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Appearance of Sézary-like Atypical Lymphocytes in the Regressing Lesions of Juvenile Xanthogranuloma*

Its Role in the Spontaneous Regression

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A case of juvenile xanthogranuloma of the skin was sequentially biopsied for 10 months. In the electron microscopic examination of the regressing lesions, we observed that cells with highly indented nuclei, Sézary-like cells, were in close apposition to vacuolated degenerating histiocytes in many foci. In immunohistochemical stain, the number of UCHL-1+ cells were increased in regressing lesions compared with early lesions. We speculate that these Sézary-like atypical lymphocytes may be closely related to the spontaneous regression of juvenile xanthogranuloma. ***Key word: UCHL-1$^+$ lymphocyte.***

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Juvenile xanthogranuloma is a benign histiocytic proliferative disorder of unknown etiology, most frequently seen in infants. Although the lesions usually involute spontaneously within a year, they may persist for several years (1, 2).

Sequential biopsies of the various stages of the lesions of juvenile xanthogranuloma were performed to observe the progressive changes that occur during regression. In the present communication, detection of Sézary-like atypical lymphocytes and increased UCHL-1$^+$ cells in the regressing lesions of a patient with juvenile xanthogranuloma and their significance are reported.

CASE REPORT

A 7-month-old female infant was examined at our clinic for the evaluation of multiple skin lesions scattered over the whole body, which had been observed since 100 days after birth. Her family and past history revealed nothing significant.

On physical evaluation, there were 3–5 mm sized, discrete, yellowish nodules on the scalp, face, inner surfaces of the ear lobe, trunk, and extremities (Fig. 1). The parent of the patient stated that as the lesions progressed, they gradually enlarged in size and the initial yellowish color turned red. The regressing lesions finally flattened, leaving dark red patches (Fig. 2).

The laboratory findings, including CBC with differential count, urinalysis with microscopic findings, liver function test, triglyceride and cholesterol level, were all within normal limits. Roentgenograms of chest P-A, skull A-P and lateral were all normal. Biopsy specimens were taken four times from the skin lesions of the patient in accordance with the progression of the disease. Specimens were embedded in paraffin for light microscopic study and in epoxy resin (Epon 812) for electron microscopic study. Ultrathin sections for electron microscopy were stained with uranyl acetate and lead citrate.

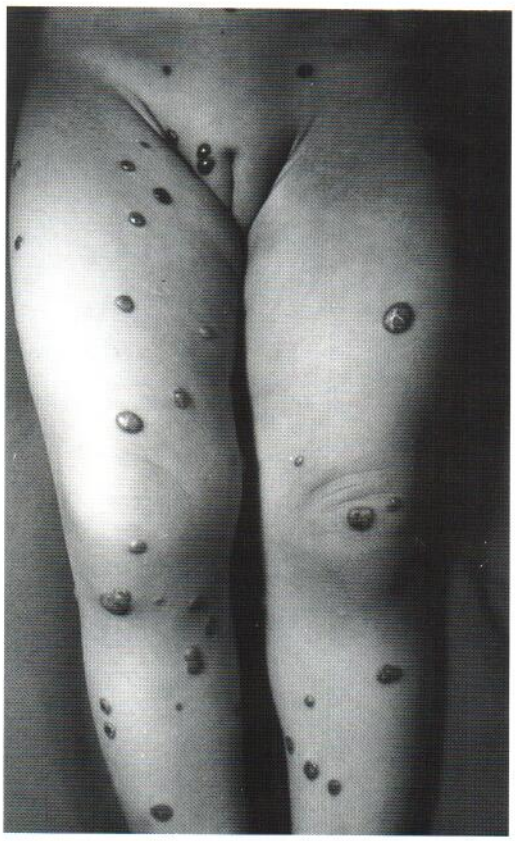

Fig. 1. Mature lesions: papulonodules on the lower limbs.

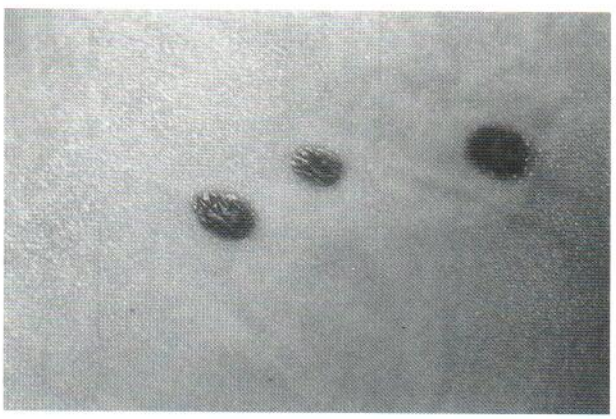

Fig. 2. Regressing lesions: flattened papulonodules on the trunk.

