Virchows Archiv (1994) 424:601–606

ORIGINAL ARTICLE

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Cathepsin D and E co-expression in sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) and Langerhans' cell histiocytosis: further evidences of a phenotypic overlap between these histiocytic disorders

Received: 14 March 1994 / Accepted: 13 April 1994

Abstract Nosological classification of sinus histiocytosis with massive lymphadenopathy (SHML; Rosai-Dorfman disease) is difficult, and the normal cellular counterpart of Rosai-Dorfman (RD) cells is uncharacterised. The peculiar S-100+ phenotype of RD cells suggests a relationship with the dendritic cell family. Recent investigations have revealed cathepsin E to be selectively concentrated in antigen-presenting cells, whereas cathepsin D was found to be expressed in cells of macrophage lineage. Cathepsin D and E distribution was investigated by immunohistochemistry in a series of SHML biopsies and in two types of dendritic cell proliferative lesions: dermatopathic lymphadenitis (DL) and Langerhans' cell histiocytosis (LCH). In SHML biopsies, RD cells and monocyte-related elements of the sinuses and pulp co-expressed cathepsin D and E. LCH cells also stained for both these aspartic proteinases. Conversely, in DL cathepsin E and D were localised to separate cells that resembled Langerhans' cells (LC) or macrophages, respectively, in morphology and distribution. Our data outline the peculiar immunophenotype of RD and LCH cells and suggest that caution should be exercised in the identification of their normal cellular counterpart. The common expression of cathepsin D and E and of S-100 protein suggests some phenotypic overlap between SHML and LCH cells, despite their striking morphological divergence.

Key words Cathepsin D · Cathepsin E · Rosai-Dorfman disease · Langerhans' cell histiocytosis
Immunohistochemistry

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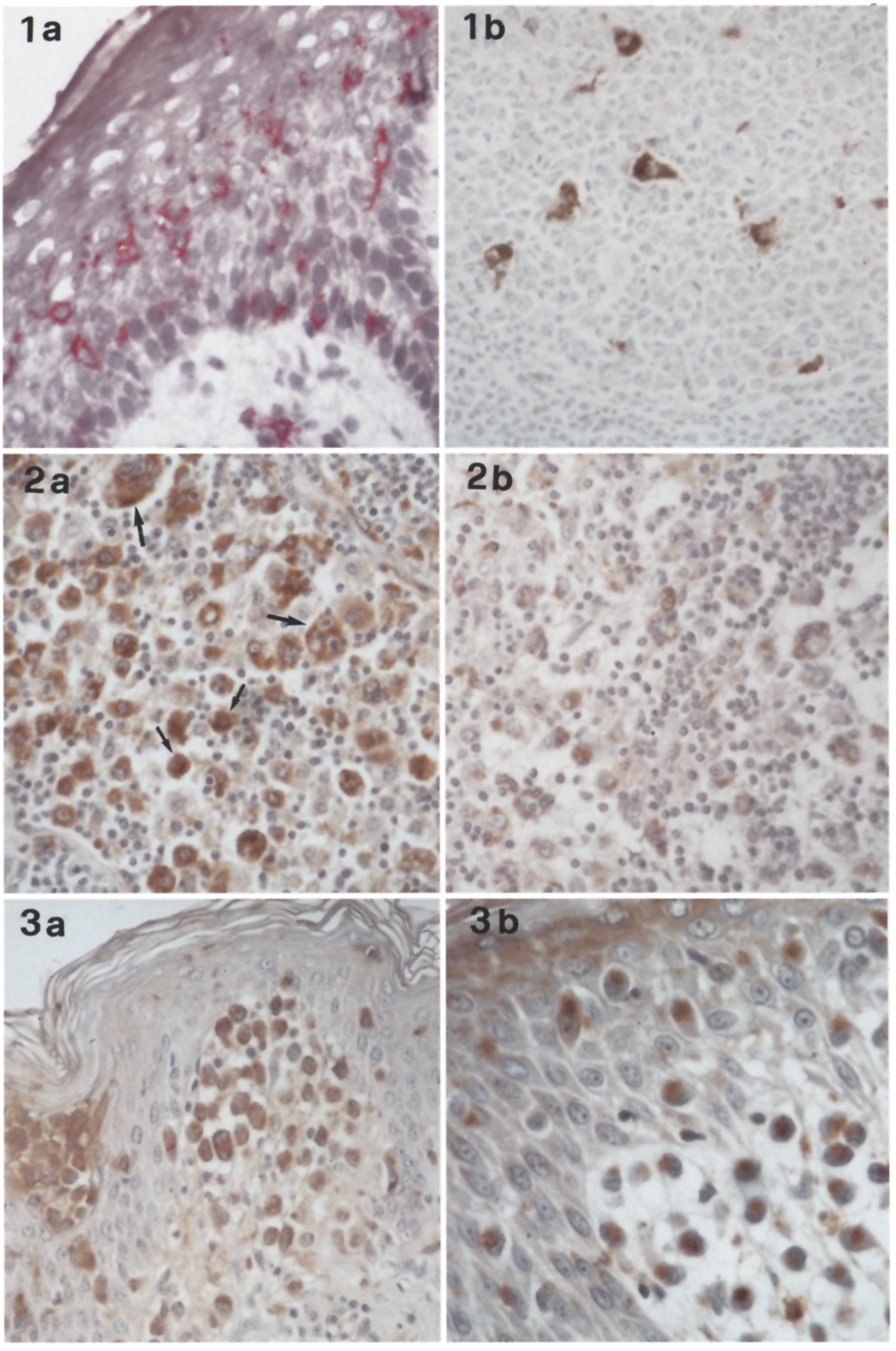
Introduction

