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Brief Note

Re-evaluation of Hodgkin's Disease: Report of Twelve Cases with Strict Morphological Criteria and Immunohistochemical Aids

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Hodgkin's disease remains an enigma. As the eponymic designation, Hodgkin's disease, indicates, in the past the malignant nature of the disease and the identification of malignant cells were uncertain. Although the malignant neoplastic nature of Hodgkin's disease has been demonstrated, the origin of malignant cells is still uncertain. The diagnosis of Hodgkin's disease requires the presence of Reed-Sternberg cells and Reed-Sternberg cell variants in the polymorphic cellular background.[1] But, while Reed-Sternberg cells are necessary for the diagnosis, their presence alone is not sufficient to make that diagnosis. Cells individually indistinguishable from Reed-Sternberg cells may be encountered in other malignant tumors and even exuberant benign proliferative conditions.[2] In addition, Hodgkin's disease is characterized by a broad range of morphologic expressions. With a better understanding of malignant lymphomas, it has been shown that some T-cell lymphomas may quite closely resemble the histology of Hodgkin's disease and may cause some diagnostic difficulties.[3,4] In fact, Mikata *et al.* pointed out that cases diagnosed as Hodgkin's disease in Japan in the past actually included cases of T-cell lymphomas.[3] In the meantime, disease entities such as IBL, AILD and IBL-like T-cell lymphoma have been separated from cases designated as Hodgking-like lesions or Hodgkinoid reticulosis.[5—8] Recent advances in immunohistochemistry have provided adjuncts to distinguish Hodgkin's disease from non-Hodgkin's lymphoma. One of these is Leu-M1.[9—12] With advances in our understanding of Hodgkin's, non-Hodgkin's lymphomas and other simulants, therefore, we decided to re-evaluate those cases diagnosed as Hodgkin's disease or Hodgkinoid reticulosis in our institute. We first re-examined hematoxylin-eosin-stained sections and the immunohistochemical results were taken into consideration for the final diagnosis.

For this study, twelve cases were selected from the surgical pathology file of the Kawasaki Medical School Hospital. Nine of these had been diagnosed as Hodgkin's disease, while the other three were considered to be Hodgkinoid reticulosis. Tissues had been fixed in buffered formalin and/or B5 fixative, routinely processed and embedded in paraffin. Original sections, stained with hematoxylin-eosin, were re-diagnosed without any additional information by two of the authors, using standard histopathologic criteria.[1,13] For immunohistochemical studies with antibodies of LCA (Dakopatts, Copenhagen, Denmark), Leu-M1 (Becton Dickinson, California, USA), MT-1, and MB-1 (Bio-Science,

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Emmenbrucke, Switzerland), the ABC (Avidin-biotin complex) immunoperoxidase technique was used. The ABC kit was purchased from Vector (Burlingame, USA).

Tables 1 and 2 summarize our results. Three of the nine cases originally diagnosed as Hodgkin's disease and two out of the three cases originally called Hodgkinoid reticulosis were re-diagnosed as non-Hodgkin's lymphomas. All of them showed polymorphic cellular infiltration but typical Reed-Sternberg cells were absent. Case 11 was consistent with so-called IBL-like T-cell lymphoma. Among the original group of Hodgkin's disease, six cases had been correctly diagnosed, but two were changed in subtype from mixed cellularity to nodular sclerosis. Immunohistochemically, all of the Hodgkin's disease cases showed Leu-M1 positivity in Reed-Sternberg cells and their variants. In four cases, most of the Reed-Sternberg cells and variants were strongly positive, but in three cases just a few were weakly positive. Usually B5-fixed materials gave more strong immunoreactivity than formalin-fixed ones. The positivity may be

