Küppers and Re, 2007; Hartmann et al., 2008; Steidl et al., 2010; Küppers 2011; Küppers et al., 2012; Pasqualucci and Dalla Favera, 2014).

Interestingly, HRS cells show aberrant somatic hypermutation of several proto-oncogenes (PIM1, RHOH (TTF), MYC, PAX5) in a considerable fraction of cases (Küppers et al., 2012; Pasqualucci and Dalla Favera, 2014).

Cytogenetics

HRS cells are clonal with variable modal chromosome numbers as indicated from direct chromosome analysis and DNA measurements and shown by the detection of clonal immunoglobulin V gene rearrangements in single HRS cells.

The modes are about twice as frequently in the triploid-tetraploid as neardiploid region. Translocations involving the immunoglobulin loci have been found in about 20% of cHL; deletions and duplications, common in other types of tumour, have also been described in cHL.

Diploid as well as aneuploid metaphases are commonly found in chromosome studies, both direct and after culturing. Using FISH 1-12% of "normal" nuclei in cHL exhibit abnormalities, especially trisomies for various chromosomes (Atkin, 1998; Jensen et al., 1998; Hartmann et al., 2008; Schmitz et al., 2009; Steidl et al., 2010; Küppers 2011).

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