Hodgkin's Disease - An Update

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Introduction

Hodgkin's disease (HD) was first described in 1823 by the pathologist Thomas Hodgkin, through correlating clinical features with subsequent postmortem findings. Surprisingly, all of the other nonHodgkin's lymphomas (NHL) were described in the 20th century. A characteristic large, binucleated or multinucleated cell of Hodgkin's disease was described by Dr. Reed and Carl Sternberg in 1902. This cell is named after them as Reed-Sternberg cell (RS) [1]. The demonstration of these cells within an appropriate reactive inflammatory background is necessary to make the microscopic diagnosis of HD. It had been thought that RS cells are pathognomonic of HD, but we know now that there are morphologically identical cells in other conditions not related to HD; these include reactive/inflammatory conditions (such as infectious mononucleosis), NHL, as well as other nonlymphomatous neoplasms (both carcinomas and sarcomas) [2]. To avoid possible confusion, the RS cells of Hodgkin's disease are now called Hodgkin's RS cells (HRS). In HD, there is a second neoplastic component in addition to HRS cell; this is a related cell, called Hodgkin's cell (HC). It has all the morphological attributes of HRS cell except that it is mononuclear. Admittedly, HC do not have the diagnostic specificity of HRS cells. HD has been divided into several subtypes that differ not only in their microscopic composition but also in their clinical features and prognosis[2]. Since the fifties, there have been relentless efforts to sub-classify HD and the reason for this is twofold; first to establish reproducible, clinically and prognostically meaningful subtypes with the aim of settling on an optimal type-specific treatment, and secondly to better understanding of the enigmatic pathogenesis of the disease. Consequently, a plethora of classifications have emerged. The most widely adopted over the years has been the Rye classification (1966), which in turn is a modification of that of Lukes and Butler (1963) [2, 3, 4]. Rye classification divides HD into four major categories namely

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1. Lymphocyte predominant (LPHD)
   A. diffuse
   B. nodular (NLPHD)
2. Nodular sclerosis (NSHD)
3. Mixed cellularity (MCHD)
4. Lymphocyte depletion (LDHD)

The LPHD is the least common variant accounting for only 3% to 8% of the cases in Western countries [4, 5]. The diagnosis of this variant relies on the presence of a specific variant of HRS cells (the 'popcorn' cells). These are scattered in a few number within an appropriate background of small mature B lymphocytes. Frequently a variable number of histiocytes are also present. In 1994, the Revised European-American Classification of Lymphoid Neoplasms (REAL) divided Hodgkin's disease into two very different broad categories

A. NLPHD
B. Classical HD (CHD)
   1. NSHD
   2. MCHD
   3. LDHD
   4. Lymphocyte rich HD (LRHD)
   5. Unclassifiable HD (UC) [6]

The reason behind such a major modification has been the realization that NLPH is clinically, morphologically and genetically distinct from other types of HD[7-10]. Indeed the accumulated evidences over the last twenty years have indicated that NLPHD is a B-cell lymphoma derived from a germinal center cells and is associated with excellent prognosis. The latter is due to the fact that this very type of HD tends to present as an early-stage disease with slowly progression and a very good response to standard therapy[7, 10]. The diffuse subtype of LPHD is omitted because it is an extremely rare entity and there have been doubts regarding its real existence [11]. Within the classical category, a recently recognized new member has been added; "the lymphocyte rich Hodgkin's disease (LRHD)". Additionally, a new category has been introduced, the unclassifiable HD, which is allocated for cases that defy the conventional rules i.e. do not fit into any one of the proposed categories. The REAL classification, unlike the Rye's, requires in addition to morphology, the application of immunohistochmical markers for the diagnosis of the cases (see below).

