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The Omenn's syndrome: histological, immunohistochemical and ultrastructural evidence for a partial T cell deficiency evolving in an abnormal proliferation of T lymphocytes and S-100+/T-6+ Langerhans-like cells

L.P. Ruco [1], A. Stoppacciaro [1], F. Pezzella [1], M. Mirolo [1], S. Uccini [1], P. Barsotti [2], A.M. Cassano [1], A.L. Boner [4], L. Businco [3], A. Di Fazio [3], and C.D. Baroni [1]

IV Chair of Pathological Anatomy, Immunopathology [1] and Ultrastructural Pathology [2] Sections, Department of Human Biopathology and Department of Pediatrics [3], School of Medicine, University "La Sapienza", I-00161 Rome, Italy

[4] Department of Pediatrics, "Borgo Roma" Hospital, I-37134 Verona, Italy

Summary. A 7 month old female infant was affected by a rapidly fatal familial disease highly reminiscent of Omenn's syndrome. She presented with widespread eczematous lesions, hepatosplenomegaly, superficial lymphadenopathy, peripheral blood lymphocytosis, eosinophilia and hyper-IgE. An axillary lymph node was involved by a marked proliferation of T-3+/T-10− lymphocytes admixed with S-100+/T-6+/Leu-3a+/Ia+ reticular cells which lacked typical LC granules; cell suspension study revealed that 90%–96% of the lymph node cells were T-11+/T-3+ lymphocytes characterized by low expression of Leu-3a and T-8 antigens and by high expression of Ia antigens (52%). Peripheral blood T lymphocytes exhibited a similar distribution of surface phenotypes. The patient died of interstitial pneumonia and an autopsy was performed. The thymus was markedly atrophic and completely devoid of lymphocytes. The peri-arteriolar lymphoid sheets of the spleen were poorly developed and were mainly composed of T-8+ lymphocytes. The mediastinal nodes were rudimentary and were populated by T-3+/T-10+ lymphocytes with low expression of Leu-3a and T-8 antigens. Our results raise the possibility that Omenn's syndrome is a peculiar primary immunodeficiency in which, despite early thymic involution, some abnormal T lymphocytes still develop in the peripheral lymphoid organs. Antigenic triggering of these cells might result in prominent proliferations of T lymphocytes and Langerhans-like cells which lead to the clinical manifestation of the disease.

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Offprint requests to: L. P. Ruco, IV Cattedra di Anatomia Patologica, Viale Regina Elena 324, I-00161 Roma, Italy

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Introduction

The Omenn's syndrome is a rare, rapidly fatal congenital familial disease which is characterized by skin lesions, severe infections, superficial lymphadenopathy, hepatosplenomegaly and leucocytosis with eosinophilia (Omenn 1965). In most of the cases, autopsy findings have revealed a combined immunodeficiency documented by severe dysplasia of the thymus and by profound lymphocyte depletion of the peripheral lymphoid tissues (Barth et al. 1972; Ochs et al. 1974). In these patients, the existence of an immune disorder was also supported by variable degrees of hypogammaglobulinemia with elevated serum IgE levels, by poor or absent mitogen and MLC (Mixed Leucocyte Culture) reactivity of lymphocytes, and by decreased T-4:T-8 ratios in the peripheral blood (Ochs et al. 1974; Karol et al. 1983).

In the present report, we describe the histological and immunohistochemical patterns of the lymphoid tissues obtained from a 7 month old female infant affected by Omenn's syndrome. Our results suggest that this entity represents a peculiar form of partial immunodeficiency in which the rudimentary T cell system is still able to be triggered by endogenous and/or exogenous antigenic stimuli resulting in abnormal proliferative responses.

Materials and methods

One axillary lymph node was obtained ante-mortem for diagnostic purposes; all the other organs were taken at the autopsy. Representative portions of fresh tissue fragments were snap-frozen, cryostat-sectioned and briefly acetone-fixed. The remaining portions were routinely processed for paraffin sectioning. SMIg+ cells were identified by PAP technique using anti-light chain (kappa and lambda) and anti-heavy chain (mu, gamma, delta) rabbit polyspecific sera (Miles Yeda, Rehovot, Israel). A three-stage biotin-avidin staining system (Wood and Warnke 1981) was used for the immunological phenotyping with T-3, T-6, T-8, T-10, T-11, Ia-1 (Ortho Diagnostics, Raritan, NJ, USA), Leu-3a (Becton Dickinson, Sunnyvale, CA) and B-1 (Coulter Electronics, Inc., Hialeah, FL, USA) murine monoclonal antibodies. Briefly, frozen-sections were sequentially stained with monoclonal antibodies, followed by purified biotinylated horse anti-mouse IgG (H and L chains) (Vectors Laboratories, Inc., Burlingame, CA, USA), followed by avidin-horseradish peroxidase conjugate (Vector Laboratories, Inc.). After each stage sections were washed in PBS. Horseradish peroxidase was visualized by incubation of frozen sections in 0.06% 3,3-diamino-benzidine (DAB) in 0.03% H_2O_2 in PBS. All sections were incubated with DAB for 5 min to minimize variations in background staining. Immunological reagent titers ranged from 5 to 50 μg/ml. Cryostat sections were also stained for α-naphtyl-acetate esterase (ANAE), for acid phosphatase (AP) and for endogenous peroxidase. Immunoperoxidase staining for cytoplasmic immunoglobulin light chains, muramidase, S-100 protein (Dakopatts, Denmark) and prekeratin was carried out on paraffin sections using the PAP technique (Sternberger et al. 1970). The guinea pig anti-human prekeratin polyspecific serum was kindly provided by Sclavo, Siena, Italy. Cell suspension studies were performed on mononuclear cells separated by Ficoll-hypaque technique from the axillary lymph node and from the peripheral blood. Indirect immunofluorescence was used to enumerate the proportions of mononuclear cells expressing antigens detected by the following monoclonal antibodies: T-11, T-3, Leu-3a, T-8 and Ia-1. Cytocentrifuge smears of the lymph node cell suspension were acetone-fixed and stained with monoclonal antibodies as described for frozen

