

A Case of Reticulohistiocytoma

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Reticulohistiocytoma, a rare form of non-Langerhans cell histiocytoses, usually presents itself as a single cutaneous nodule mainly on the head and neck of young men without associated arthritis. We describe an 18-year-old male patient with a red dome-shaped nodule of 2 months' duration on the scalp. Histologic examination of the excised mass revealed numerous large, mononucleated or multinucleated histiocytes with abundant eosinophilic, finely granular cytoplasm having a ground-glass appearance. Immunohistochemical staining was positive for vimentin, lysozyme, and factor XIIIa, supporting a dermal dendrocyte lineage. Ultrastructurally, large mononuclear or multinucleated cells exhibiting numerous peripheral villi contained pleomorphic cytoplasmic inclusions, fatty droplets and dense bodies. Our clinicopathologic findings support the concept that reticulohistiocytoma is a variant of adult xanthogranuloma. (*Ann Dermatol* 11(4) 255~259, 1999).

Key Words : Reticulohistiocytoma, Ground-glass cytoplasm, Dermal dendrocyte, Xanthogranuloma.

Solitary or multiple reticulohistiocytoma(RH) is a rare disease which, together with multicentric reticulohistiocytosis(MR), belongs to the spectrum of non-X histiocytoses, which are heterogeneous conditions whose cells generally lack Langerhans cell granules¹. Clinically, RH has no specific site of focus while MR shows acral localization. RH presents itself as a hard, yellow-to-brownish red, asymptomatic tumor characterized by rapid growth. Its most common location is on the head. The onset of the lesions may be preceded by trauma. RH mostly affects otherwise healthy young adults, especially males, without systemic involvement², whereas MR mostly appears in middle-aged women and is associated with (poly)arthropathy and/or malignancies^{3,4}. Both variants are histologically characterized by the presence of numerous large, mononucleated or multinucleated histiocytes with an abundance of eosinophilic, homogeneous to finely

granular cytoplasm having a ground-glass appearance.

There have been some reports supporting a close relationship of RH with adult XG, as evidenced by clinical and histopathologic similarities and identical immunohistochemical labelling profiles of the two entities^{2,5,6}. The purpose of this article is to describe another case of solitary reticulohistiocytoma sharing some clinical, histopathologic, immunohistochemical and ultrastructural characteristics with adult XG, further supporting the concept that RH is a variant of adult XG among the confusing potpourri of non-Langerhans cell histiocytoses.

CASE REPORT

An 18-year-old Korean male was seen at our department with a pea-sized brownish red dome-shaped nodule on the scalp (Fig. 1). The firm, smooth-surfaced, asymptomatic nodule was first noticed 2 months previously. The patient appeared in good general health, with normal weight and height. In the past, the patient had been diagnosed as having vitiligo and lichen simplex chronicus on the neck 6 months previously, but a detailed physical examination revealed no arthropathy

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Fig. 1. Pea-sized, firm, brownish red, dome-shaped nodule of reticulohistiocytoma on the scalp.

or any other abnormality. No trauma preceded the appearance of the lesion. His family history was negative. Laboratory investigation revealed a normal blood cell count and differential, sedimentation rate, electrolyte levels, liver and renal function tests, rheumatoid factor test, antinuclear factor analysis, immunoglobulin levels, and urinalysis. The scalp nodule was completely excised under local anesthesia. The resected tumor was 0.7×0.7 cm in size, spherical in shape, and well demarcated from the surrounding normal tissue.

Sections from the biopsy specimen were stained with hematoxylin-eosin and PAS with and without previous diastase digestion. Other sections were stained immunohistochemically for S-100 protein,

Fig. 2. (a) Scanning magnification of well-demarcated nodule of RH (H & E, $\times 10$).
(b) Medium-power magnification shows dense infiltrate of mononuclear and multinucleated histiocytes with abundant, eosinophilic, ground-glass cytoplasm. A few Touton-like multinucleated histiocytes are also shown in this field (arrows) (H & E, $\times 100$).
(c) Numerous bizarre multinucleated histiocytes with irregularly distributed nuclei, scalloped cellular outlines and a ground-glass appearance are seen as well as oncocytic mononuclear histiocytes, vacuolated cells, and xanthomatized histiocytes (H & E, $\times 400$).
(d) Factor XIIIa labeling shows diffuse cytoplasmic labeling of mononuclear and, to a lesser degree, multinucleated histiocytes ($\times 400$).