Sinus histiocytosis with massive lymphadenopathy (SHML; Rosai-Dorfman disease) is a rare idiopathic disorder of the mononuclear phagocyte and immunoregolatory effector (M-PIRE) system (Foucar and Foucar 1990), originally described as a distinct entity by Rosai and Dorfman in 1969 and 1972. SHML is more common in children and adolescents than in adults (Foucar et al. 1990; Maennle et al. 1991; Paulli et al. 1992a) and shows no significant difference in incidence between white and black people. In most cases, the disease runs a favourable course. Rare cases with a poor prognosis are generally associated with immunological disease and/or involvement of unusual sites (kidney, lower respiratory tract; Foucar et al. 1990). Cervical lymph nodes are frequently affected, particularly at presentation, but SHML may involve other lymph nodes and/or extranodal sites such as the skin, bone, respiratory tract mucosa and soft tissues (Montgomery et al. 1992). In typical cases the structure of the lymph node is effaced by an accumulation in dilated sinuses and also in the parenchyma of large "histiocyte-like" cells exhibiting cytophagocytosis (Rosai-Dorfman or RD cells; Rosai 1991; Rosai and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Dorfman 1969). Immunophenotypically, RD cells express the S-100 protein and various monocyte-macrophage-associated antigens (Eisen et al. 1990; Maennle et al. 1991; Miettinen et al. 1987; Paulli et al. 1992b; Rosai 1991; Weisenburger et al. 1986). These findings suggest that RD cells belong to the monocyte-macrophage family (Eisen et al. 1990). However, their regular expression of the S-100 protein and, in some cases, CD1a antigen (Bonetti et al. 1987; Eisen et al. 1990; Maennle et al. 1991; Miettinen et al. 1987; Paulli et al. 1992b), may support a relationship with the immune accessory cell family, rather than with phagocytes (Murphy et al. 1981; Samloff et al. 1987; Van der Valk et al. 1984). Although useful for diagnostic purposes, the peculiar antigenic profile of RD cells makes it difficult to identify their normal cellular counterpart and to define the exact nosological classification of SHML.

Cathepsin E, an aspartic proteinase purified from bone marrow, spleen and stomach (Lapresle and Webb 1962; Puizdar et al. 1985; Samloff et al. 1987), has been shown to play a crucial role in antigen processing by a B cell lymphoma cell line (Bennet et al. 1992). It has been suggested that another aspartic proteinase, cathepsin D, is involved in antigen processing in macrophages (Diment et al. 1988). Recent studies (Finzi et al. 1993; Solcia et al. 1993) showed cathepsin E to be selectively concentrated in antigen presenting cells, such as Langerhans' cells (Fig. 1a), interdigitating reticulum (IDR) cells and epithelial M cells. Moreover, a high content of cathepsin E has previously been observed in a case of cutaneous LCH (Solcia et al. 1993). In contrast, cathepsin D was found to be expressed widely in cells of the macrophage lineage (tingible body macrophages) in the germinal centre (Fig. 1b), sinus histiocytes and littoral cells (Whitaker and Rhodes 1983; Diment and Stahl 1985; Reid et al. 1986; Solcia et al. 1993). In this study, we used light microscopy immunohistochemistry to investigate and compare the expression of cathepsin D and E and various monocyte-macrophage markers (CD1a; CD68 and LN5) in 12 cases of SHML and in other proliferative lesions of the dendritic cell system, including 4 cases of dermatopathic lymphadenitis (DL; Rausch et al. 1977; Van der Oord et al. 1984) and 8 cases of Langerhans' cell histiocytosis (Beckstead et al. 1984; Favara et al. 1986).

