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Case Report

Sternberg-Reed Cells With Intracytoplasmic Lymphocytes

Phagocytosis or Emperipolesis?

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Summary. Phagocytosis by Sternberg-Reed cells is a rare phenomenon. A case of nodular sclerosis type of Hodgkin's disease with large numbers of apparently vital lymphocytes in the cytoplasm of the Sternberg-Reed cells is described in this paper. The question whether this feature is the result of phagocytosis or emperipolesis is discussed.

Key words: Sternberg-Reed cells – Phagocytosis – Emperipolesis – Lysozyme.

Introduction

Phagocytosis by Sternberg-Reed cells which is evident on light microscopy has been reported to be a very rare phenomenon (Jackson and Parker, 1947). In electron microscopic studies, phagocytosis of lymphocytes was observed by Bernhard and Leplus (1964). Fresh suspensions of lymph nodes from Hodgkin's disease do not reveal phagocytosis of India ink or immunoglobulin-coated sheep erythrocytes; nor is phagocytosis of lymphocytes found, although these cells usually show strong adherence to Sternberg-Reed cells. In tissue culture studies of spleen cells from Hodgkin's disease, Long et al. (1977) reported the absence of phagocytosis in histiocytic cell lines, whereas Kaplan and Gartner (1977) found marked phagocytosis of India ink and immunoglobulin-coated sheep erythrocytes.

Another mechanism that may be responsible for the presence of lymphocytes in the cytoplasm of other cells was described by Humble et al. (1956) as "emperipolesis". Emperipolesis is defined as the migration of lymphocytes over the surface and into the cytoplasm of other cells. Such migration of lymphocytes has been found in tumor cells (Humble et al., 1956) and macrophages (Berman,

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1966). An important feature of emperipolesis is the absence of apparent damage to either cell.

This is a report on a case of Hodgkin's disease with large numbers of lymphocytes in the cytoplasm of a number of Sternberg-Reed cells.

Case Report

A 61-year-old man was admitted because of lymphadenopathy in several regions. Apart from alcohol associated pain, no general symptoms were found at the time of biopsy. An enlarged left supraclavicular lymph node, whose largest diameter was 2 cm, was removed for histological diagnosis.

Materials and Methods

The lymph node was routinely fixed in formalin and embedded in paraffin. Sections were stained with Giemsa, hematoxylin and eosin, periodic acid Schiff (PAS), and Gomori reticulin stain.

Special sections were stained with the peroxidase-antiperoxidase technique as described by Sternberger (1974) and used for the demonstration of immunoglobulins in tissue sections by Taylor (1974). The sections were incubated with rabbit antisera against kappa, lambda, gamma, alpha, and mu chains and lysozyme, followed by incubation with a sheep anti-rabbit antiserum and with a rabbit peroxidase-antiperoxidase complex. The peroxidase was subsequently stained with diaminobenzidine and H_2O_2 as described by Karnovsky (1966). Further details of the procedure are given by Papadimitriou et al. (1978).

Results

Light Microscopy

The normal architecture of the node was effaced and replaced by a nodular proliferation of predominantly small lymphocytes. In and between the nodules there were typical and so-called lacunar Sternberg-Reed cells (Fig. 1). The capsule was expanded, and a few sclerosing bands could be found. Many segmented leukocytes and some eosinophil leukocytes were seen in the internodular area. Because of the presence of lacunar cells and a few sclerosing bands, the node was diagnosed as Hodgkin's disease of the nodular sclerosis type.

As a special feature, intracytoplasmic lymphocytes were found in a number of Sternberg-Reed cells (Fig. 2). These lymphocytes often seemed to lie together in a large vacuole. Up to eight lymphocytes were seen in the Sternberg-Reed cells. Lymphocytes were even found in the cytoplasm of a very large atypical mitosis, apparently of a Sternberg-Reed cell. Both the intracytoplasmic lymphocytes and the Sternberg-Reed cells appeared to be vital by morphologic criteria. No other types of cells were found in the cytoplasm of Sternberg-Reed cells.

