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Immunohistological analysis of Rosai-Dorfman histiocytosis

A disease of S-100 + CD1-histiocytes

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Summary. Five cases of Rosai-Dorfman histiocytosis (RDH) (also called Sinus Histiocytosis with Massive Lymphoadenopathy; SHML) have been studied by immunohistochemical methods with heteroantisera and monoclonal antibodies. One case was also studied by Southern blot hybridization analysis with DNA probes specific for T cell receptor beta chain and immunoglobulin heavy chain. Immunophenotyping of large histiocytes, characteristic of RDH, evidenced the presence of S-100 protein and the absence of CD1 and other markers usually found in histiocytes and macrophages. DNA hybridization study showed the absence of clonal T or B lymphoid populations.

Key words: Rosai-Dorfman histiocytosis – Lymph node – Immunohistochemistry

Introduction

Histiocytic proliferations constitute a heterogeneous group of benign and malignant diseases which express a diversity of clinical, histopathological, histochemical and immunophenotypic characteristics (Watanabe et al. 1983; Turner et al. 1984).

Rosai-Dorfman histiocytosis (RDH), formerly called sinus histiocytosis with massive lymphadenopathy (SHML), is a distinctive clinicopathological entity among histiocytic proliferations (Rosai and Dorfman 1969; Rosai and Dorfman 1972). This disease, which most commonly occurs in children and in adolescents, is characterized by painless, massive peripheral lymphadenopathy which is caused by the proliferation of lympho-phagocytic histiocytes which distent the lymph node sinuses. The patients exhibit an indolent, protracted clinical course with a benign outcome, except in those instances where the disease involves extranodal sites such as the central nervous system, in which case the patients may have a fatal outcome (Foucar et al. 1984).

The nature of the proliferating histiocytes in RDH has remained an enigma since they lack well established macrophage markers (Isaacson et al. 1981) such as alpha l-antichymotrypsin (@l-ACT) and lysozyme (LSZ) (Ngendhayo et al. 1983). Recently Aoyama et al. (1984) and Chan et al. (1985) reported the presence of S-100 protein in RDH histiocytes.

The aetiology and pathogenesis of RDH is also obscure; suggestions that the disease is caused by various infectious agents have remained debatable (Rosai and Dorfman 1972; Lampert and Lennert 1976).

Recently, somatic cell hybridization techniques have been used to prepare monoclonal antibodies which detect monocyte-associated cell surface antigens (Breard et al. 1980; Talle et al. 1983; Hanyan et al. 1982). These antibodies are useful in delineating distinct monocyte subpopulations and probing stages of monocyte differentiation and/or activation. Moreover, recent studies have demonstrated that certain malignant neoplasms, once believed to originate from histiocytic precursors, actually are clonal B or T cell lymphocyte proliferations since they express rearrangements of the genes which encode the antigen recognition molecules specific to B and T cells, immunoglobulin and T cell receptor(s), respectively (Isaacson et al. 1985; Weiss et al. 1985).

In this study we performed a thorough immunophenotypical analysis with antibodies recognizing monocyte and macrophage related antigens in

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5 cases of RDH involving lymph nodes. In addition, Southern blot hybridization analysis was performed in a single case to demonstrate that this disease does not represent a monoclonal B or T lymphocyte proliferation.

We correlated the results of these studies with those of other histioproliferative disorders and discuss the findings in relationship to normal monocyte/histiocyte differentiation.

Materials and methods

Patients. Lymph node tissue obtained from five patients with the histopathological diagnosis of Rosai-Dorfman histiocytosis was available from the files of Departments' of Pathology of Verona (Case No 1, No 2, No 3) and New York University (Case No 4, No 5) for immunohistological studies. All of the patients had clinical findings which were compatible with the diagnosis of RDH. The patients were either children or young adults who presented with massive peripheral, often cervical, lymphadenopathy and lymphocytosis, leukocytosis and/or hypergammaglobulinaemia (Table 1).