sections. Additional lymph node fragments were processed for electron microscopy by fixation in buffered paraformaldehyde, post-fixation in osmium-tetroxide and embedding in Epon. Ultrathin sections from selected blocks were treated with uranyl-acetate and lead citrate.

Results

Clinical findings

The patient was born in a mountain village in northern Italy from related parents (second cousins of an inbred family). Of three siblings, one sister died at the age of 4 months of a disease characterized by widespread skin eruptions, oral candidiasis, hepatosplenomegaly, diarrhoea, severe malnutrition, anaemia and interstitial pneumonia. The haematological investigations revealed anaemia (Hb: 6.9 g/dl), peripheral blood leucocytosis (Total WBC: 25×10^9 leucocyte/l) with eosinophilia (10×10^9 eosinophil/l) and hypogammaglobulinaemia with elevated IgE (IgA 9.04 mg/dl; IgG 105 mg/dl; IgM 51.6 mg/dl; IgE 4800 IU/ml). An autopsy was not performed. One 3-yr-old brother is alive and in good health.

The patient was delivered vaginally after a full-term uncomplicated pregnancy and had a birth weight of 3240 g. She was breast-fed and gained weight normally until the age of 40 days when she developed erythematous lesions on the face. At the age of 3 months she was hospitalized because of diffuse eczematous skin lesions and severe diarrhoea. The physical examination revealed scaly, itching dermatitis oozing serous fluid, superficial lymphadenopathy, hepatosplenomegaly and oral candidiasis. The haemogram revealed peripheral blood leucocytosis (Total WBC: 23.7×10^9 leucocyte/l) with eosinophilia (11×10^9 eosinophil/l). Serum levels of IgG, IgA and IgM were in the normal range, but serum IgE was markedly increased (1845 IU/ml). A lymph node biopsy was taken for diagnostic purposes. Despite therapy, the patient died at the age of 7 months of interstitial pneumonia. Adenosine deaminase and purine nucleoside phosphorylase activities in erythrocytes were normal. HLA typing failed to reveal the presence of circulating maternal cells.

Lymph node biopsy

The axillary lymph node was markedly enlarged and showed architectural effacement due to diffuse proliferation of clear cells and lymphocytes (Fig. 1). The clear cells were characterized by abundant cytoplasm, round, oval or lobated nuclei, finely dispersed nuclear chromatin and distinct nucleoli (Fig. 1, inset). Immunoperoxidase staining revealed that most of these cells were S-100+, T-6+ and Ia+ (Fig. 2a–c) thus suggesting that they were closely related to Langerhan's cells (LC) (Rowden et al. 1977; Fithian et al. 1981; Takahashi et al. 1981; Wood et al. 1983).

Characterization of the large cells on cytocentrifuge smears confirmed the observations made on tissue sections and allowed us to establish that the T-6+ cells were also diffuse or dot Leu-3a+, dot AP+, weakly ANAE+ and muramidase negative (Fig. 3a–d).

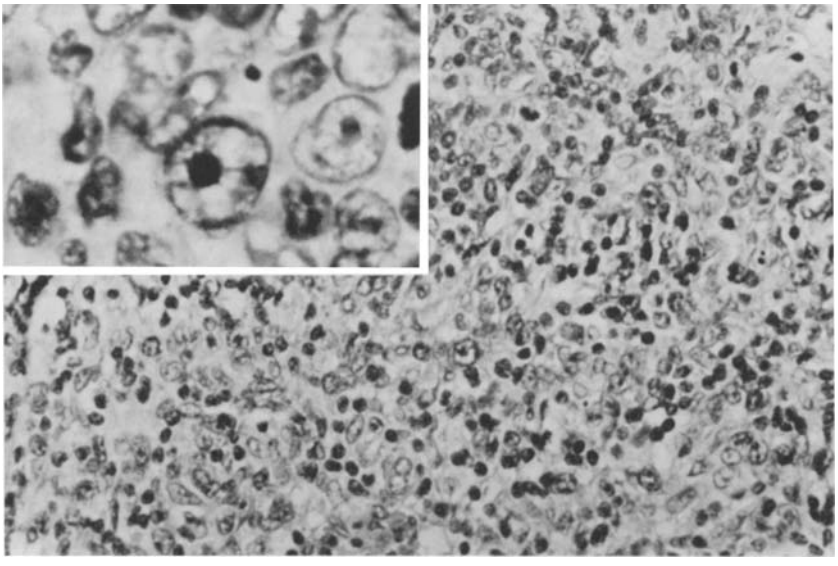

Fig. 1. Axillary lymph node. The architecture is completely effaced by a diffuse proliferation of clear cells and lymphocytes (H & E, ×250). The clear cells have round, oval, or lobated nuclei with finely dispersed chromatin and distinct nucleoli (Inset: H & E, ×1000)

The lymphoid cell component was mainly constituted of mature T lymphocytes which were recognized by T-11, T-3, Leu-3a and T-8 antibodies (Fig. 4a–c); the Leu-3a staining was more evident than the T-8 staining probably because of the presence of numerous large Leu-3a+ cells (Fig. 3b, c). The Ia reactivity was present in the reticular cells and in many lymphoid cells as well (Fig. 2c). Germinal centers were not present, but few small collections of T-3 negative centrocyte-like cells reminiscent of primary follicles (Fig. 4d) were observed; however, we were unable to demonstrate the B-cell origin of these structures by SMIg or B-1 staining. Macrophages laden with melanin pigment and numerous eosinophils were also noted. Plasma cells and T-10+ cells were never observed. Mitoses were frequent and always normal.

