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ERYTHEMA MULTIFORME BULLOSUM

Report of a Severe Case Studied by Electron Microscopy

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Abstract. Study by electron microscopy of lesions from a case of severe erythema multiforme bullosum revealed that the most marked changes were epidermal. Lysosomes were present in basal cells around bullae in a disorganized dermal–epidermal junction.

The purpose of the present paper is to report an unusually severe case of erythema multiforme bullosum in a patient who made a complete recovery, and to present the results of studies of the involved skin by electron microscopy.

REPORT OF A CASE

A 40-year-old man was hospitalized for fever and hemoptysis of 3 days' duration.

He had had rheumatic fever at the age of 9 and subsequently developed aortic stenosis. He also had a seizure disorder and had been taking 400 mg of Dilantin daily for years.

On admission he had fever of 102°F, a pulse rate of 140, rales in the lower fields of the lungs. The diagnosis was pulmonary edema and the patient was treated with oxygen by nasal catheter, 2 cc of mercuhydrin given intramuscularly, ampicillin 6 g intravenously, and digitalis by mouth.

The hospital course was stormy. He developed lobar pneumonia, and a rise in blood urea nitrogen. Within a week there was definite renal failure. The blood urea nitrogen was 195 mg%, and there were numerous granular casts and protein in the urine. He required peritoneal dialysis for 3 days which led to improvement in renal function. Ampicillin was continued intravenously in a dose of 8 g daily. Other medications were also administered. During the hospitalizaton, a total of 17 different drugs were given. These were as follows: aspirin, Ampicillin, Oxacillin, Keflin, erythromycin, mercuhydrin, lasix, ethacrynic acid, Dilantin, Librium, Valium, Thorazine, phenobarbital, Nembutal, morphine, digoxin, and heparin.

On the 10th day, a generalized eruption developed which was initally erythematous and maculopapular, then urticarial, and quickly thereafter bullous. (Figs. 1 *a* and *b*). Target or iris-haped lesions were prominent.

SPECIAL STUDIES AND RESULTS

Viral studies for influenza showed a titer of 1/40 for influenza A in blood taken on admission to the hospital and 1/2 000 ten days later.

Immunologic studies. Skin tests for immediate wheal-and-flare reactions with penicillin antigens were negative, but were positive after 48 hours. Assay for penicillin antibodies by hemagglutination revealed low titers, 1/40, of IgM only. Indirect immunofluorescent studies for pemphigus-type antibodies were also negative.

Histopathologic studies

1. *By conventional methods.* Two skin biopsies were taken, one from skin of the scapula which showed erythematous macules and papules, and another from a fresh bullous lesion. Sections from the areas of the macular and papular lesions showed edema in the superficial dermis leading to the formation of a subepidermal bulla. There were degenerative changes in the epidermal roof of the bulla. Some edematous areas also showed a fibrinous exudate, extravasated crythrocytes and polymorphonuclear leukocytes. The upper third of the dermis showed many patchy perivascular infiltrates with numerous polymorphonuclear eosinophils. Sections from the area of skin which showed bullae clinically revealed the following histologic findings: a larger subepidermal bulla containing a serofibrinous exudate and many polymorphonuclear eosinophils (Fig. 2). The roof

