

Eosinophilic Granuloma Associated with a 16q22 Chromosomal Defect of Cutaneous T Lymphocytes

SUSANNE BISBALLE,¹ KRISTIAN THESTRUP-PEDERSEN,² PETER BJERRING,² JØRGEN J. JENSEN,² PETER D. OTTOSEN³ and KELD KALTOFT¹

¹*Institute of Human Genetics, University of Aarhus,* ²*Department of Dermatology, Marselisborg Hospital, DK-8000 Aarhus C. and* ³*University Institute of Pathology, Aarhus Kommunehospital, University of Aarhus, Aarhus, Denmark*

Bisballe S, Thestrup-Pedersen K, Bjerring P, Jensen JR, Ottosen PD, Kaltoft K. Eosinophilic granuloma associated with a 16q22 chromosomal defect of cutaneous T lymphocytes. *Acta Derm Venereol (Stockh)* 1984; 64: 548-551.

A 61-year-old woman presented with circumscribed eczematous eruptions with maceration, erosions and patchy infiltration in the perineum and inframammary regions. A diagnosis of eosinophilic granuloma (cutaneous histiocytosis X) was established. T lymphocytes from a skin biopsy were grown *in vitro* for three weeks after which chromosomal studies revealed a break or gap at chromosome 16q22 in 15% of the lymphocytes. The addition of α -interferon increased the percentage of affected cells to 28%. T lymphocytes from the patient's blood did not show the defect.

The biological significance of the chromosomal defect is uncertain. It has been described before in healthy persons, malignant lymphoma, cold urticaria and IgA deficiency, and mental retardation. It has not been seen in patients with eosinophilic granuloma. (Received April 2, 1984.)

K. Thestrup-Pedersen, Department of Dermatology, Marselisborg Hospital, 8000 Aarhus C, Denmark.

Eosinophilic granuloma is a benign, localized form of histiocytosis X. We have observed a specific chromosomal defect in cutaneous T lymphocytes from a patient with this disease. This defect has not been observed before in histiocytosis X.

CASE REPORT

A 61-year-old woman presented with a one-year-old itching and painful skin eruption in the intertriginous areas of the perineum and inframammary regions. All laboratory examinations were normal including bone marrow aspiration, chest X-ray, and bone scintigraphy. Computerized tomography was performed twice, demonstrating a pathological change in the supracellar cisternal region. It was judged as an aneurism of the basilar artery. A tuberculin skin test was strongly positive (previous Calmette vaccination).

Excision biopsy from the affected areas showed an infiltration of eosinophilic leucocytes with histiocytes in the papillary dermis and epidermis (Fig. 1 *a, b*). Electron microscopy revealed cytoplasmic Birbeck's granules in the histiocytes (Fig. 2).

The patient was initially treated with topical mechlorethamine (application of 10 mg in a volume of 20 ml saline for 15 min), but she quickly became sensitized towards the drug and the treatment had to be cancelled. She was then treated with X-rays receiving a total of 44 Gy, 18 MeV (perineal region) and 20 Gy, 9MeV (inframammary region). This treatment induced almost complete remission. But six months later she had a relapse of symptoms with new eruptions on the back, buttocks, and axillary regions. At the moment she is receiving topical steroids, which relieve some of her worst symptoms.

METHODS

Before therapy was given, a piece of skin was minced with a knife and placed in RPMI 1640 tissue culture medium containing 10% fetal calf serum, 10% human AB serum, and penicillin 100 IU/ml, streptomycin 50 μ g/ml, and 30% T cell growth factor. In short, T cell growth factor was prepared by a modified procedure of Mier & Gallo (1), in which phytohemagglutinin-stimulated lymphocytes after 4 h were extensively washed and the cells further incubated for 48 h. The supernatant was then used as a source of T cell growth factor.