Immunohistology

Although many histiocytic reticulum cells and segmented and eosinophil leukocytes stained positively for lysozyme, no staining was found in the Sternberg-

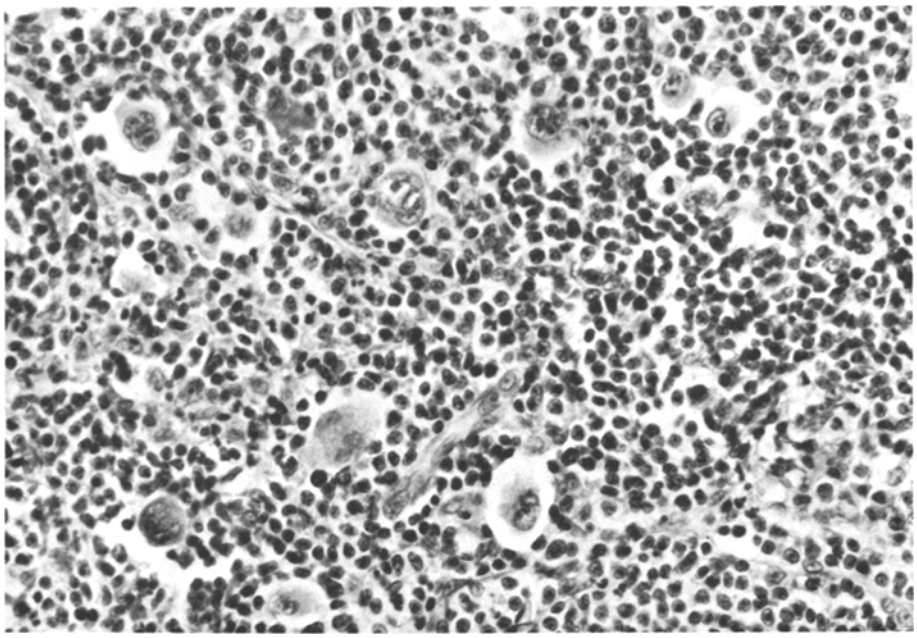

Fig. 1. Nodular sclerosis type of Hodgkin's disease with a large number of lacunar type Sternberg-Reed cells. Hematoxylin-eosin, ×350