TABLE 1. Histological and immunohistochemical study of 12 cases

case No.	histological diagnosis before review	histological diagnosis after review	cell origin of lymphoma	immunoreactivity of RS-cell or RS-like cell			
				LCA	Leu-M1	MT-1	MB-1
1	HD, LP	NHL, diffuse large	T-cell	−	−	−	+
2	HD, NS	HD, NS		−	+	−	−
3	HD, NS	HD, NS		−	+	−	−
4	HD, MC	HD, NS		−	+	−	−
5	HD, MC	HD, NS		−	+	−	−
6	HD, MC	HD, MC		−	+	−	−
7	HD, MC	NHL, diffuse large	T-cell	−	−	−	−
8	HD, LD	HD, LD		−	+	−	−
9	HD, LD	NHL, diffuse large	T-cell	−	−	−	−
10	Hodgkinoid	HD, UC		−	+	−	−
11	HD, UC	NHL, diffuse large	T-cell	−	−	+	−
12	Hodgkinoid	NHL, diffuse mixed	B-cell	−	−	−	+

HD : Hodgkin's disease
LP : lymphocyte predominance
MC : mixed cellularity
RS : Reed-Sternberg
NHL : non-Hodgkin's lymphoma
NS : nodular sclerosis
LD : lymphocyte depletion
UC : unclassified

TABLE 2. Immunoreactivity of Reed-Sternberg cells for Leu-M1 in Hodgkin's disease

case No.	histological type	fixation	cell membrane	granular cytoplasmic	globular cytoplasmic
2	NS	formalin	+++	++	+
3	NS	B5	++	+/−	+++
4	NS	formalin	+/−	−	−
5	NS	B5	+++	++	+++
6	MC	formalin/B5	+	−	+
8	LD	formalin	−	−	+/−
10	UC	formalin	−	−	+/−

NS : nodular sclerosis
LD : lymphocyte depletion
MC : mixed cellularity
UC : unclassified

divided into three staining patterns; namely, cell membranous, diffuse cytoplasmic granular, and juxtanuclear cytoplasmic globular. Cells with intense immunoreactivity exhibited all three patterns, and weakly positive cells showed one of them.

That five of the twelve cases diagnosed as Hodgkin's disease or Hodgkinoid reticulosis were in fact non-Hodgkin's lymphomas was surprising. Four of them were T-cell lymphomas. We consider that polymorphous cellular proliferation and the presence of Reed-Sternberg-like cells in lymphomatous tissue might have led to the erroneous diagnosis of Hodgkin's disease. The idea that lymphomas are composed of a monotonous proliferation of atypical cells now seems dated, although it is still applicable to the majority of cases. Four out of the five cases rediagnosed as non-Hodgkin's lymphomas were diagnosed several years before new concepts were entertained. We think that the presence of typical Reed-Sternberg cells and normal small lymphocytes in a background is the prerequisite for a diagnosis of Hodgkin's disease.

Leu-M1 is a monoclonal antibody raised against a human histiocytic cell line. Recently, several reports clearly demonstrated that Leu-M1 may be a useful marker for the Reed-Sternberg cells and their mononuclear variants; Hodgkin cells.[9—12] In our study, all cases of Hodgkin's disease were Leu-M1 positive for Reed-Sternberg celle, while, non-Hodgkin's lymphomas were completely negative. Leu-M1, however, does not seem to be specific for Reed-Sternberg cells or Hodgkin's cells. Some non-Hodgkin's lymphoma, anaplastic myeloma and non-hematopoietic neoplasm cases are known to have cells which are positive for Leu-M1.[14,15] Sheibani *et al.* found Leu-M1 positivity in 12 of 18 peripheral T-cell lymphomas and concluded that Leu-M1 positivity alone was of no value in supporting as diagnosis of Hodgkin's disease.[14] Hodgkin's disease should be diagnosed on a histological basis, and immunoreactivity with Leu-M1 and/or other monoclonal antibodies should be taken as an adjunct for the diagnosis. On the other hand, immunohistochemical studies may be useful for demonstration of the nature of proliferating cells. Oka *et al.* suspected that Reed-Sternberg cells may be derived from monocyte/macrophage lineage, which is expressed as the pan-T antigen$^-$/HLA-DR$^+$/Leu3a$^+$/OKT6$^-$ phenotype.[16] Unfortunately, however, even with technological advances, it still remains unclear what the origin of Reed-Sternberg cells really is.