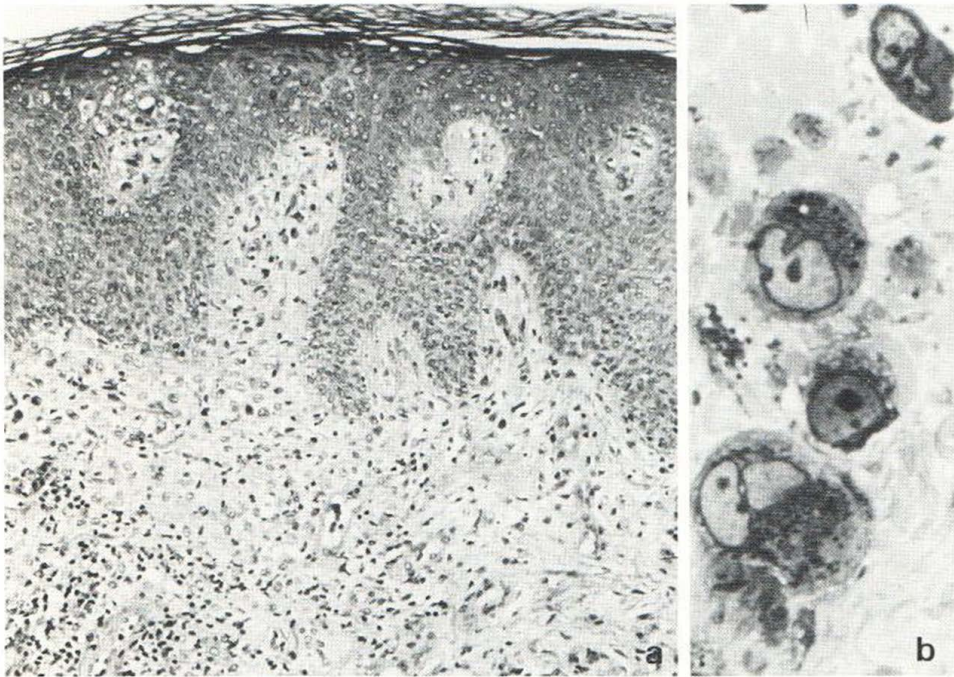


Fig. 1. Light micrograph of skin biopsy from the inframammary region. Large histiocytic cells are seen in the papillary dermis, often close to the epidermis with a few histiocytic cells in the epidermis, too (Fig. 1a: $\times 140$, hematoxylin-eosine). At a higher magnification the histiocytic cells are seen to contain many small granules. The nucleus is often clefted with large nucleoli (Fig. 1b: $\times 1400$, toluidine-blue stained Epon section).

During the following days lymphocytes migrated out from the pieces of skin. These lymphocytes were kept in culture with two weekly changes of culture medium. After three weeks the E-receptor positive lymphocytes (T cells) were grown in the presence or absence of added α -interferon (100 IU/ml) for three days and processed for chromosome analysis according to the quinacrine mustard banding technique (2). Phytohemagglutinin-stimulated lymphocytes from peripheral blood grown in Eagle's minimal essential medium with 30% human A serum were processed similarly for chromosome analysis.

RESULTS

We found that 15% of cutaneous T lymphocytes had a 16q22 chromosomal break or gap. This means that one of chromosome pair 16 has a fragile side on along arm of the chromosome (location 22). The incidence increased to 28% after addition of α -interferon (Fig. 3). The defect was apparently found in a subgroup of T lymphocytes with receptors for IgG (T γ cells), because the incidence of the defect diminished after depletion of the T γ cells. The defect was only seen in one of 114 analysed lymphocytes from peripheral blood and only after addition of α -interferon.

DISCUSSION

Our patient's disease is similar to that of a recently reported patient with eosinophilic granuloma (case 2) (3); chromosomal studies were not done (3).