The TEM study revealed the presence of round cells with abundant electron-lucent cytoplasm containing polysomes, few ribosomes and mitochondria; the nuclei were fairly regular with finely dispersed chromatin and multiple nucleoli with prominent fibrillar centers (Fig. 5a). Other cells, were characterized by reticular shape, by irregular nuclei with finely dispersed chromatin and small nucleoli, and by the presence in the cytoplasm of short strands of rough endoplasmic reticulum, free ribosomes, few lysosomes and some microfilaments (Fig. 5b). Typical LC granules were not identified; however, rod-shaped profiles containing electron-dense amorphous material were occasionally observed (Fig. 5b, inset). Tubulo-reticular structures (TRS) were frequently detected in the cytoplasm of endothelial and lymphoid cells (Fig. 6).

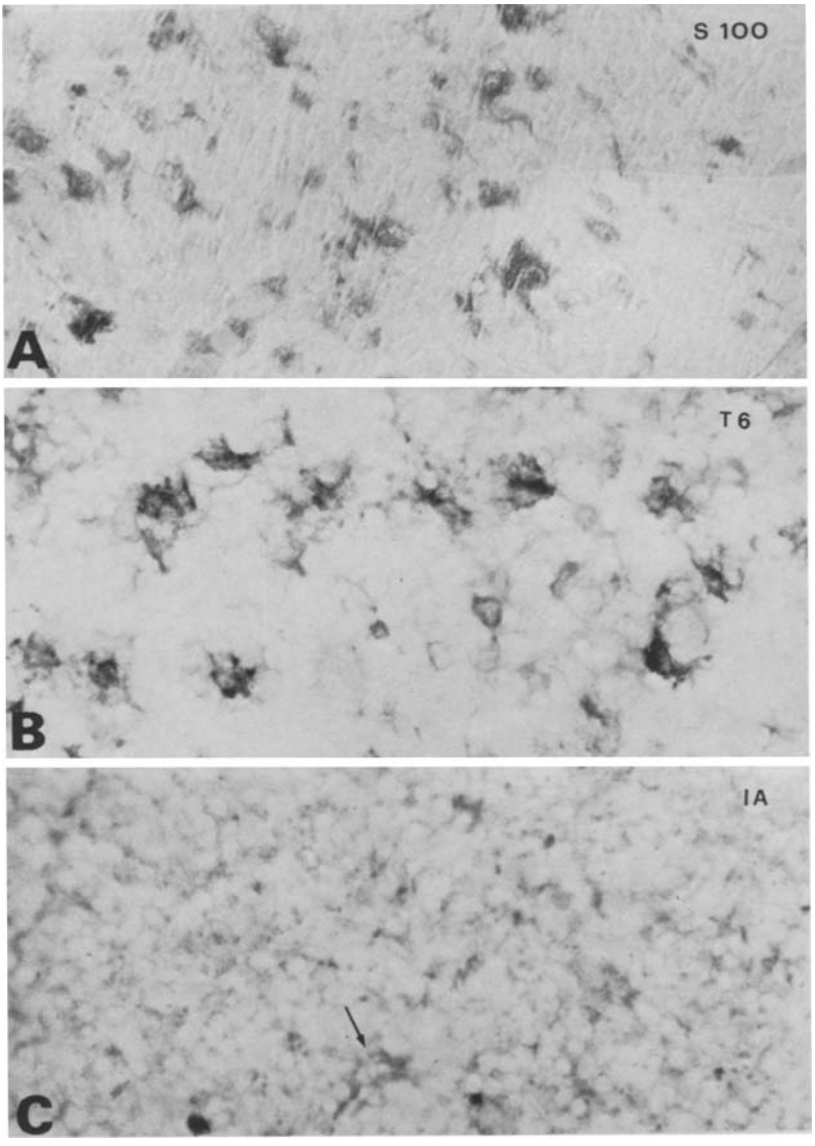

Fig. 2. Axillary lymph node. Immunoperoxidase stainings show numerous reticular cells with reactivity for S-100 protein **A**, T-6 **B** and Ia (**C**, *arrow*). Several Ia+ lymphocytes are also present. (Indirect immunoperoxidase method, ×250)

The relative proportions of the T-cell subsets was estimated by indirect immunofluorescence on cell suspensions prepared from the lymph node and from the peripheral blood (Table 1). In both tissues, it was found that the cell population was mostly composed of T-11+/T-3+ cells, that the Leu-3a(T-4):T-8 ratio was respectively 1.5 and 1, that a consistent percentage (20%) of T-11+ cells was Leu-3a and T-8 negative, and that about 50% of T-11+ lymphocytes were also Ia+.