Light microscopic examination of the mature lesions showed typical juvenile xanthogranuloma features: a granulomatous infiltrate containing a large number of foam cells, foreign body giant cells, and Touton giant cells as well as histiocytes, lymphocytes and eosinophils

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(Fig. 3). The histopathologic findings of a flattened lesion showed extravasation of red blood cells, increased number of inflammatory cells and the decrease of total number of giant cells (Fig. 4). Also, in a magnified light microscopic view Sézary-like lymphocytes were seen (Fig. 5).

Immunohistochemical staining was performed. Paraffin sections were cut and immunohistochemically labelled, using a three-step avidin-biotin immunoperoxide method. The antibodies of UCHL-1$^+$ (DAKO, Kyoto, Japan) and CD45 (DAKO, Kyoto, Japan) were used as the primary antibody at a dilution of 1:100 and 1:200 in room temperature for 60 min. Peroxidase was labelled using 3′3′ diaminobenzidine and hydrogen peroxide. The sections were then counterstained with 1% hematoxylin, and UCHL-1$^+$ cells were counted independently by two observers. We chose ten high-power fields (×400) of entire dermis in a blind fashion. The positive cells were counted in absolute numbers. The mean of positive cells was 17 in early lesions and 36 in late resolving lesions, respectively (Figs. 6, 7). CD45-positive cells were rarely observed in early and late lesions. These results indicated that atypical lymphocytes (UCHL-1$^+$) were mainly composed of T-lymphocytes.

Electron microscopic examination of the regressing flattened lesions revealed atypical lymphocytes with indented, convoluted nuclei with features of Sézary-like cells, in close apposition to vacuolar degenerating histiocytes in many foci. A close apposition between the plasma membrane of the atypical lymphocyte and the nuclear membrane of the histiocyte was observed (Fig. 8). The atypical lymphocytes were not observed in the early lesions of juvenile xanthogranuloma.

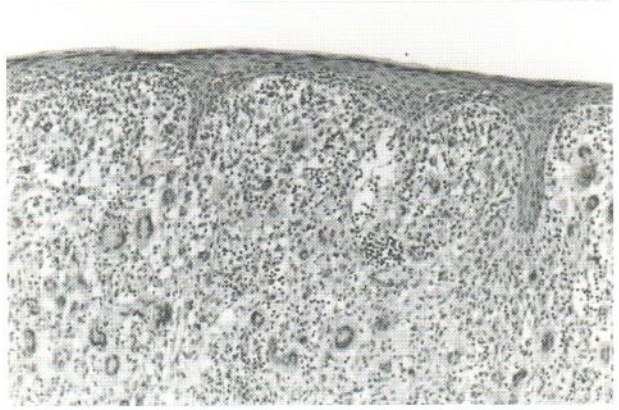

Fig. 3. Earlier lesion (2nd biopsy); granulomatous infiltrate contains a large number of foam cells, foreign body giant cells, and Touton giant cells as well as histiocytes, lymphocytes and eosinophils (H&E stain; ×100).

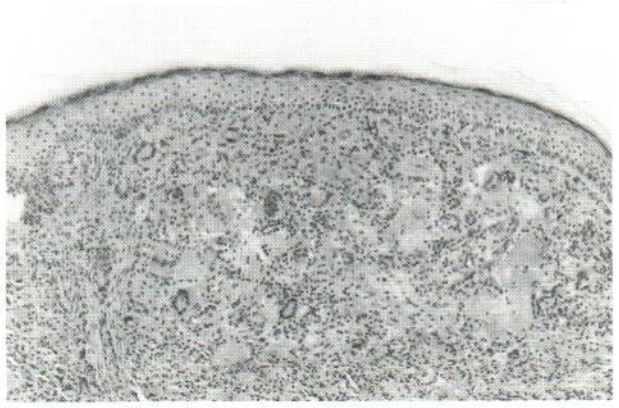

Fig. 4. Regressing flattened lesion (4th biopsy); the increased number of inflammatory cells and the decrease of the total number of giant cells are noted (H&E stain; ×100).

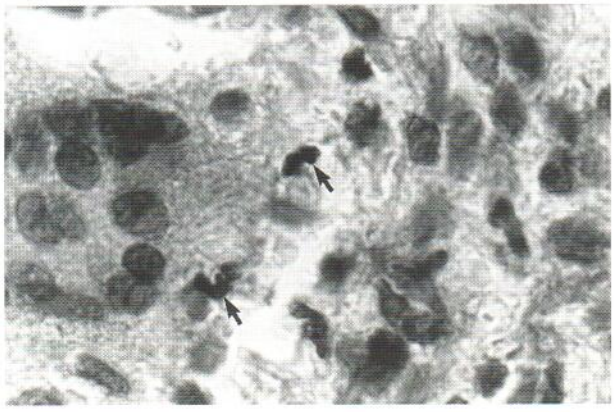

Fig. 5. Magnified light microscopic view of Sézary-like atypical lymphocytes (H&E stain; ×1000).

