EXPERT'S COMMENT

Although it is not difficult to make a differential pathological diagnosis in typical cases of Hodgkin lymphoma (HL) and peripheral T-cell lymphoma (PTCL), it is sometimes challenging to distinguish HL and PTCL with "Hodgkin and Reed/Sternberg (HRS) like" cells. Recent studies on pathogenesis declared that both have similar conditions of a local immunosuppressive microenvironment associated with T-cell functions.[1,2] HRS cells attenuate the immune function of T-cells through PD-L1 expression in HL.[1] The proliferation of neoplastic T-cells causes a local immunosuppressive condition, which enables the survival of HRS-like cells, in PTCL.[2] Although these diseases are similar in morphology and pathophysiology to a certain extent, the characteristics of neoplastic cells, including the clinical course and effects of chemotherapies, are different.[3,4] Therefore, a precise differential diagnosis is needed. We comprehensively consider the following points in making a differential diagnosis between HL and PTCL:

Morphologically typical HRS cells

HL has morphologically typical HRS cells.[5] Indeed, the presence of typical HRS cells leads to diagnosis of HL, whereas their absence leads to a diagnosis of PTCL. The morphological evaluation of HRS is important and valuable.

Morphological abnormalities of T-cells

Neoplastic T-cells proliferating in PTCL usually have morphological abnormalities.[6] This finding is useful for the differential diagnosis. The morphological evaluation of T-cells should be carefully performed.

Proliferation of blood vessels

PTCL that is difficult to differentiate from HL may originate from follicular helper T-cells (Tfh).[6] PTCL with the Tfh phenotype always exhibits the proliferation of blood vessels, especially high endothelial venules. Although we cannot consider cases without the proliferation of blood vessels as HL, novel proliferation may lead to a diagnosis of PTCL.

CD15 protein expression

Although CD30 expression has a high sensitivity, its specificity for HL is low, whereas CD15 expression is useful for diagnosing HL because of its high specificity.[5] However, the possibility of HL should not be excluded based on the negativity of CD15 because of its low sensitivity.

PD-L1 protein expression

As mentioned above, recent studies revealed that copy number gain and protein expression of PD-L1 leading to immune escape play essential roles in the progression of HL.[7] Therefore, the detection of PD-L1 expression is considered to be significant for a diagnosis of HL. On the other hand, care is required for a diagnosis in cases with EBV-positive HRS cells because the EBV infection itself can induce PD-L1 expression regardless of whether the cells are neoplastic.

The differential points between HL and PTCL with HRS-like cells are above. Even expert hematopathologists may have difficulty in distinguishing them because of composite lymphoma including HL and PTCL. They have different clinical characteristics, which enables a diagnosis. Diagnostic accuracy can also be improved using clinical information. If the differential diagnosis is impossible, it is necessary to discuss the clinical treatment instead of forcing a diagnosis.

REFERENCES

1 Chen BJ, Chapuy B, Ouyang J, *et al*. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clin Cancer Res. 2013; 19 : 3462-3473.
2 Eladl AE, Satou A, Elsayed AA, *et al*. Clinicopathological study of 30 cases of peripheral T-cell lymphoma with Hodgkin and Reed-Sternberg-like B-cells from Japan. Am J Surg Pathol. 2017; 41 : 506-516.
3 Momotow J, Borchmann S, Eichenauer DA, Engert A, Sasse S. Hodgkin lymphoma-review on pathogenesis, diagnosis, current and future treatment approaches for adult patients. J Clin Med. 2021; 10 : 1125.
4 Iżykowska K, Rassek K, Korsak D, Przybylski GK. Novel targeted therapies of T cell lymphomas. J Hematol Oncol. 2020; 13 : 176.
5 Stein H, Pileri SA, Weiss LM, *et al*. Hodgkin lymphomas. In: Swerdlow SH, Campo E, Harris NL, *et al*. (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed, Lyon, IARC. 2017; pp. 423-441.
6 Dogan A, Gaulard P, Jaffe ES, *et al*. Angioimmunoblastic T-cell lymphoma and other nodal lymphomas of T follicular helper cell origin. In: Swerdlow SH, Campo E, Harris NL, *et al*. (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed, Lyon, IARC. 2017; pp. 407-412.
7 Sakakibara A, Kohno K, Eladl AE, *et al*. Immunohistochemical assessment of the diagnostic utility of PD-L1: a preliminary analysis of anti-PD-L1 antibody (SP142) for lymphoproliferative diseases with tumour and non-malignant Hodgkin-Reed-Sternberg (HRS)-like cells. Histopathology. 2018; 72 : 1156-1163.

Hiroaki Miyoshi
Department of Pathology, Kurume University School of Medicine
E-mail: miyoshi_hiroaki@med.kurume-u.ac.jp