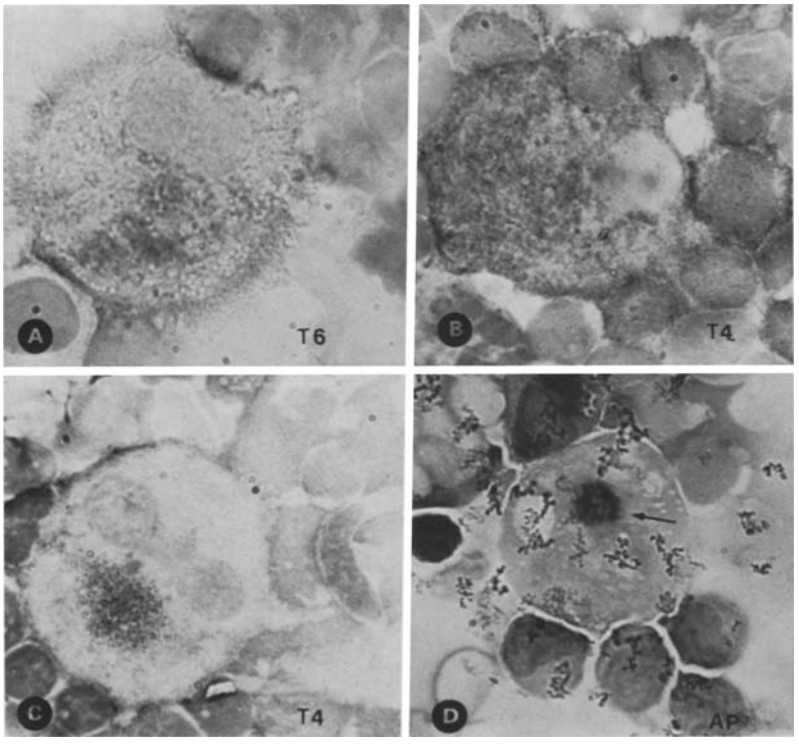

Fig. 3. Cytocentrifuge smears from the axillary lymph node. The majority of the large cells are T-6+ **A** and Leu-3a(T-4)+ **B, C**. The immuno-reactivity for Leu-3a is either diffuse **B** or dot-like **C** (Indirect immunoperoxidase method, counterstained with haematoxylin, ×1000). Round spots of acid phosphatase activity (**D**, *arrow*) are present in some large cells. (Acid phosphatase staining, counterstained with haematoxylin, ×1000)

Autopsy findings

Thymus. The fatty tissue obtained from the thymic area contained atrophic thymic lobules which were separated by fibro-adipose septa; Hassall's bodies were absent. In some lobules, signs of cortico-medullary "stromal" differentiation (Grosseye et al. 1983) were evident (Fig. 7a). This histological pattern was probably due to a higher density of prekeratin positive cells in the cortical area (Fig. 7b) and to the presence of numerous ANAE+/AP+ cells in the medullary zone (Fig. 7c). In a few lobules, numerous large myeloperoxidase positive mononuclear cells were present (Fig. 7d). S-100+ cells were extremely rare and were always located in the medulla. The lymphoid component of the thymus was completely absent as demonstrated by the negative staining with T-11/T-3/Leu-3a/T-8/T-6/T-10 monoclonal antibodies.

Spleen. The histology of the spleen was characterized by absence of germinal centers, by small periarteriolar lymphoid sheets (PALS), by red pulp congestion and by prominence of the fibrous septa. Heavily erythrophagocytic