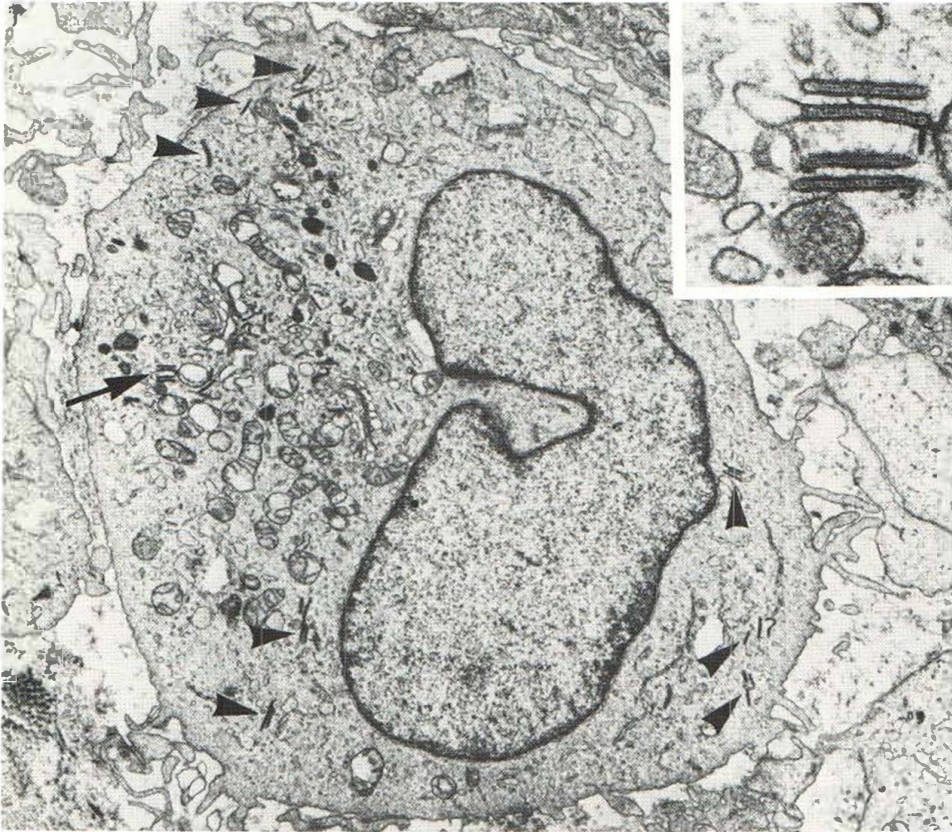


Fig. 2. Electron microscopy showing a histiocytic (Langerhans) cell from the same biopsy (Fig. 1). Many rodshaped granules are present in the cytoplasm (arrowheads). ($\times 6200$.) A large magnification ($\times 20000$) of granules at arrow is shown as inset. The typical structure of Birbeck granules with parallel membranes and a central electron dense line with the characteristic periodicity is demonstrated.

We have previously described a 16q22 chromosomal defect in a boy with an atypical Epstein-Barr virus infection leading to death from a Burkitt-like lymphoma (4). The 16q22 defect was also found in several of the boy's family members (5).

The significance of the defect is not known. It does not seem to be associated with Epstein-Barr virus infections (6). It has previously been described in association with cold urticaria and IgA deficiency (7), mental retardation (8), and may be the locus which controls the concentration of haptoglobin (9).

Recently, an infant with histiocytosis X and retinoblastoma was found to have a deletion of 13q14 \rightarrow q31 in between 27% and 50% of lymphocytes from peripheral blood (10). It is well known that chromosomal defects are present in several patients with retinoblastoma (11). Our patient had a chromosomal defect in lymphocytes from the skin and she did not suffer from other diseases, but histiocytosis X.

In more than 7000 routine analyses of peripheral blood lymphocytes performed at the Institute of Human Genetics, Aarhus, the 16q22 defect has not been observed. However, interferon is not routinely used although γ -interferon is produced by phytohemagglutinin-stimulated lymphocytes and is also present in the T cell growth factor used to amplify the patient's cutaneous lymphocytes.

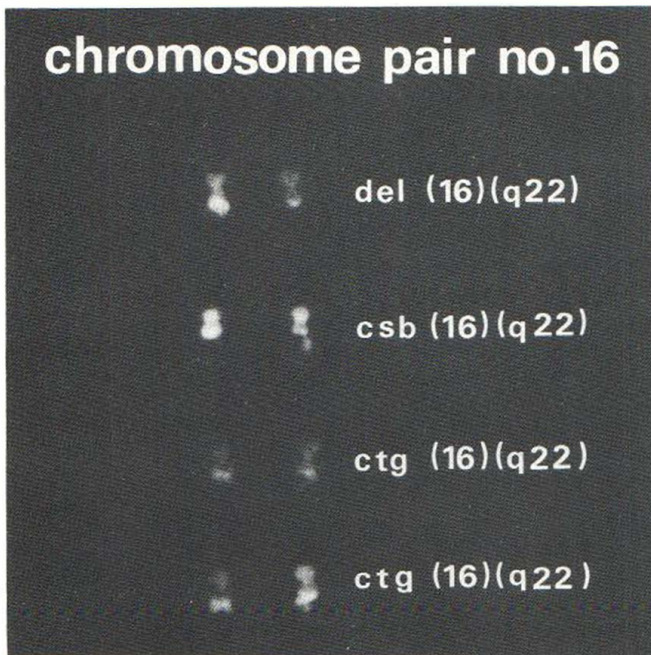


Fig. 3. The picture demonstrates chromosome pair no. 16 with either deletion (del), break (csb), or gap (ctg) at the 16q22 area.

We hope that other patients with eosinophilic granuloma will be studied similarly in order to gain insight into the possible coincidence of a rare, specific chromosomal abnormality with a rare disease.

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