Fig. 1. a Normal human skin. The epidermal Langerhans' cell express cathepsin E (streptavidin-peroxidase, × 400). **b** Hyperplastic human lymph node. The tingible body macrophages express cathepsin D (streptavidin-peroxidase, × 250)

Fig. 2a, b Lymph node affected by sinus histiocytosis with massive lymphadenopathy. Most Rosai-Dorfman cells *(arrows)* and the medium-sized mononuclear cells *(smaller arrows)* coexpress cathepsin E (**a** streptavidin-peroxidase, 160×) and D (**b** streptavidin-peroxidase, × 160)

Fig. 3a, b Skin biopsy in a case of Langerhans' cell histiocytosis (LCH). LCH cells stain positively for both **a** cathepsin E, with diffuse cytoplasmic reactivity (Streptavidin-peroxidase method, × 250) and **b** cathepsin D, often with paranuclear "dot-like" reactivity (Streptavidin-peroxidase, × 630)

Materials and methods

Twelve lymph node and two skin biopsies of 11 patients were collected from the files of the Departments of Pathology and Dermatology of the Universities of Pavia, Lübeck, Brescia, Verona, Ghent and Heidelberg. In all cases we diagnosed SHML according to the usual histological criteria (Foucar et al. 1990; Rosai and Dorfman 1969; Rosai and Dorfman 1972). In addition, 4 cases of DL and 8 cases (4 skin and 4 lung biopsies) of Langerhans' cell histiocytosis (LCH), formerly known as histiocytosis X, were available. Samples of macroscopically normal skin (5) and lymph nodes (6) were taken from biopsy and/or surgical specimens.

Formalin-fixed, paraffin-embedded tissue samples were obtained from all cases. Paraffin sections (3 μ m thick) were stained with haematoxylin-eosin, Giemsa, periodic acid-Schiff (PAS) and Gomori silver impregnation (the latter for reticulin fibres). Immunohistochemistry with monoclonal antibodies (MoAbs) and antisera (Table 1) was performed by means of the streptavidin-peroxidase method (Shi et al. 1988). Antiserum to human cathepsin E was prepared in rabbits as previously described (Samloff et al. 1987). The specificity of the antiserum, including lack of cross-reactivity with other aspartic proteinases, such as cathepsin D and pepsinogens, was assessed with immunodot-blotting and with radioimmunoprecipitation. Endogenous peroxidase activity was blocked by pre-incubation of the sections with H_2O_2/methanol solution. After washing in 0.05 M Tris-HCl in 0.5 M NaCl pH 7.6 (TBS), sections were incubated (for 18 h at 4°C) with rabbit anti-human cathepsin E (diluted 1:4000 in TBS), rabbit anti-human cathepsin D (diluted 1:200 in TBS) and rabbit anti-cow S-100 protein (diluted 1:4000 in TBS). The sections were also incubated with mouse monoclonal antibodies (diluted 1:5 to 1:80 in TBS) for 1 h at room temperature. After washing, the slides were incubated first with either donkey anti-rabbit (Amersham cod. RPN1004) or sheep anti-mouse biotin-labeled Ig (Amersham cod. RPN 1001) and then with horseradish streptavidin-peroxidase complex (Amersham cod. RPN 1051). Reaction products of the immunostaining were developed by immersion of the sections in 3,3′-diaminobenzidine hydrochloride/H_2O_2 solution or in 3-amino-9-ethylcarbazole/H_2O_2 solution. The slides were lightly counterstained with haematoxylin before dehydratation and mounting. Control experiments included the use of positive controls for each antiserum or antibody, while negative controls were obtained by the substitution of primary antibodies with normal rabbit and mouse serum or unrelated mouse monoclonals. We performed double labelling with cathepsin D and E according to Van Noorden et al. (1986), respectively coupled with benzidine and carbazole.

Table 1 Monoclonal antibodies (MoAbs) and polyclonal antisera employed and their specificity

MoAbs, antisera/source[a]	Specificity
Cathepsin E / Samloff	Human cathepsin E (polyclonal)
Cathepsin D / Ortho	Human cathepsin D (polyclonal)
Cathepsin D / Triton Biosciences	Human cathepsin D (monoclonal)
010 (CD1a) / Dr. Boumsell	CD1a antigen
S-100 protein / Dako	S-100 protein
LN5 / Biotest	Macrophages and B cell subsets
KP1 / Dako	CD68; macrophages
LN3 / Biotest	HLA-DR