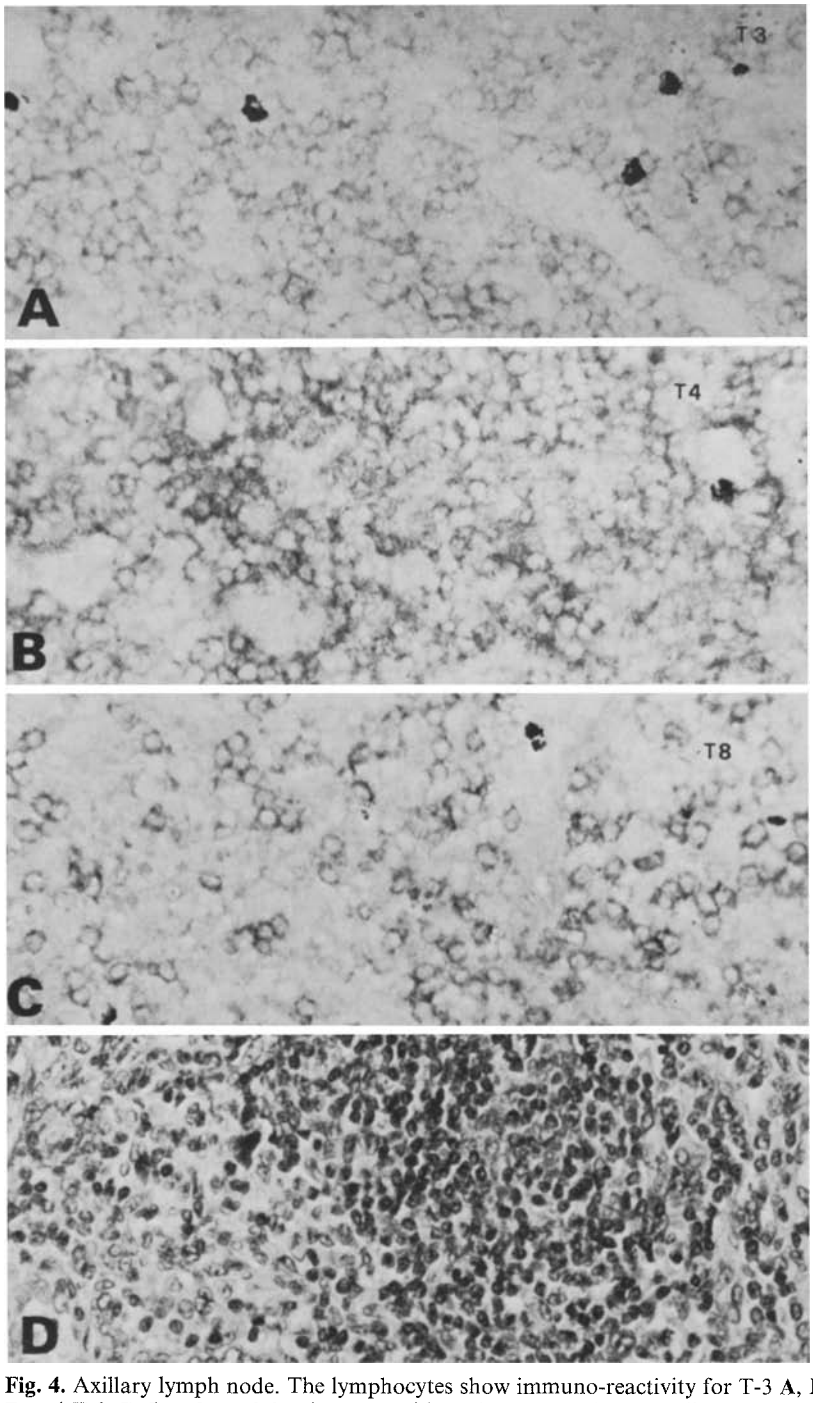

Fig. 4. Axillary lymph node. The lymphocytes show immuno-reactivity for T-3 **A**, Leu-3a(T-4) **B** and T-8 **C**; Leu-3a staining is more evident than T-8 staining (Indirect immunoperoxidase staining $\times 250$). Few small collections of T-3 negative centrocyte-like cells are occasionally observed **D** (H & E, $\times 250$)

