Commentary

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Rearrangement Of Hodgkin Lymphoma Classification For Daily Pathology Practice

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To the Editor:

Hodgkin lymphoma (HL), previously referred to as Hodgkin's disease (HD), had been classified into four types since the Rye classification in 1966 [1]. However, the fifth type was extracted from the lymphocyte predominant HD (LP-HD) as 'LP-HD (nodular paragranuloma)' in the revised European-American classification of lymphoid neoplasia (REAL classification [2] in 1994. The remaining of LP-HD was renamed as lymphocyte-rich classical HD (LRCHD), and was regarded as a provisional entity [2]. In the third edition of the World Health Organization (WHO) classification of neoplasms of the hematopoietic and lymphoid tissues (WHO-3) [3] which was regarded as a minor modification of the REAL classification, the fifth type was renamed as nodular LP-HL (NLPHL), and LRCHD was promoted to a real disease entity as LRCHL. In addition, some HDs classified as 'LP-HD (nodular paragranuloma)' in the REAL classification were reclassified as a nodular variant of LRCHL (nLRCHL) based on the cytologic and immunophenotypic features of the proliferating fraction, resulting in LRCHL to be composed of nodular and diffuse variants, the latter being equivalent to LRCHD in the REAL classification. At that time, an inclusive term, classical HL (CHL), was given to LRCHL and the traditional three types, i.e., nodular sclerosis HL (NS-HL), mixed cellularity HL (MC-HL), and lymphocyte-depleted HL (LD-HD). This classification scheme was succeeded to the 4th and the revised 4th editions of the WHO classification [4,5] (WHO-4 and WHO-4R, respectively) with a change of the term 'classical' to 'classic' in the latter [5]. Although recently published 5th edition of the WHO classification of hematolymphoid tumors (WHO-5) [6] included both NLPHL and CHL in the category of B-cell neoplasia, HL classification scheme itself has not been changed. However, it is now possible to update the scheme of the CHL classification by taking NS-HL on one hand and nLRCHL on the other hand into consideration.

Each of the traditional four types of HD (or four types of CHL since WHO-3) has long been regarded as being in the same dimension, but it has been widely accepted that NS-HL is distinctive among them. This type differs from other CHL types in terms of clinical characteristics (relatively frequent in; adolescents and young adults, female individuals, small families with high standard of living, and mediastinum) and histopathological features (nodular appearance by banded fibrosis and lacunar, but not classic, Hodgkin/Reed-Sternberg cells). Thus, CHL can be separated into either nodular or diffuse at the first step of classification (Table). This separation, however, may not be applicable to nLRCHL, because close relation between this variant and NS-HL or continuity of the two types has been pointed out since the proposal of the REAL classification. This indication, probably being triggered by characterization of nLRCHL as follicular HL [7,8], is supported by a report showing the presence of LRCHL or LP-HL histology in the tissue of NS-HL [9] and this feature is mentioned in both WHO-4[10] and WHO-4R [11]. Furthermore, Kojima and associates reported two patients with follicular HL which later relapsed as NS-HL [12]. Cytologically, lacunar as well as classic Reed-Sternberg cells are known to be present in LRCHL and the former image has been presented [11,13].

There appears to be a consensus regarding the background constituent of nLRCHL that small B lymphocytes with meshwork of follicular dendritic cells predominate over T lymphocytes, whereas eosinophils and plasma cells are virtually absent or few in number even if they are present. In contrast, presence or absence of histiocytes in its background has not been mentioned in many major textbooks, including WHO-4 and WHO-4R. However, in one textbook, the reactive component is documented to consist of some histiocytes with/without microgranuloma formation, in addition to B lymphocytes [14]. Thus, difference in the background features does not appear to rule out the possibility that NS-HL and nLRCHL may constitute a spectrum of a single type. Regarding the site of presentation, the author could not find any report describing frequent mediastinal involvement in LRCHL. It is, however, possible that NS-HD without fibrosis, which was characterized as a cellular phase of NS-HD (NS-CP) in the past [15-17], was actually equivalent to nLRCHL. Although NS-CP would resemble MC-HD, rather than NS-HD, in terms of a positive rate of Epstein-Barr virus in the proliferative fraction and prognosis of the patients [16,17], this possibility has already been indicated by the European Task Force

World Journal of Hematology and Oncology

on Lymphoma [18]. In this context, there is an interesting report showing 20 of 67 patients with pediatric NS-HD to be NS-CP [15]. Furthermore, a given CHL corresponding to NS-CP cannot be assigned to NS-HL in WHO-4R and WHO-5, because the classification defines NS-HL as CHL being associated with fibrosis, and it does not mention NS-CP except for listing it as one of synonyms of NS-HL in WHO-4R [18].

The ideal classification of neoplasms including HL should, in no doubt, be based on genetic abnormalities which are responsible for the neoplastic process. In HL, however, such abnormalities have not been elucidated so far. Tumor microenvironment (TME) is a current topic in the field of tumor biology as exemplified by WHO-5 in which an item for TME was newly establish in each lymphoma section. HL and T follicular helper-cell lymphoma, angioimmunoblastic type (previous angioimmunoblastic T-cell lymphoma) are two representative types which are rich in TME and researches for this theme are vigorously in progress. However, accumulating data of TME at least in CHL are apparently inadequate to construct TME-based classification. In conclusion, classification of HL (or CHL since WHO-3) can be updated as shown in the right column of Table, in which HL/CHL is separated into either nodular or diffuse type. The former is composed of nLRCHL or NS-HL, while the latter of the diffuse variant of LRCHL, MC-HL, or LD-HL. It is hoped that reliability of this proposed update is evaluated by multi-institutional systematic studies.

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