Cell of origin of HD

Recently, several investigators [12-15] convincingly demonstrated that both categories of HD (the classic and NLPHD) are malignant B-cell lymphomas of germinal center origin. In most

instances HRS cells represent a clonal population of transformed germinal centre B cells. In NLPHD, the popcorn cells are mantle zone, mutating and antigen-selected B cells expressing CD20 (which is a B-cell marker), and show evidence of immunoglobulin-synthetic capacity including the expression of cytoplasmic J-chain. Evidences indicate that HRS cells in classical HD (including LRHD) originate from B cells of germinal centers but at the pre-apoptotic phase of their life cycle[16]. Unlike the popcorn cells of NLPHD, they are CD20 negative but never the less, express different markers namely CD30 and frequently also CD 15. In other words the difference between HRS cells of the two groups is in the stage of evolution of the germinal center B cells from which they are derived. Further support for such B-cell derivation is the emergence of the increasingly reported composite lymphomas. In these lymphomas, the tumor has characteristics of both HD and diffuse large B-cell Lymphoma, B-CLL or follicular centre lymphoma. If the neoplastic cells of HD (HRS and HC) are derived from B cells, then why don't they express all B cell attributes e.g. immunoglobulin synthesis? The explanation has come from molecular and gene expression studies of HD cell lines, which have evidently indicated that during their evolution, HRS cells actually lose most of the B cell typical gene expression program[17]. B-cells normally undergo limited cycles of genetic rearrangement that result in immunoglobulin production. In rare cases, however, the genetic arrangements create a mutation that does produce immunoglobulins. The results are large, abnormal cells referred to as Reed-Sternberg cells[18].

Nodular lymphocyte predominant, and lymphocyte rich Hodgkin's disease; similarities and differences

In the REAL classification LRHD has been introduced within the classical category as a provisional member. However, the proposed WHO Classification that follows converted the "provisional" category of LRHD to a permanent one. LRHD characterizes cases with a background consisting predominantly of lymphocytes. At this point it simulates morphologically NLPH in that both have a similar background of mature lymphocytes. However, LRHD, which may be nodular or diffuse, and when nodular, characterized by expanded mantle zone regions that are colonized by typical, albeit relatively rare, HRS cells. There is also relative paucity of histiocytes, plasma cells and eosinophils[19]. NLPHD on the other hand, may show partial or total nodal effacement by a nodular, or nodular and diffuse proliferation of small lymphoid cells. The involved lymph node is replaced by macronodular structures that resemble progressively transformed germinal centers[1]. The important distinctive feature is the presence of a characteristic HRS cell variant, the "popcorn cell". The latter is characterized by a lobulated and twisted nucleus, and a nucleolus which is typically smaller than that seen in HRS cells of Classical HD (including LRHD). The number of popcorn cells is variable and may comprise up to 10% of the cellular population within the nodules. Classical HRS cells are extremely rare in NLPHD and actually not required for the diagnosis. It is apparent form the above that morphological distinction between the two members is possible but tentative and provisional. In fact the decisive difference between the two entities is principally immunophenotypic i.e. through the application of immunological markers. In LRHD, the tumor cells are of the classical type i.e. CD30 and/or CD15 positive, but CD20 negative, whereas NLPHD tumor cells express, as would be expected, B-cell antigens such as CD20 and rarely express CD15 or CD30[2]. This breakthrough has resulted in changing the already made diagnosis of HD in several retrospective studies to two immunolgically separable entities (i.e. NLPHD and LRHD). This reallocation of the ceases is exemplified by one study, in which the clinical data and biopsy material of all available 426 cases initially diagnosed as LPHD were collected from 17 European and American centers, stained, and reclassified by expert pathologists. The result was that 27% of the cases were reclassified as LRHD with a consequent drop in LPHD diagnoses to 51% (the rest were reclassified as mixed cellularity, NHL and reactive conditions). In this very study the comparison between the two entities had revealed that both showed similar clinical features i.e. a predominantly young, asymptomatic, male gender, early-stage disease (usually involving a single node), and a few adverse prognostic factors such as the rarity of systemic symptoms. These findings have been confirmed in several other studies[1]. The average age of patients with NLPHD is the fourth decade and the common sites of lymph node involvement include supra-hyoid neck and inguinal regions. Patients with NLPHD have earlier-stage disease, longer survival, and fewer treatment failures than those with classic Hodgkin's disease. Mediastinal involvement is usual. LRCHD patients, however, differ in two features that are relatively inconsequential as far as the differential diagnosis is concerned