Table 1. Details of the antibodies used for Immunohistochemistry

Antibody or Marker	Antibody*	Main Specificity	Source †
S100 protein	P	Nerves, melanocytes, nevus cells, and Langerhans cells	Dako
Lysozyme	P	Monocyte-derived macrophages	Dako
Vimentin	M	Intermediate filament protein of mesenchymal cells	Dako
LCA	M	Benign leukocytes, lymphoma & leukemia	Dako
UCL-1	M	T-restricted LCA, T cells, monocytes	Dako
CD68 (KP1)	M	Reactive monocytes and macrophages	Dako
Factor XIIIa	P	Dermal dendrocytes	Behring

* P indicates polyclonal; M, monoclonal

† Dako, Glostrup, Denmark; Behring, Marburg, Germany

Fig. 3. Closely set histiocytes showing irregular nuclei and cytoplasm filled with many pleomorphic inclusions, dense bodies, myelinated bodies and lipid droplets (TEM, original magnification $\times 10,400$).

vimentin, lysozyme, CD68, LCA, UCL-1 and factor XIIIa (Table 1). Histologic examination showed a well-circumscribed massive infiltration of the upper and mid dermis; the epidermis was thinned but not infiltrated (Fig. 2a). The infiltrate was composed of lymphocytes and mononucleated or multinucleated giant histiocytic cells, with an abundance of eosinophilic cytoplasm having a ground-glass appearance (Fig. 2b, c). Many of the mononuclear histiocytes had eosinophilic, homo-

geneous, slightly granular cytoplasm similar to that of thyroid oncocyctic cells and had well-demarcated cell borders with spidery, delicate cytoplasmic processes and round-to-ovoid, occasionally kidney-shaped nuclei with one to two prominent nucleoli. Others included vacuolated cells, spindle-shaped cells and xanthomatized cells. Multinucleated histiocytes were 20-30 times larger, with scalloped (bizarre) cellular outlines, numerous oval, slightly indented nuclei and leukophagocytosis. A few classical Touton multinucleated histiocytes were also present. In general, mitoses were very rare or absent. Staining for lysozyme showed perinuclear labeling in both mono- and multinucleated cells but was more intensely positive in the mononuclear cells. Immunolabeling for vimentin was diffusely positive in the cytoplasm of mononuclear and multinucleated histiocytes. Factor XIIIa, a dendritic cell marker, showed diffuse moderate cytoplasmic staining of mononuclear and multinucleated histiocytes (Fig. 2d). The cytoplasm of these cells showed no reaction or a coarse, granular PAS reaction. The histiocytic cells were not labelled with S-100 protein, CD68, LCA or UCL-1.

The ultrastructural examination of the specimen revealed the reticulohistiocytes as large cells with irregular contours and numerous peripheral villi (Fig. 3). The nucleus had a lobulated or notched nuclear outline, thin rim of peripheral heterochromatin, relatively electron-light nucleoplasm, and one or two nucleoli. In many instances, tumor cells were set together very closely, obscuring cell borders. These cells contained pleomorphic inclusions, homogeneously dense bodies, irregularly myelinated bodies and lipid droplets in their cytoplasm. No Langerhans granules were observed in

any of the cells.

The diagnosis of reticulohistiocytoma was based upon the results of histopathologic, immunohistochemical, and ultrastructural evaluations. A follow-up examination, done 6 months after the removal of the nodule, showed no evidence of recurrence.

DISCUSSION

The common denominator in the non-Langerhans cell histiocytoses is the monocyte/macrophage, which presents itself with various histologic features probably due to the influence of cytokines. Non-Langerhans cell histiocytoses are classified according to the predominant mononuclear (vacuolated, spindle-shaped, xanthomatized, scalloped, and oncocyctic) and/or multinucleate (Touton, ground-glass appearance, Langhans, and foreign body) histiocytic cell types. Variable mixtures of these cell types produce common polymorphous patterns with a prominence of vacuolated, spindle-shaped, and xanthomatized histiocytes in juvenile xanthogranulomas and of scalloped and oncocyctic histiocytes in adult xanthogranulomas. Rarely, unusual monomorphous reaction patterns are observed; oncocyctic histiocytes are evident in RH and MR⁷. Among the non-X histiocytoses, reticulohistiocytosis is one of the rarest.

Thanks to the development of cell markers specific to connective tissue cells and cells of the monocyte-macrophage series, it is now known that "histiocytes" are heterogeneous in origin. Most "histiocytes" and macrophages that occur in chronic infective granulomas and foreign body or sarcoidal granulomas derive from circulating monocytes of bone marrow origin; in histiocytomas, morphologically similar cells are probably recruited locally from the resident dermal connective tissue cells. A rabbit polyclonal antibody to factor XIIIa has been found to be an excellent marker of these dermal dendrocytes in normal skin⁵. In pathological conditions, factor XIIIa labels tumor cells of histiocytoma (dermatofibroma), angiomatoid fibrous histiocytoma, fibrous papule of the nose, atypical fibroxanthoma, xanthoma disseminatum, angiofibroma, XG, and reticulohistiocytoma⁵. The staining pattern for factor XIIIa is very characteristic in non-Langerhans cell histiocytoses, but shows time-cycle-dependent variations: early lesions with pre-

dominantly vacuolated histiocytes are diffusely and strongly positive; fully developed lesions with a mixed histiocytic profile begin to lose this reactivity with sparing or weak staining of the central parts; labelling further decreases in late lesions with predominantly spindle-shaped histiocytes and, finally, is mostly absent in predominantly oncocyctic as well as all types of multinucleate histiocytes⁷. Our case was not strongly labeled with factor XIIIa.