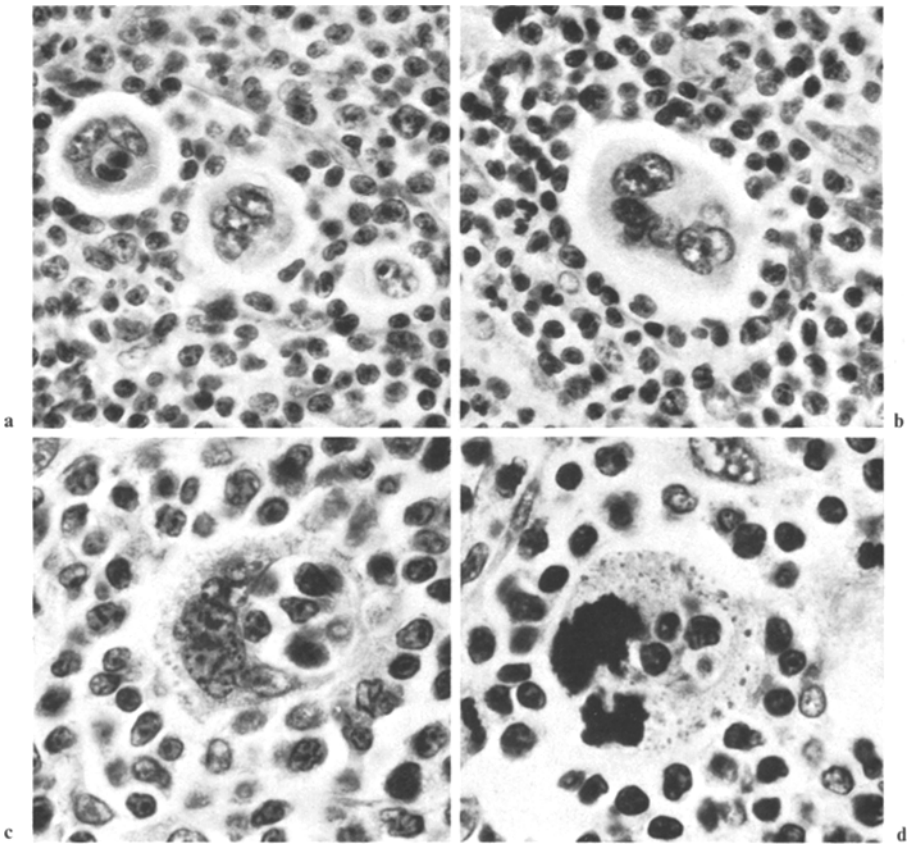

Fig. 2. a Three lacunar Sternberg-Reed cells. One contains two lymphocytes. Hematoxylin-eosin, ×560. **b** Large lacunar Sternberg-Reed cell with no intracytoplasmic lymphocytes. Hematoxylin-eosin, ×560. **c** Sternberg-Reed cell with many intracytoplasmic lymphocytes. Hematoxylin-eosin, ×882. **d** Mitosis, apparently of a Sternberg-Reed cell with intracytoplasmic lymphocytes. Hematoxylin-eosin, ×882

Reed cells with or without intracytoplasmic lymphocytes. A weak diffuse staining for IgG and for kappa and lambda chains was present in some of the Sternberg-Reed cells, both with and without intracytoplasmic lymphocytes.

Discussion

The presence of lymphocytes in the cytoplasm of Sternberg-Reed cells is a rare phenomenon. In the previous literature, it has been considered to represent phagocytosis and if this were true, it would be a strong argument in favor of the histiocytic nature of Sternberg-Reed cells. Emperipolesis (Humble et al., 1956) might also be responsible, however, for the presence of lymphocytes in the cytoplasm of other cells. A finding that supported emperipolesis was the presence of apparently vital lymphocytes lying together in large vacuoles in the Sternberg-Reed cells. Although the lymphocytes in starry-sky macrophages in germinal centers are usually pyknotic, obviously vital or even mitotic tumor cells can be seen in the macrophages in Burkitt's lymphoma (Kaiserling, 1977). In lymphadenitis with massive hemophagocytic sinus histiocytosis, vital and nonvital lymphocytes and red blood cells, segmented leukocytes, and plasma cells are phagocytosed (Lennert, 1971). Since phagocytosis of lymphocytes was not seen in the histiocytic reticulum cells in our case, it is unlikely that an abnormality in the lymphocyte cell membrane was the reason for phagocytosis. Another possibility is that the Sternberg-Reed cells were in a particular functional state in which phagocytic activity was greatly increased. It is understandable that only lymphocytes would be phagocytosed in such a state, since lymphocytes are the predominant cells in the lesion.

The absence of lysozyme from the Sternberg-Reed cells in this case is another argument against phagocytosis, because lysozyme can nearly always be demonstrated in other phagocytic cells. Although Long et al. (1977) and Kaplan and Gartner (1977) found lysozyme in the culture fluids of tissue cultures from Hodgkin's disease, lysozyme usually cannot be demonstrated in Sternberg-Reed cells in tissue sections (Taylor, 1976; Papadimitriou et al., 1978). Papadimitriou et al. (1978), however, found one case of the nodular sclerosis type of Hodgkin's disease with intracytoplasmic staining for lysozyme.