[a] Ortho, Raritan, NJ, USA; Triton Biosciences, Alameda, Calif., USA; Dr. Boumsell, Hôpital Saint-Louis, Paris Cedex, France; Dako, Glostrup, Denmark; Biotest, Frankfurt, Germany

Table 2 Immunohistochemical findings

	Normal macrophages, lymph node	RD cells	LCH cells	Normal LC cells, skin	Normal IDR cells, lymph node
Cathepsin E	–	+	+	+	–
Cathepsin D (polyclonal)	+	+[b]	+[c]	–	–
Cathepsin D (monoclonal)	+	+[b]	+[c]	–	–
010 (CD1a) (monoclonal)	–	+[b]	+	+	–/+
S-100 protein	–	+	+	+	+
LN5	+	+	+	–/+[d]	+
KP1/CD68	+	+	–	–	–
LN3/HLA-DR	+[a]	–	+	+	+

[a] Some sinus histiocytes LN3/HLA-DR negative
[b] Diffuse cytoplasmic staining
[c] Frequent paranuclear dot-like reactivity
[d] Positivity observed in two of five samples tested

Results

Our series of SHML biopsies showed the characteristic histomorphologic features previously detailed for this entity (Rosai and Dorfman 1969; Rosai and Dorfman 1972; Foucar et al. 1990; Rosai 1991). The lymphatic sinuses were expanded by large histiocyte-like cells that exhibited pale cytoplasm and cytophagocytosis (RD cells). RD cells were admixed with plasma cells, neutrophils and medium-sized mononuclear cells with indented nuclei. These latter cells were also present in the lymph node pulp. Two patients had soft tissue localizations, with RD cell involvement in the subcutaneous tissue and dermal infiltration. The LCH and DL cases showed all the classic histological features (Favara et al. 1986; Beckstead et al. 1984; Rausch et al. 1977; Van der Oord et al. 1984; Writing Group of the Histiocyte Society 1987).

Immunohistochemical results are detailed in Table 2. In the sinuses and pulp of SHML lymph nodes the anti-human cathepsin E and D specific antibodies reacted with most of the large RD cells, and also with the medium-sized mononuclear cells with indented nuclei accumulated in the sinuses and pulp (Fig. 2a, b). LCH cells stained positively for both the aspartic proteinases (Fig. 3a, b) and with most of the antibodies that stained the RD cells. In DL cases, cathepsin D was negative, other than in a few normal macrophage-like cells, while cathepsin E reactivity was confined to scattered elements with elongated and folded nuclei resembling Langerhans' cells. Differences were found between the various cell subtypes in the immunostaining pattern for cathepsin D. The RD cells showed diffuse weak cytoplasmic staining for this aspartic proteinase, whereas the monocytes in the sinuses displayed a stronger positive reaction (Fig. 2b) and the LCH cells frequently showed paranuclear, dot-like reactivity (Fig. 3b). Double immunostaining of the same section for catepsin E and D showed co-localization of the two proteinases in most RD and LCH cells whereas in DL samples cathepsin E and D were detected in separate cells, interpreted as Langerhans' cells and macrophages, respectively. The anti-CD1a MoAb 010 gave fairly intense positive reaction of Langerhans' and interdigitating reticulum cells in DL cases. This MoAb gave a positive reaction in the cells of LCH, as well as a diffuse, cytoplasmic staining in most RD cells of SHML.

Discussion

Our immunohistochemical findings (see Table 2) confirm previous observations (Solcia et al. 1993) regarding the respective expression of cathepsin E and D by epidermal Langerhans' cell and lymph node macrophage. In DL specimens we detected a variable expression of cathepsin E by IDR cells versus a uniform reactivity for this aspartic proteinase in epidermal LC. In 1991 Kampgen et al. demonstrated that during in vitro culture dendritic cells may cease processing native protein antigens while retaining their accessory function for the activation of resting T cells. Thus, differences in cathepsin E expression between normal LC in the skin and proliferating LC-like cells in DL may be in keeping both with a loss of antigen-processing function and with the acquisition of a stimulatory role for antigen presenting cells that migrate to lymphoid organs from peripheral tissues.

The literature contains variable, often contrasting data regarding CD1a expression in SHML. The use of the MoAb 010 (Krenacs et al. 1993), which detects the CD1a antigen in routinely processed tissues, permitted the detection of this antigen in most RD cells in all SHML cases and in normal IDR or LC cells, but not in macrophages. Conversely, MoAb LN5 reacted positively with RD or LCH cells as well as with normal macrophages, interdigitating reticulum cells and Langerhans' cells. It seems likely that LN5 identifies an antigen that is widely expressed by histiocyte-derived cells, irrespective of their phagocytic or antigen-presenting differentiation.