Samples of lymph node were obtained from each of the five patients at the time of biopsy. In each instance, representative portions were fixed in 10% buffered formalin and embedded in paraffin. Deparaffinized sections were stained with haematoxylin and eosin, periodic acid-Schiff, Ziehl-Nielsen, Grocott and Giemsa-stains for light microscopic histopathological examination. Additional deparaffinized sections were left unstained for immunohistochemical analysis. Representative unfixed portions of the lymph node biopsies from three of the five patients were snap frozen in a mixture of isopentane and dry ice and cryopreserved for histochemical, immunohistochemical and DNA analysis. Cryostat tissue sections, 4–6 microns thick, were prepared from these frozen tissue blocks and fixed in a 1:1 mixture of chloroform and acetone for 7 min at 4° C and air-dried for immunohistochemical staining.

Enzyme-histochemistry. The biopsy specimens were examined for the presence of alkaline phosphatase, acid phosphatase, non-specific esterase and dipeptidyl-amino peptidase according to methodologies which have been previously described in detail elsewhere (Chilosi et al. 1981a).

Table 1

Patient	Age	Sex	Site	Laboratory
1	12	F	Multiple (inguinal latero-cervical)	Lymphocytosis
2	3	M	Latero-c (bilateral)	Leukocytosis
3	44	F	Multiple left axillary and latero-cervical	Leukocytosis
4	44	M	Multiple (inguinal, axillary latero-cer)	Leukocytosis Hypergammaglobuminaemia
5	32	M	Latero-cervical	Leukocytosis

Heteroantisera and monoclonal antibodies. Lysozyme, alpha l-antichimostrypsin, and S-100 protein were demonstrated by rabbit heteroantisera (DAKO, Denmark). Monoclonal antibodies directed against HLA-DR (Ia) antigens Leu1, Leu M1, and rabbit antihuman mu heavy chains, and kappa and lambda light chains were obtained from Becton-Dickinson (Mountain View, CA, USA). Monoclonal antibodies OKM1, OKM5, OKT3, OKT6, and OKT8 were obtained from Ortho Pharmaceutical Corp. (Raritan, NJ, USA). Monoclonal antibody BA-1, obtained from Hybritech (San Diego, CA, USA), detects a B cell associated antigen (Abramson et al. 1981). OKT1 reacts with normal and neoplastic T cells, the neoplastic B cells from most cases of B-chronic lymphocytic leukaemia and from some cases of malignant B lymphoma (Knowles et al. 1983). OKT3, OKT4 and OKT8 detect T cell associated differentiation antigens which are expressed on all mature T cells, helper T cells, and suppressor/cytotoxic T cells, respectively (Reinherz and Schlossman 1980; Knowles and Halper 1982). OKT6 reacts with immature cortical thymocytes and Langerhans cells (Reinherz and Schlossman 1980; Murphy et al. 1981). OKM1 and OKM5 are monocyte associated differentiation antigens with are preferentially expressed during certain stages of monocyte differentation and on certain functionally distinct subsets (Breard et al. 1980; Talle et al. 1983; Shen et al. 1983). Leu M1 is a myelo-monocyte associated antigen also expressed by Reed-Sternberg cells and, occasionally, by T lymphocytes (Hanyan et al. 1982; Hsu et al. 1985; Wieczorek et al. 1986b).