DISCUSSION

There have been many reports on ultrastructural examinations of juvenile xanthogranuloma lesions, describing the presence of many elongated and irregular dense bodies in histiocytes (3) and varying numbers of vacuolar lysosomal structures in

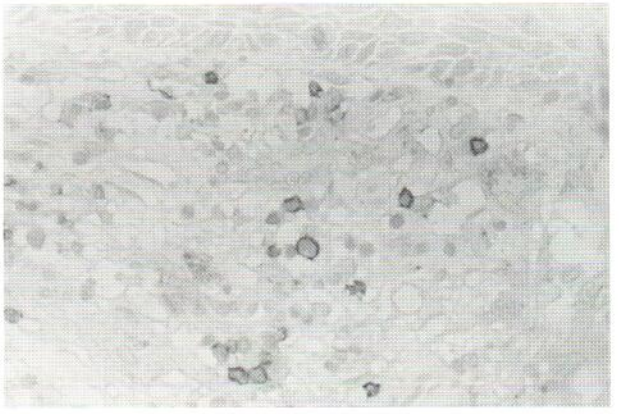

Fig. 6. In an early lesion, UCHL-1$^+$ cells are observed in the dermis, especially around giant cells (immunoperoxidase stain; ×200).

Fig. 7. In a regressing lesion, an increased number of UCHL-1$^+$ cells are observed compared with early lesions (immunoperoxidase stain; ×200).

Fig. 8. Sézary-like atypical lymphocyte (*L*). Note the close apposition (*arrow*) between the plasma membrane of the Sézary-like atypical lymphocyte and the nuclear membrane of the vacuolated degenerating histiocyte (*H*) (TEM × 2,500).

macrophages containing lipid which is not bounded by trilaminar membrane (4–6). However, there have been very few ultrastructural studies reported in the literature that might provide clues explaining the process involved in the spontaneous involution of juvenile xanthogranuloma.

In the sequential immunohistochemical staining of our clinical specimen of juvenile xanthogranuloma, we observed a progressive increase in the number of UCHL-1$^+$ lymphocytes in regressing stage lesions compared to early stage lesions. In electron microscopic examinations, we observed that interestingly, in the regressing lesion, the cells with highly indented nuclei – which we describe as Sézary-like cells – were in close apposition to vacuolated degenerating histiocytes in many foci. We also observed a close apposition between the plasma membrane of the Sézary-like atypical lymphocyte and the nuclear membrane of the histiocyte. Identical to the findings from the immunochemical staining, these Sézary-like atypical lymphocytes were rarely seen in the early lesions of juvenile xanthogranuloma.

The Sézary-like atypical lymphocytes with highly indented nuclei are thought to be similar to those observed in Sézary syndrome (7) and mycosis fungoides (8). They are "transformed" T-cells (9) and are also detected in a variety of non-lymphomatous dermatoses (10–12). Although the significance of these atypical lymphocytes has not yet been clarified, two possible roles were suggested by Flaxman et al. (10). First, it is indeed a cell of malignant character. Second, it is a non-malignant cell whose altered nuclear morphology identifies a particular functional role brought forth by certain conditions. The appearance of Sézary-like cells in benign inflammatory dermatoses, as well as in malignant disease, indicates that a common mechanism exists for such a similar change of morphology. Crossen et al. (13) showed that Sézary cells could be stimulated by phytohemagglutinin to vigorous nuclear activity, indicating active DNA synthesis and subsequent cell mitosis. It is now well known that the production of Sézary-like cells from normal human lymphocytes suggests that the cells with cerebriform nuclei may represent reactive lymphocytes.

From the electron microscopic observation in this case, we speculate that these Sézary-like atypical lymphocytes may be closely related to the spontaneous regression of juvenile xanthogranuloma. The fact that the Sézary-like atypical lymphocytes appear to be increased in late regressing stage lesions and not in early stage lesions suggests that the histiocytes of juvenile xanthogranuloma may send messages and stimulate T-cells to induce morphologic transformation. In due course, these transformed lymphocytes would act in suppressing the growth of tumorous lesions. However, this is a hypothesis, and the significance and function of these Sézary-like atypical lymphocytes involved in the process of involution will need further clarification.

We have reported an interesting sequential observation of Sézary-like atypical lymphocytes identified as UCHL-1$^+$ T-lymphocytes, suggesting that they perform a role in the regression of juvenile xanthogranuloma. These morphologic findings could provide a basis for in-depth studies of the involutional process of juvenile xanthogranuloma.

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