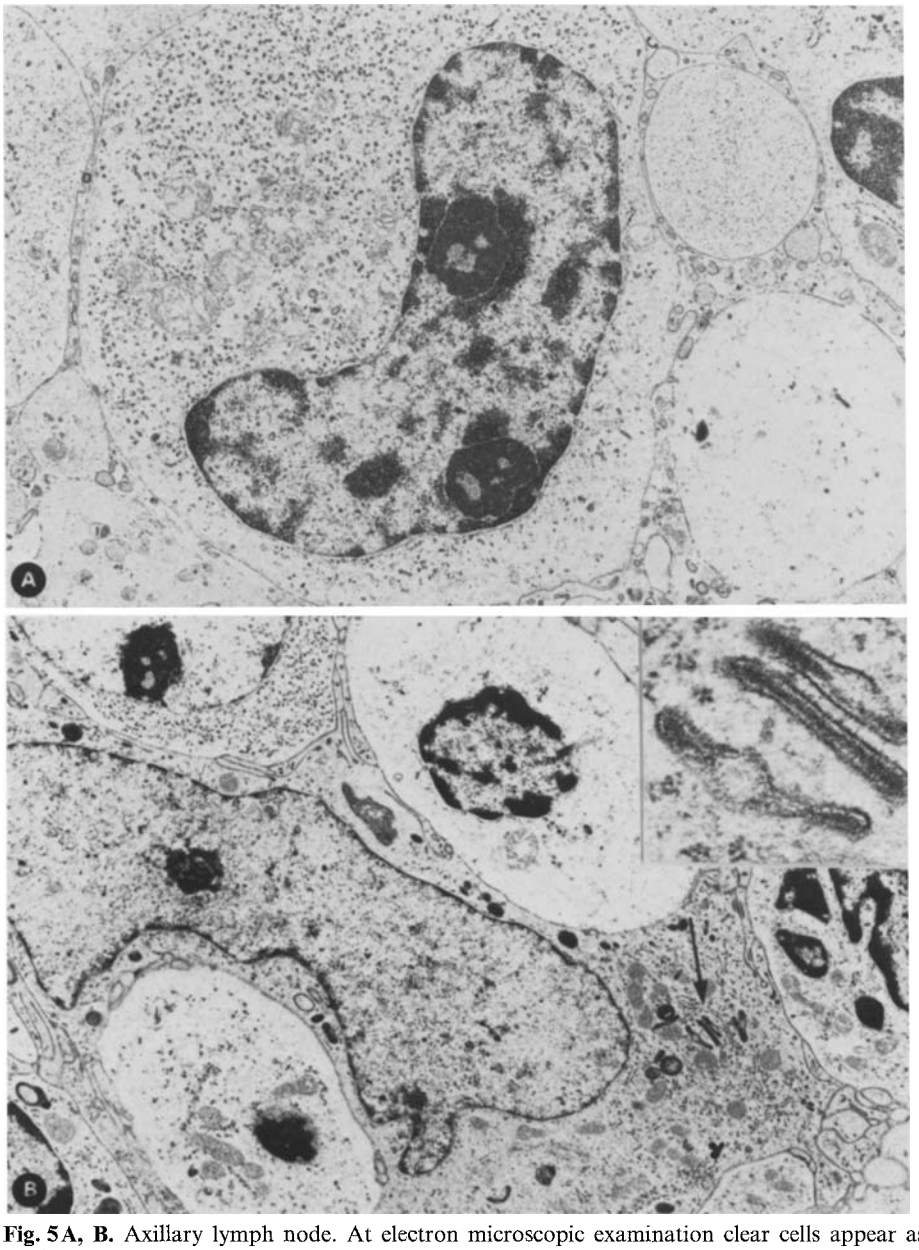

Fig. 5A, B. Axillary lymph node. At electron microscopic examination clear cells appear as undifferentiated or reticular elements. Note the large round cell with two prominent nucleoli and abundant cytoplasm rich in polysomes (**A**, × 8000). An elongated cell with irregular nucleus, a small nucleolus and numerous cytoplasmic organelles is shown in **B** (× 7000). Note the numerous interdigitating cellular processes and the intracytoplasmic rod-shaped granules (See *arrow* and detail in the inset, × 52000)

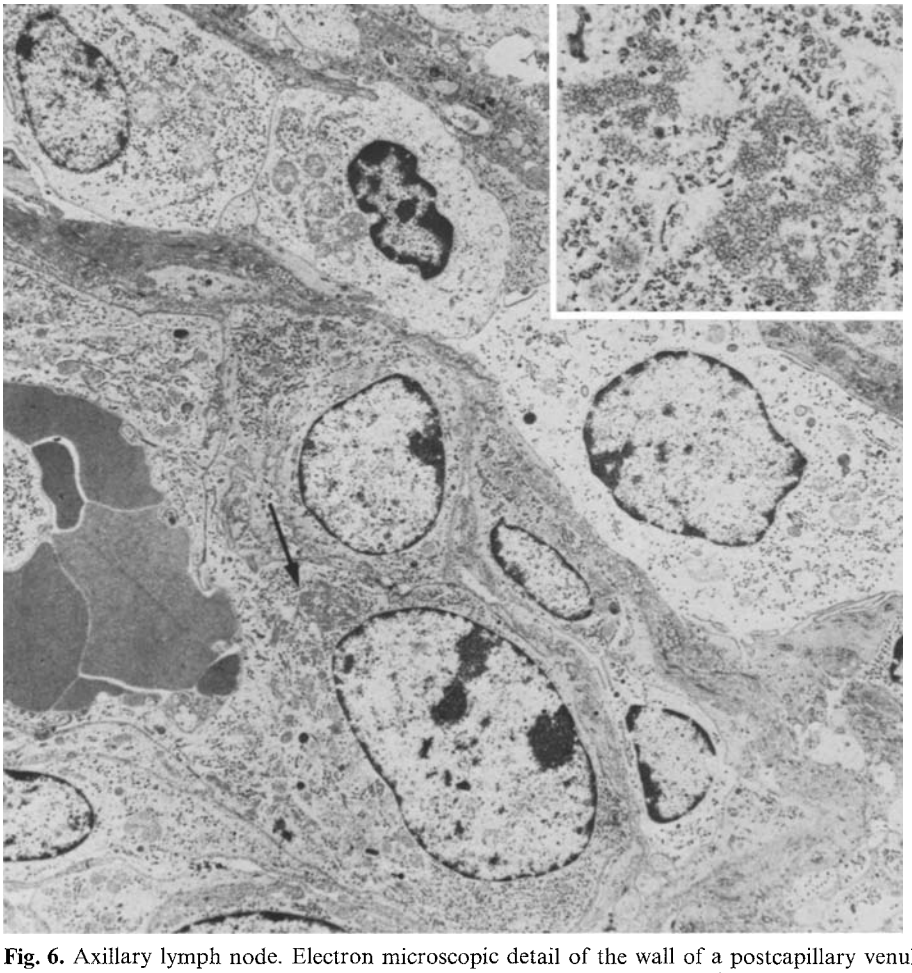

Fig. 6. Axillary lymph node. Electron microscopic detail of the wall of a postcapillary venule demonstrating tall hypertrophic endothelial cells. These elements are characterized by large oval nuclei and abundant cytoplasm containing numerous organelles (× 4500). Their cytoplasm may also contain tubuloreticular structures (See *arrow* and detail in the inset, × 19000)

Table 1. Immunological characterization with monoclonal antibodies of cell suspensions obtained from peripheral blood and from the axillary lymph node

Source of cells	T11	T3	T4	T8	Ia	T4/T8
PBL	82[a]	79	37	25	46	1.5
Lymph node	96	90	40	38	56	1.0