Immunohistochemistry. The presence of lysozyme, alpha l-antichymotrypsin, and S-100 protein was determined on deparaffinized sections by the peroxidase-antiperoxidase (PAP) technique (Sternberger et al. 1970). Briefly, deparaffinized tissue sections were soaked in methanol containing 0.3% hydrogen peroxide to prevent non-specific staining due to endogenous peroxidase. Following a 20 min incubation with 1:10 diluted normal swine serum (DAKO, Denmark) the sections were placed in a moist chamber and covered with the appropriately-diluted antisera (LSZ, 1:200, α1-ACT 1:200, S-100, 1:600) for 60 min. Sections were then washed three times in phosphate-buffered saline (PBS), incubated in a moist chamber for 30 min with anti-rabbit IgG swine serum (1:50, DAKO, Denmark), and then with PAP solution (1:200, DAKO, Denmark) for 30 min. The identical procedure was used to detect IgM with rabbit anti-human IgM on cryostat tissue sections. The final reaction product was produced by incubation with 3-3′-diaminobenzidine (Sigma Chemical Co., St. Louis, MO, USA), and H202 in tris buffer as previously described (Chilosi et al. 1981b). The specificity of reaction was verified by replacing the primary antibody with PBS and with normal rabbit serum of comparable dilution.

Immunohistological analysis with monoclonal antibodies was performed on cryostat sections using the avidin-biotin complex immunoperoxidase technique (Hsu et al. 1981). Briefly, cryostat sections, prepared as described above, were incubated serially for 30-min periods with 2% horse serum, 50–100 µl of the appropriately diluted monoclonal antibody, biotin coupled affinity purified horse anti-mouse IgG, and avidin-peroxidase complexes (Vector Laboratories Burlingame, CA, USA). The final peroxidase reaction was produced as described above.

DNA analysis. DNA was extracted by standard techniques, digested with appropriate restriction endonuclease, and analyzed for immunoglobulin (Ig) and T cell receptor beta chain (Tβ) gene rearrangements by Southern blot hybridization using various DNA clones representative of different portions of immunoglobulin and Tβ gene loci as probes (Southern 1975). The Tβ gene locus was analyzed by hybridization of EcoR1, Bam H1 and Hind III digested DNA to a Tβ gene probe (Courtesy,

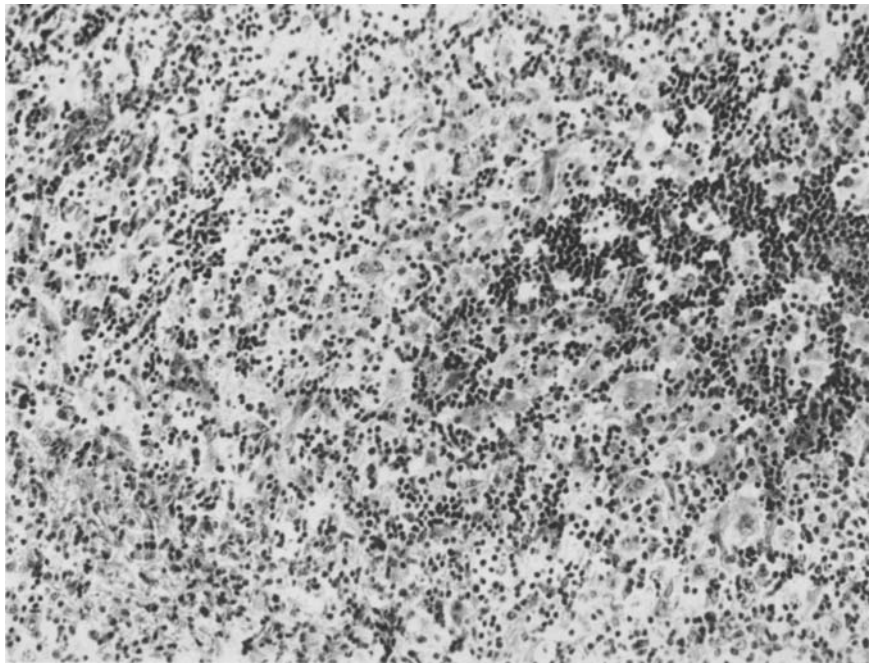

Fig. 1. Rosai-Dorfman histiocytosis in lymph node. Sinuses are dilated by large histiocytes with abundant pale cytoplasm and round nucleus with small nucleolus. H&E ×100