A previous report delineated RH from MR based on histopathologic and immunophenotypic findings²: the infiltrate in RH is more circumscribed, dense, and sheet-like than in MR; vacuolated, spindle-shaped, and xanthomatized mononuclear histiocytes and Touton multinucleated histiocytes are seen only in RH; multinucleated histiocytes with a ground-glass appearance are huge (>200 μ m) and bizarre in RH and less prominent (50-100 μ m) and roundish in MR; PAS staining is diffusely positive in MR but is negative or only shows a weak granular reactivity in RH; immunohistochemically, HHF35 and factor XIIIa stains are positive in RH but negative in MR.

Cerio *et al.*⁵ used the term reticulohistiocytoma synonymously with solitary xanthogranuloma, an eponym for adult XG. In another study² with 6 RH and 4 MR subjects, clinicopathologic findings supported the concept that RH is a variant of adult XG: clinically, at least half of RH lesions were thought to be XGs or xanthomas, respectively. In contrast to juvenile XG, adult XG is usually a solitary lesion affecting 20- to 40-year-old patients of either gender predominantly in the head-neck-shoulder region⁷, a feature identical to RH. The variable numbers of oncocyctic, vacuolated, spindle-shaped, and xanthomatized mononuclear histiocytes seen in RH appear to be identical to those in XG. In a recent report, Zelger *et al.*⁷ stated that RH is a variant of adult XG with a predominance of oncocyctic (and scalloped) histiocytes and giant cells. These oncocyctic cells have a rather pronounced, eosinophilic, homogeneous, slightly granular cytoplasm with well-demarcated cell borders. In general, mitoses are very rare or absent⁷. Giant cells with a ground-glass appearance are always associated with oncocyctic histiocytes. While Touton cells are the predominant type of giant cell associated with juvenile XG, other variants such as ground-glass, Langhans and/or foreign-body giant cells are

more common in adult XG⁷. These numerous, partially bizarre multinucleated histiocytes are identical to the ones seen in RH^{6,8}. Finally, the immunohistochemical labeling profiles of RH and adult XG are identical^{6,8}. Our case clinically and histopathologically resembles adult XG, and the immunohistochemical staining patterns are identical. In contrast to XG, xanthoma disseminatum can be distinguished from RH (and MR). Xanthoma disseminatum is strongly positive for factor XIIIa in typically scalloped mononuclear histiocytes, unlike RH and MR. Monocytic markers, HAM56, lysozyme, and 1-antitrypsin are always negative in xanthoma disseminatum but (variably) positive in MR and RH.

Ultrastructurally, the absence of Birbeck granules, but the presence of various, nonspecific organelles such as comma-shaped, dense, regularly laminated, or myeloid bodies or pleomorphic cytoplasmic inclusions in variable degrees, is characteristic in non-Langerhans cell histiocytoses. Variations within these findings are attributable to the cell type predominantly seen: oncocytic cells and giant cells with a ground-glass appearance or of Langerhans and foreign-body types exhibit numerous pleomorphic cytoplasmic inclusions and myeloid bodies; scalloped cells show a moderate amount of dense and myeloid bodies; xanthomatized cells as well as Touton giant cells are characterized by myeloid bodies and fatty droplets; vacuolated cells show comma-shaped bodies or worm-like particles and occasional dense and myeloid bodies⁷. According to this scheme, RH would show mostly numerous pleomorphic inclusions and myeloid bodies, and adult XG, the same findings plus various other nonspecific organelles such as dense bodies. Findings in our case indeed included many pleomorphic inclusions, dense bodies, myeloid bodies and lipid droplets.

Definite, mutually exclusive diagnostic criteria have not yet been settled for the numerous non-Langerhans cell histiocytoses, including RH and adult XG; however, our case conforms more closely

to the descriptions of RH rather than adult XG because of the predominance of huge multinucleated giant cells with ground-glass cytoplasm and haphazard arrangement of nuclei, and paucity of Touton-type giant cells. In conclusion, we have described another case of solitary RH with some clinical, histologic, immunohistochemical and ultrastructural features in common with adult XG and thus support the concept that RH is identical or at least closely related to adult XG.

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