In SHML biopsies, most intrasinusoidal RD cells stained for both cathepsin D and E, for the S-100 protein and for the MoAb 010/CD1a (diffuse cytoplasmic staining), as well as for the pan macrophage MoAbs KP1 (CD68) and LN5. RD cells did not display the LN 3/HLA-DR antigen, indicating defects in MHC class II biosynthesis and in related antigen-presenting capacity. LCH cells exhibited CD1a and HLA-DR, as well as cathepsin D and E and S-100 protein. As a whole, these staining patterns showed co-expression in the RD and LCH cells of both macrophages and Langerhans' cell markers. The peculiar phenotype of the RD and LCH cells suggests both their inappropiate differentiation from a common precursor cell and a lack of segregation of the two pertinent lineages.

The simultaneous expression of cathepsin D and E probes may be of diagnostic value, as it enables us to

distinguish both RD and LCH cells from normal skin LC (cathepsin D–/cathepsin E+), from proliferating LC-like cells in DL (cathepsin D–/cathepsin E–/+) and from normal phagocytes (cathepsin D+/cathepsin E–). Although useful for diagnostic purposes, the unique RD and LCH cell antigenic profile does not allow an effective comparison with other monocyte-derived cells of the lymphoid parenchyma. Caution should be exercised in attempts to define relationships with normal cell populations on the basis of the antigens expressed by abnormally proliferating cells.

Originally, Lennert et al. (1972) proposed that the monocytic cells that accumulate in the pulp and sinuses of SHML lymph nodes might be the precursors of RD cells. Subsequent immunohistochemical investigations (Paulli et al. 1992b) have stressed the phenotypic similarities between these monocyte-like cells and RD cells. In this study we have proved the coexpression of cathepsin D and E in both kinds of cells in SHML lymph nodes as well as in the histiocytes of LCH. Thus, notwithstanding their clear morphological divergences, monocyte-like cells of SHML and RD and LCH cells demonstrate striking functional and/or phenotypic overlap. These similarities support the hypothesis of a close relationship between these subsets of the mononuclear phagocytic system.

Langerhans' cells and macrophages originate and proliferate in bone marrow, from which they migrate into peripheral tissues under normal and reactive conditions. The growth and differentiation of haematopoietic (progenitor) cells is regulated by a complex network of cytokines and by a variety of microenvironmental factors (Metcaf 1989). The bone marrow-derived elements, namely granulocytes, erythrocytes, megakaryocytes, lymphocytes, eosinophils, mast cells, monocytes and Langerhans' cells, are prompted by colony-stimulating factors (CSFs) to differentiate and mature (Wakefield et al. 1990). Previous studies proved that the granulocyte/macrophage-colony stimulating factor (GM-CSF) induces in vitro activation of Langerhans' cells. Whitmer-Pack et al. (1987) and Heufler et al. (1988) demonstrated that the cooperation between GM-CSF and tumour necrosis factor is crucial for the differentiation of Langerhans' cells from CD34-positive haematopoietic progenitors (Caux et al. 1992). In addition, it has been shown that intradermal administration of GM-CSF in human patients induces a local accumulation of Langerhans' cells (Kaplan et al. 1992).

Recently, Emile and co-workers (1993) used immunohistochemical staining to demonstrate in situ the presence of GM-CSF in a series of skin and bone LCH biopsies. In a previous study, performed on fresh SHML lymph node biopsies, we detected, by means of the reverse transcriptase-polymerase chain reaction (RT-PCR) technique, the presence of mRNA transcripts for GM-CSF and for gamma interferon, as well as for a wide range of cytokines, including IL-1, IL-2, IL-6, IL-7, IL-9 and IL-10 (Paulli et al. 1992c).

Taken together, these findings suggest a common cytokine-mediated pathogenetic mechanism for RD disease and LCH, which might represent two clinical variants in the wide spectrum of monocyte-related disorders. The release of different locally acting factors could be responsible for the divergent morphology of proliferating RD and LCH cells.

Although we cannot exclude the hypothesis that RD and LCH cells originate from a resident population, the immunophenotypical overlap between these mononuclear-derived populations points to recently immigrated monocytes as RD and LCH cell precursors. The exact agents inducing the morphological and immunophenotypical modification of such monocytes remain unknown. Moreover, we do not know whether these peculiar histiocytic disorders are reactive or neoplastic. Further studies are needed to address these issues.

Acknowledgements This work was supported in part by grants from the Italian Ministry of University, Scientific Research and Technology (M.U.R.S.T.) to I.R.C.C.S. Policlinico San Matteo

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