Tak Mak, Ontario Cancer Institute, USA) that hybridizes to both alleles (CB 1 and CB 2) of the constant region (Yanagi et al. 1984; Flug et al. 1985). The immunoglobulin heavy chain (IgH) gene locus and the Kappa (*K*) and Lambda (*Λ*) light chain gene loci were studied by hybridization of Hind III and EcoR 1 digested DNA to a J region (JH) specific probe, by hybridization of Bam H1 digested DNA to a constant region Kappa specific (Ck) probe and by hybridization of EcoR1 and Hind III digested DNA to a constant region lambda specific (C*Λ*) probe, respectively (Courtesy, Stanley Korsmeyer, National Institutes of Health, USA) (Ravetch et al. 1979). DNA fragments were 32P-labelled by nick translation for use as probes. Non-lymphoid control DNA was always analyzed simultaneously in order to identify the germline position. The sensitivity of this techique is very high and allows the detection of minor clonal population within a mixed cell population. Zehnbauer et al. (1986) demonstrated that it is possible to detect clonal rearrangement in bone marrow involved by ALL with less than one leukaemic cell in 500 normal cells.

Results

Light microscopy

The lymph node biopsies obtained from all patients exhibited histopathological features characteristic of sinus histiocytosis with massive lymphadenopathy as originally described by Rosai and Dorfman (1969, 1972). The lymph nodes displayed capsular thickening due to dense pericapsular fibrosis. The internal lymph node architecture was distorted due to marked sinusoidal dilatation by large histiocyes which contained abundant acidophilic, granular and occasionally foamy cytoplasm and large round vesicular nuclei with small, centrally prominent nucleoli (Fig. 1). The histiocytes often contained variable and sometimes large numbers of lymphocytes, plasma cells or even granulocytes within their cytoplasm (Fig. 2a). These cells did not show evidence of apoptosis.

Mitotic figures were virtually absent. The lymphoid tissue which was compressed between the markedly dilated sinuses contained abundant lymphocytes and plasma cells and rare germinal centers. Occasional necrotic foci surrounded by granulocytes were present in the lymph node biopsy from patient No 4. Each one of three separate lymph node biopsies, obtained at yearly intervals from patient No 4, showed identical histopathologic features except for an increased number of necrotic foci in the latest biopsy. Numerous special stains for various micro-organisms were performed in each of the lymph node biopsies obtained from each of the 5 patients and were consistently negative.

Histochemistry

The large lymphophagocytic histiocytes which distended the lymph node sinuses were weakly to moderately positive for non specific esterase and acid phosphatase. Other enzymes tested (alkaline phosphatase and dipeptidyl-amino peptidase) were negative in large histiocytes.

Immunohistochemistry

The large majority of the lymphophagocytic histiocytes in the lymph node biopsies from three pa-