1. On average the patients are older
2. Presentation as a large mediastinal mass is more frequent

Survival with adequate therapy was similar for patients with LPHD and LRCHD, and appeared to be stage-dependent. Surprisingly, the survival of the above two types is not significantly better than stage-matched cases belonging to the rest of CHD cases i.e. MCHD, NSHD and LDHD (German trial data). This means that the major determinant of prognosis is the stage of the disease rather than its histological subtypes. The better prognosis of NLPHD and LRHD in comparison with the other members is due to the fact that the majority of the former are discovered in their early stages.

J chain and nodular lymphocyte predominant Hodgkin's disease

J-chain is a polypeptide that links immunoglobulin molecules into groups of two (IgA) or five (IgM). Kelenyi[20] reported that J-chain had significant prognostic power in multiple myeloma. Briefly, the presence of J-chain indicates the ability of the cell to produce immunoglobulins, and therefore, is a reflection that the cell is well differentiated and retains its functionality as a B cell. As such, this property would logically be expected to correlate with a lower degree of malignancy. Although it has been investigated in LPHD and CHD by various authors[21, 22], there was no attempted correlation of this finding to clinical characteristics. In one study, the test for J-chain was positive for most LPHD cases but negative for most cases of CHD. Absence of J-chain seems to define a minor subgroup of LPHD cases with a poorer prognosis than J-chain positive cases[1].

NonHodgkin's lymphomas complicating Hodgkin's disease (Secondary NHLs)

There are two sets of secondary cancers complicating HD

1. Treatment induced (Leukemias and solid tumors)
2. Transformation of the initial HD in to NHLs[23].

The significance of these complicating secondary cancers is derived from the fact that they are the cause of death in a significant number of HD cases (32% in one study) [23-26]. However, only a minority of these deaths is caused by NHL, but these differ from the first group in that they are not treatment related in the majority of the cases[24, 25]. Recently, and through molecular techniques, a clonal relationship between large-cell lymphoma complicating LPHD and the initial tumor could be established[22, 26-28]. It appears that secondary NHL complicates NLPHD relatively more frequently than the classical members. An analysis from the International Database on Hodgkin's disease estimated a secondary NHL rate of 0.8% of cases at 25 years Vs 3.8% for NLPHD cases [25]. Most of these complicating lymphomas were diffuse large B-cell lymphoma, but rare cases of peripheral T-cell lymphoma were also described. The higher rates of secondary NHL (together with the B-cell origin of the tumor cells) have led to speculation that LPHD is not HD, but a low-grade B-cell NHL. The development of secondary non-Hodgkin's lymphoma is usually associated with multiple relapses.

Prognosis and treatment policy in NLPHD

Several authors have reported a more benign course for LPHD, and Miettinen reported an 80% 10-year survival for untreated NLPHD cases[23, 29-31]. These reports have led some clinicians to reduce the therapy regimes and to apply the "watch-and-wait" strategy for LPHD. The main advantage of the "watch-and-wait" approach would be the avoidance of side effects and late effects of radiotherapy or chemotherapy. Some authors, however, object to a less intensive treatment of LPHD, because there are still no prospective trials to test whether a reduction of therapy is safe for patients with this disease. To answer the question of whether patients with LPHD, at least in stage I, would be left without immediate treatment, a global study is proposed to compare the "watch-and-wait" strategy with current standard protocols. Classical Hodgkin's lymphoma cells do not express CD20, which is a B and T cell surface antigen. The antibody used for monoclonal antibody therapy in non-Hodgkin's lymphomas targets the CD20 antigen, and that is why this therapy is not used for most the classical Hodgkin's lymphoma patients. However, it is now being recognized that there is a subset of Hodgkin's lymphomas that does express CD20, namely NLPHD and therefore may respond to monoclonal anti-CD20 treatment. Other monoclonal antibodies, targeting other aspects of the cancer cells, are under development, and so monoclonal antibody therapy may be available for Hodgkin's lymphoma in the future. Hodgkin's lymphoma has a high cure rate using current therapies[32].

