Acta Derm Venereol (Stockh) 1993; 73: 52–54

# Epidermodysplasia Verruciformis Accompanied by Familial Large Granular Lymphocytosis and a Decrease in T Lymphocytes

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**A 40-year-old man with epidermodysplasia verruciformis showed a decrease in peripheral blood T cells and abnormal expansion of large granular lymphocytes, accompanied by increased natural killer cell activity. Surface marker analysis of his large granular lymphocytes demonstrated that the subset, CD 57+ and CD 16+, had increased. His father, who had no skin lesions of epidermodysplasia verruciformis, displayed similar blood changes and his brother showed a decrease in T cells and a slight increase in CD 16+ natural killer cells, whereas his mother revealed only a slight decrease in T cells. Our present study indicates that epidermodysplasia verruciformis might be associated with hereditary abnormal expansion of large granular lymphocytes and a decrease in T cells.**

(Accepted August 3, 1992.)

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Epidermodysplasia verruciformis (EV) is a rare, hereditary disease with lifelong, generalized flat warts caused by human papilloma virus (HPV) infection from childhood. There is no spontaneous regression of flat warts as noted in normal individuals (1), but in about a third of the patients malignant conversion occurs in HPV-infected lesions later in life. Various immunological abnormalities have been reported in patients with EV, e.g. decreased T cell mitogenic response, reduced delayed-type hypersensitivity (DHT) reaction, and increased natural killer (NK) activity (2–5). Recently we reported an EV patient who showed abnormal expansion of large granular lymphocytes (LGL) in addition to these immunological abnormalities (6). Shortly afterwarts we encountered another EV patient who also exhibited an extreme increase in NK activity, accompanied by abnormal expansion of LGL. Further investigation of the peripheral mononuclear cells (MNC) of other members of his family who still had no signs of EV disclosed similar abnormalities together with a decrease in T lymphocytes.

## MATERIAL AND METHOD

### *Patient*

A 40-year-old mentally retarded Japanese man was admitted to our hospital with a diagnosis of EV associated with its malignant conversion. He had first developed white spotty eruptions on his palms in adolescence. At the age of 33 years he began to have scattered reddish papules on the scalp. One of the papules on his left temporal region later became tumorous and oozy.

Physical examination revealed multiple flat whitish papular lesions on the palms (Fig. 1) and posterior neck, and disseminated brownish pityriasis versicolor-like lesions about 10 mm in diameter on the whole scalp and chest. There were many flat non-infiltrated erythematous patches, 5–10 mm in diameter, on the forehead and the frontal and temporal scalp regions. An elevated crusty and partially exudative erythematous lesion, about 5 cm in diameter, was seen on the left temporal region. He had no systemic symptoms except for skin involvements and neurogenic bladder. Biopsy specimens from the palmar flat wart-like lesions showed numerous large cells with pale staining cytoplasm and perinuclear vacuolation in the spinous and granular layers (Fig. 2), resembling the features of the pityriasis versicolor-like lesions, which revealed the typical features of EV. In both types of lesions, HPV antigen (Dako) was demonstrated immunohistologically but no further typing for viral DNAs was performed. He underwent total resection of the tumor on the left temporal region, which was diagnosed as Bowen's disease histologically.

Because the small erythematous patches on the scalp responded poorly to topical treatment with 5% fluorouracil ointment, we started oral administration of etretinate, 40 mg daily. With a gradual disappearance of the lesions, the dosage of etretinate was tapered off to 10 mg daily, with which he has remained almost free lesions for the past 2 years.

Laboratory data consistently showed normal liver and renal functions and a normal blood cell count (WBC: 5600/μl). There was a slight increase in IgA (638 ng/ml). Delayed type reactions to purified protein derivate (PPD) or Candida albicans antigen (Torii Co, Tokyo) were negative. Using the sensitization procedures of Catalona et al. (7), he was successfully contact-sensitized to 2,4-dinitrochlorobenzen (DNCB) like our previous case (6). Blood MNC from the patient showed low mitogenic responses to concanavalin A and pokeweed mitogen.

No warty eruption was found in the skin of his 73-year-old father, 69-year-old mother or 45-year-old brother. There was no consanguineous marriage in his family.