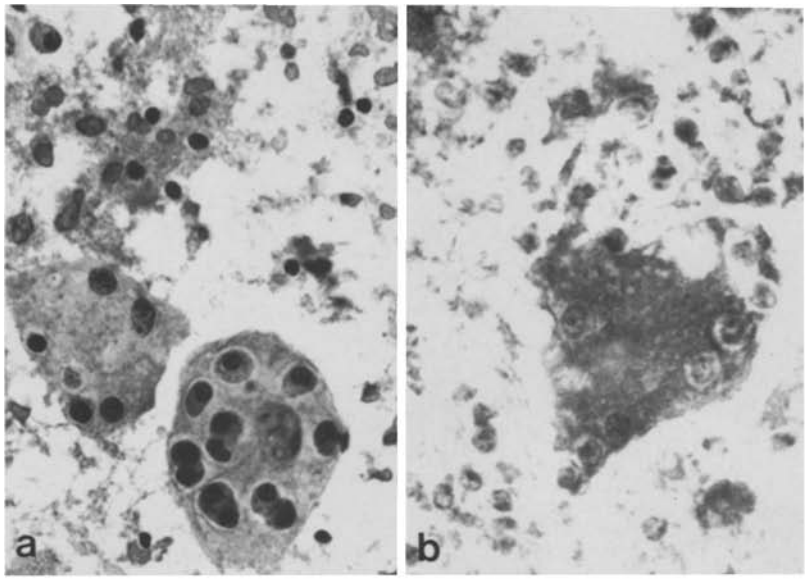

Fig. 2. Rosai-Dorfman histiocytosis in lymph node (serial sections).
a Large histiocyte with numerous lymphocytes engulfed in cytoplasm. H&E, ×400
b Large histiocyte intensively staining for S-100 protein, with lymphocytes engulfed in cytoplasm. PAP ×400

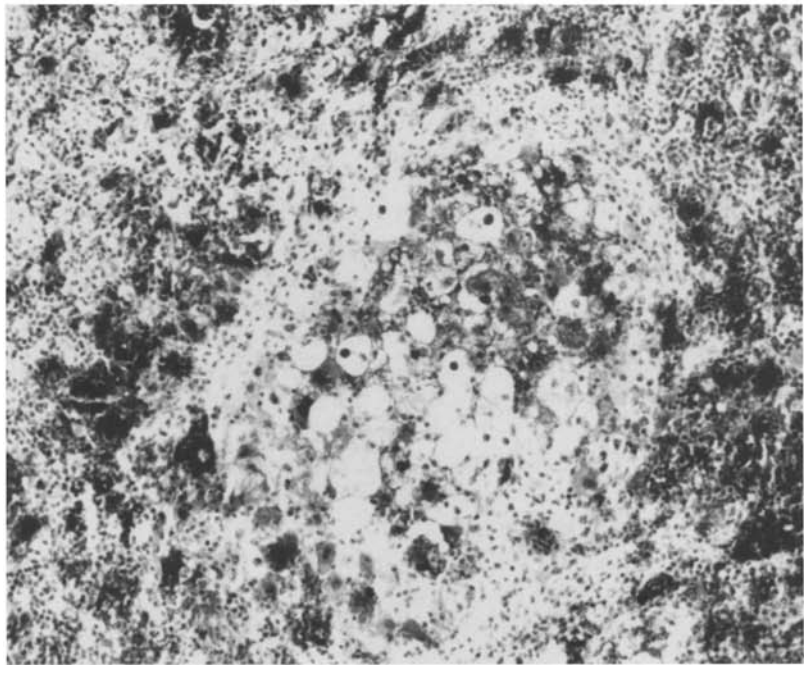

Fig. 3. Rosai-Dorfman histiocytosis in lymph node. Numerous histiocytes stain intensively for S-100 protein; foam cells, in the center, are mostly negative. PAP ×100

tients (No 2, No 4, No 5) were strongly positive for S-100 protein while only approximately 30–50% of them stained positively for S-100 protein in the lymph node from the other two patients (No 1, No 3) (Figs. 2b, 3). The lymphophagocytic histiocytes in all lymph node biopsies were consistently negative when stained for the presence of lysozyme and alpha 1-anti-chymotrypsin.

Cryostat tissue sections were available in three instances for immunohistochemical staining with monoclonal antibodies. Results are summarized in Table 2. The proliferating histiocytes were consistently unreactive with monoclonal antibody OKT6 but exhibited a weakly positive reaction for HLA-DR (Ia) antigens. In addition, the histiocytes exhibited weak and diffuse positivity when stained with monoclonal antibody OKT4. Other monoclonal antibodies which detect monocyte/macrophage cell associated antigens, OKM1, OKM5 and LeuM1, were unreactive with the lymphophagocytic histiocytes of RDH. The majority of the lymphocytes engulfed within the cytoplasm of the histiocytes of RDH expressed the Leu1 + T4 + T8- phenotype, i.e. the phenotype commonly asso-