Hodgkin's disease and Epstein Barr Virus (EBV)

The incidence of Hodgkin's disease shows significant geographic variations; it comprises about 20% to 30% of all malignant lymphomas in the United States and Western Europe but a much lower percentage in Japan and other Oriental countries. Approximately 40% to 50% of cases of Hodgkin's disease occurring in Western populations are associated with the Epstein-Barr virus (EBV). In these cases, EBV is found in the neoplastic elements; the HRS cells and Hodgkin's cells. EBV is probably not present in all cases, but neither the positive nor the negative groups have any other viruses[33]. Since peripheral B cells that do not express immunoglobulins die from apoptosis, it has been suggested that the regulation of apoptosis is defective in Hodgkin and Sternberg Reed cells. Several laboratories are currently working intensely to clarify the defective apoptosis pathway in HD[34]. It has been postulated that EBV may play a role in

the pathogenesis of Hodgkin's disease through the activation of anti-apoptotic factors in the premalignant germinal center B-lymphocyte i.e. providing them with immortality and cell proliferation attributes. If proved, the potential contribution of EBV in the pathogenesis of HD may open the way for possible immune therapy through targeting EBV antigens. A recent study from Vietnam showed that EBV is associated with almost all histological subtypes of Hodgkin lymphoma in Vietnamese children[34]. This study demonstrates that in an area with an earlier mean age of onset of EBV infection, nearly all cases of pediatric HD (whether NLP or classical), may be related to EBV infection. Early acquisition of Epstein-Barr virus (EBV) infection is prevalent in developing countries, especially in populations with low socioeconomic status. Among the 46 cases of Vietnamese children with HD, the mean age at presentation was 6.6 years. In situ hybridization for EBV-encoded RNA revealed that the tumor cells were positive in 93.2% of cases, including all 3 cases of nodular lymphocyte predominance HL. This is in marked contrast to the finding in Western countries where NLPHL (and most cases of NSHL) lacks EBV infection in tumor cells. The high incidence of EBV in the Vietnamese cases of HD was correlated with an earlier mean age (5.3 years) of presentation of primary EBV infection (infectious mononucleosis) in this patients' population. This contrasts with an average of 15 to 19 years reported in developed countries. According to a 2003 study[35], if the malignancy develops in young people who have had infectious mononucleosis, it does so on an average, of about four years later. EBV is also well-known for its association not only with HD but with several other cancers, including nasopharyngeal carcinoma, Burkitt lymphoma, and nasal natural killer T-cell lymphoma. Because a substantial proportion of HD in Western countries is EBV-negative, two hypotheses have been proposed to explain the role of EBV in the pathogenesis of HL. One is the "hit-and-run" theory, which postulate that EBV-negative cases may be due to viral fragments integration in the host nucleus, or alternatively because of a defective viral genome. The second is the "two-disease" hypothesis, which proposes that HD seen in the younger group is infectious in nature whereas that in older persons shares similar causes with other lymphomas that are not related to EBV infection. Thus, there exist two pathways for HD tumorigenesis: one is EBV associated and the other is EBV-independent[36].

In summary, it is obliging to depict what Clive R. Taylor wrote down in a recent editorial "Hodgkin's disease is a non-Hodgkin lymphoma, or, to be more accurate, two non-Hodgkin lymphomas, or perhaps more than two. Or, it is a syndrome, the various elements of which are connected by the common occurrence of peculiar dysfunctional giant cells that we know as Reed-Sternberg cells, cells that over the years have come to define a disease, where in fact, more than one disease exists[37].

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