### *Cell preparation*

Blood MNC were prepared from heparinized venous blood of the patient, his parents and his brother and used for NK assay as reported before (6), except for using FL cells as NK insensitive target cells.

### *Immunofluorescence test of MNC*

To identify the surface phenotype of MNC, monoclonal antibodies (MAb), CD 3 (Leu 4), CD 4 (Leu 3a), CD 8 (Leu 2a), CD 57 (Leu 7), CD 16 (Leu 11), (Becton-Dickinson Co, Mountain View, California)

*Fig. 1.* Verruca plana-like flat whitish papules on the palm.

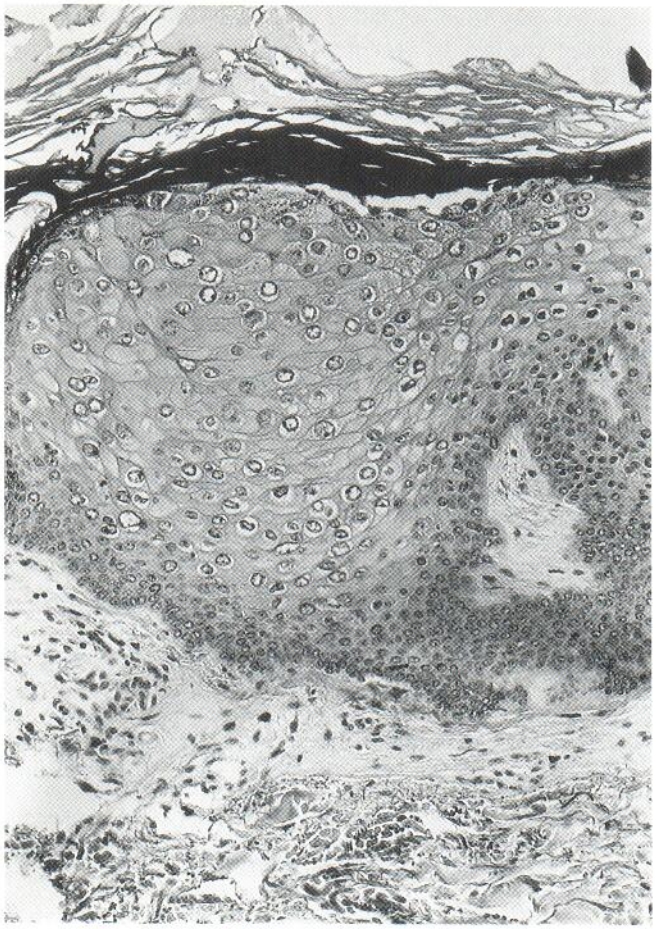

*Fig. 2.* Biopsy specimen from the verruca plana-like papule shows prominant vacuolating cells in the spinous and granular layers (HE, × 200).

were used in conjunction with an indirect immunofluorescence (IF) test as reported before (6).

## RESULTS

Surface markers of the MNC in the patient analyzed by a series of MAb showed a decrease in T cells reactive with CD 3 and CD 4 and demonstrated an increase in CD 57+ and CD 16+ cells. His father also showed a decrease in T cells reactive with CD 3, CD 4 and CD 8 and an increase in CD 57+ and CD 16+ cells. Compared with the patient and his father, the patient's brother showed a slight decrease in T cells reactive with CD 3 and CD 4 and a slight increase in CD 16+ cells. By contrast, surface markers of the MNC in his mother were within normal range except for a slight decrease in CD 3+ cells (Table I).

The MNC of the patient demonstrated increased cytotoxic activity against an NK-sensitive target, a K562 cell. For this study only the cells of his mother were available among his family members, and they showed normal cytotoxic activity against the K562 cell. An NK-insensitive target, an FL cell, was not killed either by the MNC of the patient or by the mother's cells (Table II).