Table 2. Immunohistochemical analysis of Rosai-Dorfman histiocytosis

	S-100	LYS	@1CHY	CD1	LeuM1	HLA-DR	OKM1	OKM5	Acp	NSE
No. 1	+/−	−	−	ND	ND	ND	ND	ND	ND	ND
No. 2	+++	−	−	ND	ND	ND	ND	ND	ND	ND
No. 3	−/++	−	−	−	−	−/+	−	−	++	+/++
No. 4	+++	−	−	−	−	−/+	−	−	++	+/++
No. 5	+++	−	−	−	−	−/+	−	−	++	+/++

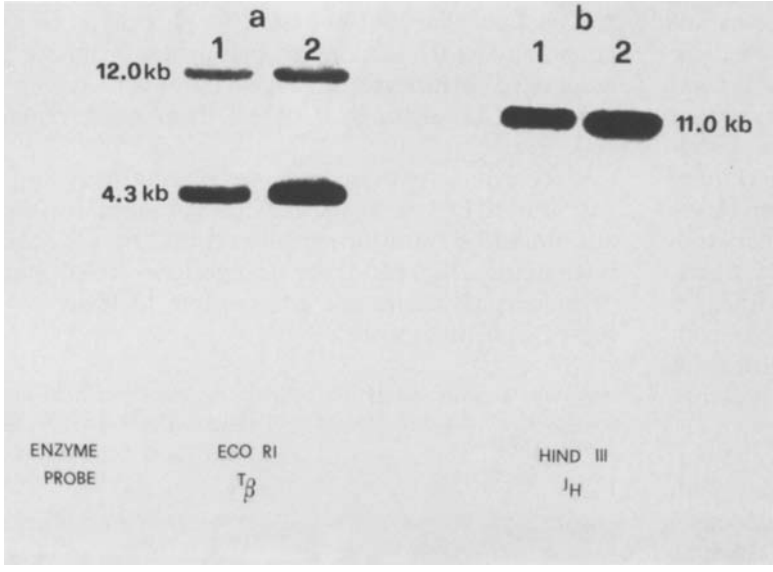

Fig. 4a, b. Southern blot of case No 5 analyzed for immunoglobulin heavy chain (*IgH*) and T cell receptor beta (*Tβ*) chain gene rearrangements. Panels **a** and **b** show DNA extracted from normal human fibroblasts (*lanes 1*) and from case No 5 of SHML (*lane 2*). Digestion with EcoR1 and Hind III and hybridization with T and IgH gene probes, respectively, show absence of clonal rearrangements and expression of the germ line configuration

ciated with helper/inducer T cells. Polyclonal B cells were confined to nodular aggregates in the medullary cords and were absent from the cytoplasm of the histiocytes of RDH. The latter cells were invariably negative for surface immunoglobulin but positive for cytoplasmic immunoglobulin (both kappa and lambda).

DNA analysis

Immunogenotypic analysis was performed on DNA extracted from fresh, unfixed portions of solid tissue obtained from patient No 5. This analysis demonstrated that the cell populations of RDH display the germline DNA pattern of the immunoglobulin heavy and light chain and the T cell receptor beta chain gene loci following digestion with EcoRI Bam HI, and Hind III (Fig. 4). These results suggest the absence of monoclonal B and T cell populations from RDH.

Discussion

In this study we demonstrate that the lympho-phagocytic histiocytes which characterize the lymph node lesion in RDH exhibit a peculiar phenotype (S-100+, CD1−, @1CHY−, LSZ−) similar to that observed in T-zone histiocytes (Watanabe et al. 1983).