Emperipolesis is the result of an active adherence of lymphocytes to tumor cells or macrophages with a subsequent inclusion in vacuoles inside the cytoplasm of these cells (Humble et al., 1956). During the past few years, strong adherence of lymphocytes, sometimes specified as T lymphocytes, to Sternberg-Reed cells has been described (Pretlow et al., 1973; Braylan et al., 1974; Kadin et al., 1974; Stuart et al., 1977). This indicates the possibility that the inclusion of lymphocytes in Sternberg-Reed cells is the result of emperipolesis. Arguments in favor of this mechanism are the presence of apparently vital lymphocytes and absence of other cells in Sternberg-Reed cells.

The data on the intracytoplasmic lymphocytes in the patient presented here neither support nor refute a histiocytic origin of Sternberg-Reed cells.

References

Berman, L.: Lymphocytes and macrophages in vitro. Their activities in relation to functions of small lymphocytes. Lab. Invest. **15**, 1084–1099 (1966)

Bernhard, W., Leplus, R.: Structure fine du ganglion humain normal et malin. Oxford: Pergamon Press 1964

Braylan, R.C., Jaffe, E.S., Berard, C.W.: Surface characteristics of Hodgkin's lymphoma cells. Lancet **1974 II**, 1328–1329

Graham, R.C., Jr., Karnovsky, M.J.: The early stages of absorption of injected horseradish peroxidase in the proximal tubules of mouse kidney: Ultrastructural cytochemistry by a new technique. J. Histochem. Cytochem. **14**, 291–302 (1966)

Humble, J.G., Jayne, W.H.W., Pulvertaft, R.J.V.: Biological interaction between lymphocytes and other cells. Brit. J. Haemat. **2**, 283–294 (1956)

Jackson, H., Jr., Parker, F., Jr.: Hodgkin's disease and allied disorders. New York: Oxford University Press 1947

Kadin, M.E., Newcom, S.R., Gold, S.B., Stites, D.P.: Origin of Hodgkin's cell. Lancet **1974 II**, 167–168

Kaiserling, E.: Non-Hodgkin-Lymphome. Ultrastruktur und Cytogenese. Veröff. Path., Heft 105. Stuttgart: G. Fischer 1977

Kaplan, H.S., Gartner, S.: "Sternberg-Reed" giant cells of Hodgkin's disease: Cultivation in vitro, heterotransplantation, and characterization as neoplastic macrophages. Int. J. Cancer **19**, 511–525 (1977)

Long, J.C., Zamecnik, P.C., Aisenberg, A.C., Atkins, L.: Tissue culture studies in Hodgkin's disease. Morphologic, cytogenetic, cell surface and enzymatic properties of cultures derived from splenic tumors. J. exp. Med. **145**, 1484–1500 (1977)

Papadimitriou, C.S., Stein, H., Lennert, K.: The complexity of immunohistochemical staining pattern of Hodgkin and Sternberg-Reed cells – Demonstration of immunoglobulin, albumin, $alpha_1$-antichymotrypsin and lysozyme. Int. J. Cancer **21**, 531–541 (1978)

Pretlow, T.G., II, Luberoff, D.E., Hamilton, L.J., Weinberger, P.C., Maddox, W.A., Durant, J.R.: Pathogenesis of Hodgkin's disease: Separation and culture of different kinds of cells from Hodgkin's disease in a sterile isokinetic gradient of Ficoll in tissue culture medium. Cancer **31**, 1120–1126 (1973)

Sternberger, L.A.: The unlabeled antibody enzyme method. In: Immunochemistry, pp. 129-171. Englewood Cliffs, New Jersey: Prentice-Hall 1974

Stuart, A.E., Williams, A.R.W., Habeshaw, J.A.: Rosetting and other reactions of the Reed-Sternberg cell. J. Pathol. **122**, 81–90 (1977)

Taylor, C.R.: The nature of Reed-Sternberg cells and other malignant "reticulum" cells. Lancet **1974 II**, 802–807

Taylor, C.R.: An immunohistological study of follicular lymphoma, reticulum cell sarcoma and Hodgkin's disease. Europ. J. Cancer **12**, 61–75 (1976)

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