[a] Percentage of positive cells was estimated by indirect immunofluorescence

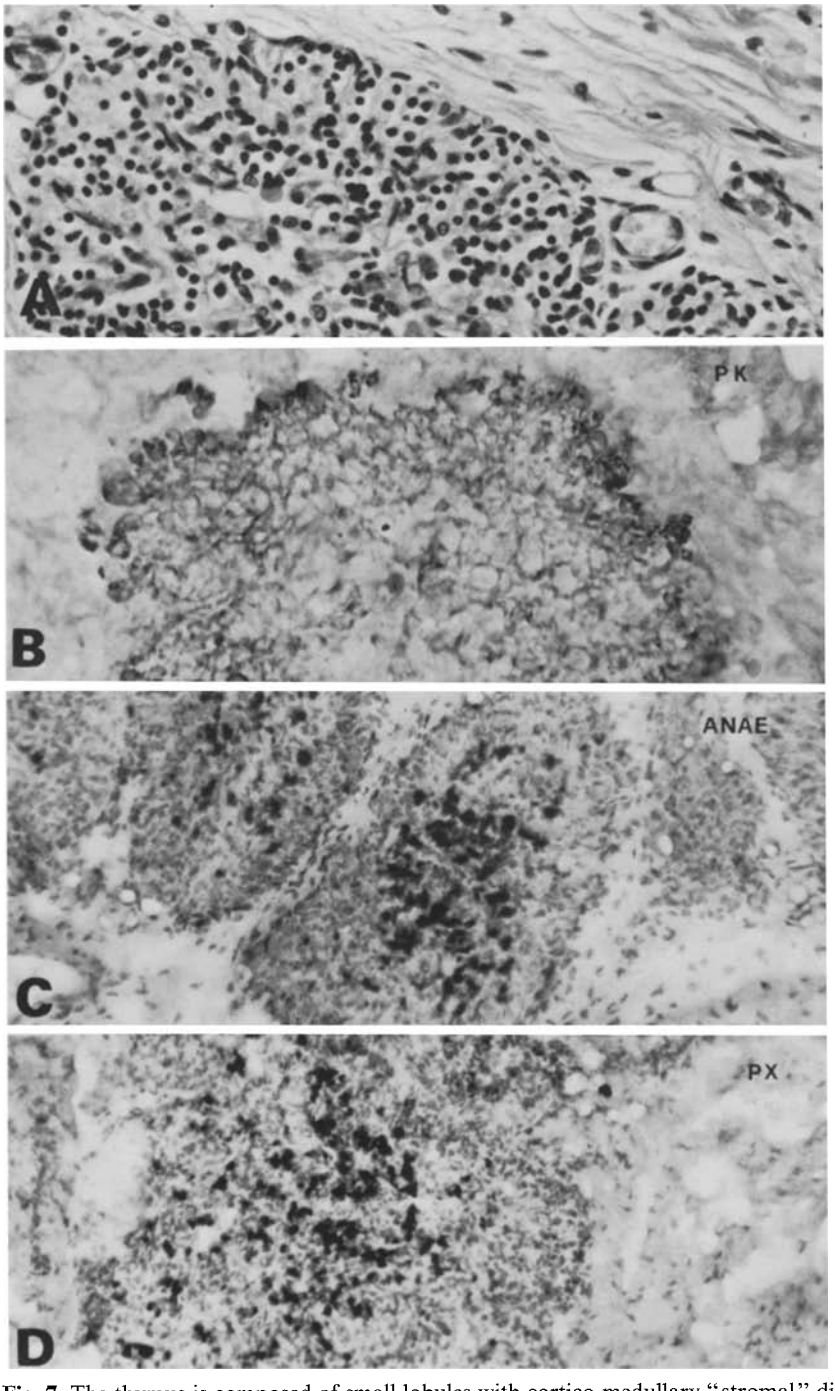

Fig. 7. The thymus is composed of small lobules with cortico-medullary "stromal" differentiation **A** (H & E, ×250). Immuno-reactivity for prekeratin is more evident in the cortical area **B** (Indirect immunoperoxidase method, ×250). The medullary area is occupied by numerous ANAE+ cells **C** (α-naphtyl acetate esterase staining, counterstained with haematoxylin, ×250). Several large peroxidase positive cells are present in a minority of the lobules **D** (Peroxidase staining, counterstained with haematoxylin, ×250)

macrophages and eosinophils were the prevalent cell types in the red pulp. The PALS were mainly composed of T-8+ lymphocytes and were surrounded by ANAE+/AP+ cells. T-3+ and Leu-3a+ cells were found scattered throughout the spleen; few S-100+ cells were present in the PALS and in the red pulp as well.

Superficial lymph nodes. The morphological and immunohistochemical features of right and left inguinal nodes were similar to those observed in the diagnostic lymph node biopsy.

Mediastinal lymph nodes. The mediastinal nodes were characterized by an "empty" appearence; germinal centers and primary lymphoid follicles were completely absent. The cellular population was mainly composed of reticular and lymphoid cells. The reticular cells were Leu-3a+, T-6− and muramidase negative; a minority of these cells was S-100+. The lymphoid cell component was composed of T-3+ and T-10+ cells; the T-10 antigen was present on the majority of scattered lymphocytes and on some large round cells grouped in small clusters. Leu-3a+ and T-8+ lymphocytes were observed, but were less numerous than T-3+/T-10+ cells. T-6+ lymphocytes were absent. Rare CIg+ plasma cells, numerous eosinophils and some large muramidase positive mononuclear cells were also noticed. The subcapsular and medullary sinuses were distended and were lined by a single layer of ANAE+ cells.

Large intestine. Solitary lymphoid follicles and Peyer's patches could not be detected in the intestinal tract. Plasma cells and lymphocytes were virtually absent in the intestinal mucosa.

Bone marrow. The haematopoietic tissue was characterized by severe hypoplasia of the erythroid cell lineage and by marked hyperplasia of myeloid and eosinophil cell lineages. Few megakaryocytes were present. Nodular aggregates of lymphocytes were observed.

Skin. The skin was involved by chronic, non-specific, lichenoid dermatitis. The epidermis was slightly atrophic. Satellite cell necrosis was absent. Band-like lymphomononuclear infiltrates were present at the dermo-epidermal junction, around skin-appendages and around small vessels. These infiltrates were mainly composed of T-4+ and T-8+ lymphocytes intermixed with few large S-100+ cells.