Table I. *Surface markers of MNC in the patient and his family*

(Percentage against total mononuclear cells (%).)

| MAb | CD 3 | CD 4 | CD 8 | CD 57 | CD 16 |
|---|---|---|---|---|---|
| Pt | 44 ↓ | 18 ↓ | 31 | 51 ↑ | 43 ↑ |
| Father | 18 ↓ | 23 ↓ | 12 ↓ | 41 ↑ | 60 ↑ |
| Mother | 58 ↓ | 38 | 25 | 17 | 20 |
| Brother | 50 ↓ | 28 ↓ | 18 ↓ | 20 | 28 ↑ |
| Normal range | 68–82 | 35–55 | 20–36 | 13–27 | 8–22 |

## DISCUSSION

Recent studies have successively demonstrated that EV patients display higher NK activity (4, 5). In our previous study (6) we reported a case of EV with increased NK activity that was found to be due to abnormal expansion of LGL in the peripheral blood. Despite the abnormal expansion of LGL, CD 57 positive cells never appeared in the skin. In addition, we found a prominent decrease in T cells reactive with Leu 1 (CD 5) and CD 4 that was accompanied by an extraordinary low mitogenic response to T cell mitogens. Because they were not affected by a removal of the NK cells from the test system, we concluded that the decreased mitogenic response of MNC was not due to the suppressor function of LGL or NK cells, but that it represented a primary T cell defect. In the present study we found that the surface phenotypes of MNC in our patient were almost similar to those of our former patient. Our immunohistological analysis of the skin, challenged with various test agents (PPD, Candida albicans antigen, DNCB, interferon β or interferon γ), also showed results similar to those in the former one (data not shown) (6). A unique clinical feature in this case is the presence of persistent flat warts, whose histologic feature resembled those of the pityriasis versicolor-like lesions, on his palms anexceptional site for flat warts despite its anatomical closeness to the common site on the dorsum of the hands.

Furthermore we could study for the first time the surface phenotype of MNC of the patient's family members, none of whom had skin involvement. Interestingly, his father showed an abnormal surface phenotype pattern of MNC similar to his own, whereas his brother revealed a decrease in T cells and a slight increase in CD 16+ cells. Although his mother did not show any abnormal expansion of LGL, she exhibited a slight decrease in T cells. From the present results it is clear that all the family members of this EV patient tend to show a decrease in peripheral blood T cells with or without an abnormal expan-

Table II. *NK cell cytotoxicity of MNC in the patient and his mother*

(Percentage of specific lysis.)

| ET ratio | Target cell | 40:1 | 20:1 | 10:1 | 5:1 | 2.5:1 |
|---|---|---|---|---|---|---|
| Pt | K562 | 94.5 | 88.4 | 79.4 | 69.8 | 44.9 |
| | FL | 11.5 | 10.6 | 2.7 | <1 | <1 |
| Mother | K562 | NT | 44.1 | 34.5 | 30.0 | NT |
| | FL | NT | 19.9 | 11.2 | 7.6 | NT |

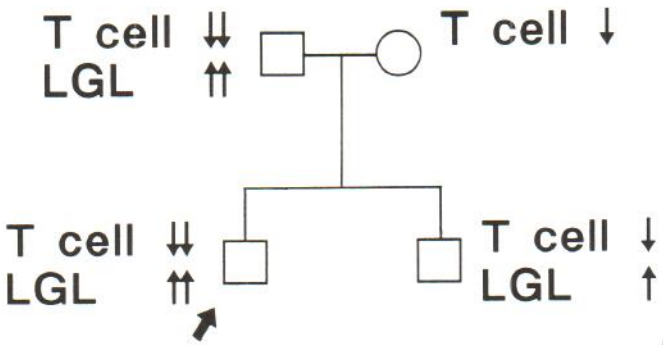


*Fig. 3.* Pedigree of the described EV patient. Arrow indicates propositus.

sion of LGL. We could not find any direct evidence for the pathomechanisms of the extraordinary expansion of LGL in our patient and his family members. However, with refesence to the absence of EV lesions in any of his family members, we believe that it is not due to a state of persistent viral infection.

Genetic factors have been suspected to play a role in the pathogenesis of EV, since this disease often occurs in the same family. The mode of heredity is reported to be autosomal recessive, but the exact fashion has not been established. No consanguineous marriage was noted in the present family. Because the tendency for a decrease in the peripheral blood T cells is a common finding among the patient and his parents, it is likely that such a trait might be inherited recessively from his parents, facilitating the development of EV skin lesions, together with the trait for abnormal expansion of LGL that was inherited only from his father (Fig. 3). Although his father disclosed changes in both LGL and T cells similar to the patient, he had no history of EV skin lesions. Thus we think that these cellular abnormalities alone are still not sufficient for the development of the unique HPV infection of EV.

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