The T-zone histiocytes consist of non-phagocytic, T-cell zone associated antigen presenting cells that express S-100 protein, variably express the CD1 antigen and lack lysozyme and alpha 1-antichymotrypsin. This lineage includes cutaneous Langerhans cells, so-called indeterminate cells of epidermis and oral mucosa and interdigitating dendritic cells (IDC) of lymph nodes and tonsils (Watanabe et al. 1983). In some reactive lesions, such as dermatopathic lymphadenopathy, Langerhans cells are highly enriched in the T-zone of lymph node (Lawrence et al. 1986). Langerhans cells represent the cell of origin for eosinophilic granuloma, Letterer-Siwe disease and Hand-Schuller-Christian disease, which are collectively referred to as Histiocytosis X (Lichtenstein 1953) or Langerhans cell granulomatosis (Liebermann et al. 1980). In addition, rare malignant tumours thought to arise from the IDC population of lymph nodes have been reported (Feltkamp et al. 1981; Lennert 1978; Bonetti et al. 1985).

Nevertheless, the mononuclear phagocyte system (MPS) is composed of phagocytic macrophages that lack S-100 protein and the CD1 antigen but express lysozyme and alpha 1-antichymotrypsin (Meister and Nathrath 1981). This cell lineage gives rise to cases of true histiocytic lymphoma (Isaacson et al. 1983), cases of malignant histiocytosis (Watanabe et al. 1983; Turner et al. 1984; Pileri et al. 1985) and Familial Erythrophagocytic Lymphohistiocytosis (Wieczorek et al. 1986a).

Although the conventional monocyte-histiocyte cell populations have been divided into these two major lineages, the T-zone histiocytes and MPS lineages, the neoplastic cells of malignant histiocytosis have been demonstrated to be phenotypically heterogeneous and also cases which share phenotypic characteristics of both groups have been described (Watanabe et al. 1983; Turner et al. 1984; Salisbury et al. 1985). Thus, our understanding of the T zone histiocytes and MPS lineages and the neoplasms thought to be derived from these lineages is undergoing further modification as additional cases are studied with new monoclonal antibodies.

It is of interest that most lesions previously referred to as malignant histiocytosis of the small intestine (Isaacson et al. 1985) and certain cases previously characterized by Turner et al. (1984) as being malignant histiocytosis were recently shown to be T cell neoplasms based on clonal rearrangements of the genes which code for the T cells by Southern blot hybridization analysis using specific DNA probes (Weiss et al. 1985).

The studies performed here confirm and extend the results of prior studies on RDH. Our data demonstrate that RDH lesions do not contain monoclonal proliferations of B or T cells as assessed by Southern blot hybridization analysis using specific DNA probes, thus confirming RDH as a true histioproliferative disorder.

The immunophenotypical analysis (presence of S-100 protein, absence of lysozyme, @1 ACT, CD1 and monocyte associated antigens such as Leu M1, OKM1 and OKM5) evidences a peculiar phenotype distinct from that typical of MPS lineage.

RDH histiocytes are characterized by the presence of lymphocytes within their cytoplasm. However, this may not represent simple phagocytosis as typically seen in MPS derived histioproliferative disorders. This phenomenon has been considered to represent emperipolesis by some investigators (Reid et al. 1979). In our cases the vast majority of lymphocytes observed within the histiocyte cytoplasms did not show signs of apoptosis and belong to the CD4+ helper/inducer subset. This selective inclusion of CD4+ lymphocytes within RDH histiocytes may reflect an exaggeration and/or derangement of the process by which histiocytes contact T-lymphocytes for antigen presentation (Reid et al. 1979; Mir et al. 1985). In summary, the histiocytes of RDH may not be functionally phagocytic and they also express a phenotype (S-100+ CD1−LSZ−@1ACT−) which is inconsistent with cells derived from the MPS lineage.

The peculiar S-100+CD1− phenotype suggests that RDH histiocytes belong to T cell-zone associated histiocytes lineage. However the absence of CD1 distinguish RDH from Langerhans cell.

According to these data we orientatively suggest that RDH is a disease characterized by the accumulation and/or proliferation of T-zone histiocytes different from Langerhans cells, but producing tissue lesions comparable to those observed in histiocytosis X.

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