Liver. The enlarged liver was nearly normal. Mild fatty changes of the hepatocytes and small infiltrates of lymphomononuclear cells in the portal tracts were the main features. S-100+ cells were absent.

Lungs. Microscopic examinations of the lungs demonstrated bilateral extensive interstitial pneumonia with the characteristic honey-combed alveolar exudate of Pneumocystis carinii. Plasma cells and S-100+ cells were virtually absent.

Discussion

The Omenn's syndrome was first described in 1965 as a familial form of reticuloendotheliosis (Omenn 1965). A subsequent report (Barth et al. 1972), demonstrating that the systemic histiocytosis was associated with a primary immunodeficiency, raised the possibility that this syndrome might represent either a variant of Letterer Siwe disease, or a GVHD in infants with SCID or a distinct entity. More recently (Wyss et al. 1982), the hypothesis of histiocytosis X was eliminated on histological and ultrastructural grounds, whereas the GVHD was not supported by the failure to demonstrate circulating maternal cells with HLA typing. In the same case, it was found that the T lymphocytes present in the peripheral blood were abnormal cells characterized by low expression of T-4 and T-8 antigens and by high expression of Ia antigens. This observation led to suggest that Omenn's syndrome might derive from a benign proliferation of immature T lymphocytes possibly due to early thymic involution and/or to extrathymic T cell differentiation.

In our case HLA typing confirmed the absence of maternal cells. Moreover, our data strongly suggest the existence of a partial T cell defect. In fact, though the thymus was markedly atrophic and completely devoid of lymphocytes, the mediastinal nodes still contained numerous T-3+ and T-10+ cells characterized by low expression of Leu-3a(T-4) and T-8 antigens. Furthermore, the T lymphocytes present in the peripheral blood and in the axillary lymph node exhibited the same unusual phenotype distribution of the mediastinal nodes (20% of T-11+/T-3+ cells were negative with both Leu-3a and T-8 antibodies), but differed in as much that they were T-10 negative. These findings suggest that peripheral blood and superficial and mediastinal nodes were all populated by the same abnormal T lymphocytes which, however, presented different degrees of maturation. In fact, the high content of T-3+/T-10+ cells in the mediastinal nodes is similar to that observed in the peripheral lymphoid organs of 16–20 week fetuses (Asma et al. 1983) and is probably indicative of a maturation delay. The absence of T-10 antigen on T lymphocytes present in superficial nodes might be explained either by micro-enviromental factors or by antigen driven differentiation. We believe that the role of antigenic stimulation is strongly supported by the hyper-IgE and by the abnormally high number of "activated" Ia+ T lymphocytes.

The histological pattern of the axillary lymph node was extensively studied. It was demonstrated that the lymph node architecture was completely effaced by a mixed cell population composed of lymphocytes and of clear cells with abundant cytoplasm. These latter cells were already noted in other cases of Omenn's syndrome and were interpreted either as histiocytes (Barth et al. 1972) or as immature T cell blasts (Wyss et al. 1982). Our data indicate that the clear cells lacked typical LC granules, but were characterized by the same antigenic and enzymatic profile as Langerhan's cells (Rowden et al. 1977; Fithian et al. 1981; Takahashi et al. 1981; Wood et al. 1983). Prominent proliferations of S-100+/T-6+ cells have been de-

scribed in histiocytosis X (Beckstead et al. 1984) and in dermatopathic lymphadenitis (Rausch et al. 1977; van den Oord et al. 1984). The absence of X bodies in the reticular cells, the cellular pleomorphism of the lesion, the prominent presence of T lymphocytes, the selective involvement of superficial nodes and the concomitant chronic dermatological affection are all elements which fail to support the diagnosis of histiocytosis X. Furthermore, the presence of TRS in lymphoid and endothelial cells was previously described in systemic immune disorders such as SLE (Gyorkey et al. 1971) and AIDS (Anderson et al. 1984), and was never reported in histiocytosis X. Thus it seems likely that the superficial nodes were involved by dermatopathic lymphadenitis associated with the chronic dermatological affection. However, it should be emphasized that abnormal T cell functions were recently demonstrated in 12/17 patients affected by histiocytosis X and that in 5/7 patients histological alterations of the thymus were also noted (Osband et al. 1981). These data may indicate that some abnormal proliferations of Langerhan's cells are closely related to a profound imbalance of the T cell system, and may suggest that a clear-cut distinction between these two disorders is not always possible. Independently of the nosologic definition, it seems likely that peripheral T lymphocytosis, hyper-IgE, striking eosinophilia, chronic dermatitis and superficial lymphadenopathy are all expressions of an abnormal immune reaction. A similar immune disorder has been described in the hyper-IgE syndrome (Buckley et al. 1972; Businco et al. 1979); however, inheritance, early onset of the symptoms and severity of the clinical course allow us to differentiate Omenn's syndrome from the hyper-IgE syndrome.

In conclusion, our results indicate that the Omenn's syndrome is characterized by clinical, immunological and histopathological features which allow us to differentiate it from other SCID syndromes. It can be speculated that this immune disorder results from antigenic triggering of poorly developed T lymphocytes in the absence of proper regulatory mechanisms. This interpretation is strongly supported by the observation (Akhter et al. 1981) that a SCID patient developed skin lesions, systemic lymphadenopathy, hepatosplenomegaly and peripheral blood T lymphocytosis after repeated immunizations with diphtheria and tetanus toxoid.

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