Hodgkin's disease may constitute a heterogenous group of diseases. In the near future, some of these diseases may be separated from so-called Hodgkin's disease as newly defined entities.

In conclusion, the cases of Hodgkin's disease diagnosed previously in our institute contained cases of non-Hodgkin's lymphomas. We consider that new concepts regarding Hodgkin's disease and non-Hodgkin's lymphoma may make it possible to make distinction between these cases. Immunohistochemical studies may help or facilitate the diagnosis of Hodgkin's disease, but they are not perfect and, therefore, such a diagnosis should be based on strict histologic criteria.

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REFERENCES

1) Lukes, R.J. and Butler, J.J.: The pathology and nomenclature of Hodgkin's disease. Cancer Res. **26** : 1063-1081, 1966
2) Mikata, A.: Histopathological diagnosis of Hodgkin's disease. Pathol. Clin. Med. **1** : 372-381, 1983 (in Japanese)
3) Mikata, A., Suzuki, S., Watanabe, S., Nemoto, K. and Sato, E.: Histopathological study of Hodgkin's disease, with special reference to histological differentiation from T-cell lymphomas. Recent Adv. RES Res. **22** : 130-136, 1982
4) Sato, E.: Hodgkin's disease and T cell malignancy. Pathol. Clin. Med. **1** : 382-392, 1983 (in Japanese)
5) Lukes, R.J. and Tindle, B.H.: Immunoblastic lymphadenopathy. A hyperimmune entity resembling Hodgkin's disease. N. Engl. J. Med. **292** : 1-8, 1975
6) Frizzera, G., Moran, E.M. and Rappaport, H.: Angioimmunoblastic lymphadenopathy with dysproteinemia. Lancet **1** : 1070-1073, 1974
7) Shimoyama, M., Minato, K., Watanabe, S., Saito, H., Takenaka, T., Nagatani, T. and Naruto, N.: Immunoblastic lymphadenopathy (IBL)-like T-cell lymphoma. Jpn. J. Clin. Oncol. **9** : 347-356, 1979
8) Waldron, J.M., Leech, J.H., Glick, A.D., Flexner, J.M. and Collins, R.D.: Malignant lymphoma of peripheral T-lymphocyte origin. Cancer **40** : 1604-1617, 1977
9) Swerdlow, S.H. and Wright, S.A.: The spectrum of Leu-M1 staging in lymphoid and hematopoietic proliferations. Am. J. Clin. Pathol. **85** : 283-288, 1986
10) Hyder, D.M. and Schnitzer, B.: Utility of Leu M1 monoclonal antibody in the differential diagnosis of Hodgkin's disease. Arch. Pathol. Lab. Med. **110** : 416-419, 1986
11) Strauchen, J.A. and Dimitriu-Bona, A.: Immunopathology of Hodgkin's disease, characterization of Reed-Sternberg cells with monoclonal antibodies. Am. J. Pathol. **123** : 293-300, 1986
12) Dorfman, R.F., Gatter, K.C., Pulford, K.A.F. and Mason, D.Y.: An evaluation of the utility of anti-granulocyte and anti-leukocyte monoclonal anti-bodies in the diagnosis of Hodgkin's disease. Am. J. Pathol. **123** : 508-519, 1986
13) The Non-Hodgkin's Lymphoma Pathologic Classification Project: National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphoma: Summary and description of a working formulation for a clinical usage. Cancer **49** : 2112-2135, 1982
14) Sheibani, K., Battifora, H., Burke, J.S. and Rappaport, H.: Leu-M1 antigen in human neoplasms, an immunohistologic study of 400 cases. Am. J. Surg. Pathol. **10** : 227-236, 1986
15) Pinkus, G.S. and Said, J.W.: Leu-M1 immunoreactivity in nonhematopoietic neoplasms and myeloproliferative disorders, an immunoperoxidase study of paraffin sections. Am. J. Clin. Pathol. **85** : 278-282, 1986
16) Oka, K., Mori, N. and Kojima, M.: Anti-Leu-3a antibody reactivity with Reed-Sternberg cells of Hodgkin's disease. Arch. Pathol. Lab. Med. **112** : 139-142, 1988