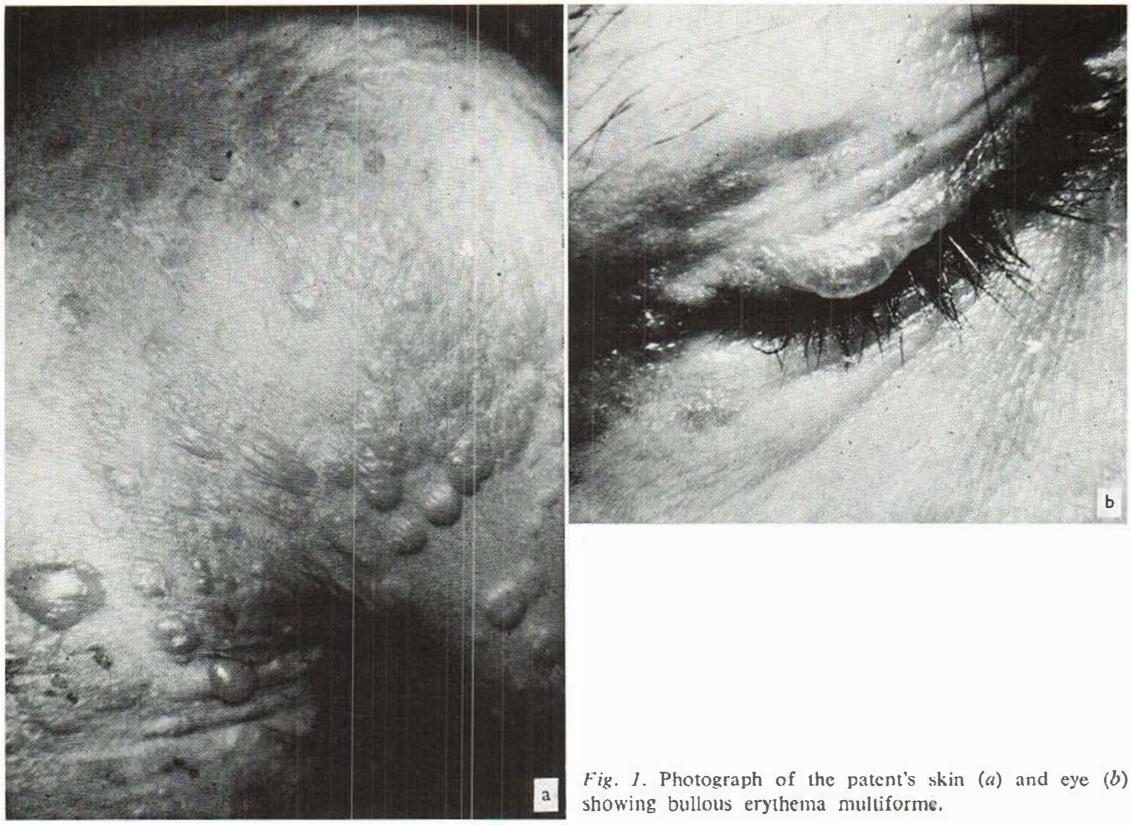

Fig. 1. Photograph of the patent's skin (*a*) and eye (*b*) showing bullous erythema multiforme.

of the bulla was formed by a compressed epidermis with evidence of degenerative changes. In the floor of the bulla the superficial dermis showed a dense vascular inflammatory reaction with a large number of polymorphonuclear eosinophils, and edema. There were also areas with extravasated erythrocytes and some evidence of superficial necrosis.

2. *By electron microscopy.* Some biopsy tissue was studied for acid phosphatase while the other biopsies were minced into 1 mm^3 pieces. All tissue excluding those studied for acid phosphatase was placed into 5% glutaraldehyde in phosphate buffer for 1.5 hours followed by fixation in 2% osmium tetroxide, buffered to pH 7.4. The tissues were then dehydrated in graded strengths of ethanol and embedded in Epon 812. One-micron-thick and ultrathin sections were cut on a Reichert Ultramicrotome, stained with uranyl acetate followed by lead citrate and then examined in an RCA-EMU 2E electron microscope. Some bullous tissue was fixed in 6% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.2, for 1.5 hours at 4°C, washed in cold buffer containing 5% sucrose for 30 min and put in a liquid nitrogen bath. Frozen sections were cut at 70 μm on a freezing microtome. The tissue was incubated in the Barka & Anderson modification (1) of the Gomori medium for 45 min at 37°C. The tissue was then washed in cacodylate buffer, post-fixed in 1% osmium tetroxide and then run up for routine electron microscopy.

There was marked intercellular edema limited to the lower strata of the epidermis. Sections taken from bullous areas revealed subepidermal bulla. The most severe changes were in the epidermis in skin sections taken from maculopapular areas of the patient's eruption. Marked intercellular edema was evident in the lower strata of the epidermis. Some of the basal cells showed intracellular edema. In many regions of the lower epidermal strata there was disorganization of the architecture of the basal cells as well as the tonofibrils with loss of desmosomal attachments (Fig. 3). Abundant membrane-bounded bodies were noted within the cells. In many areas

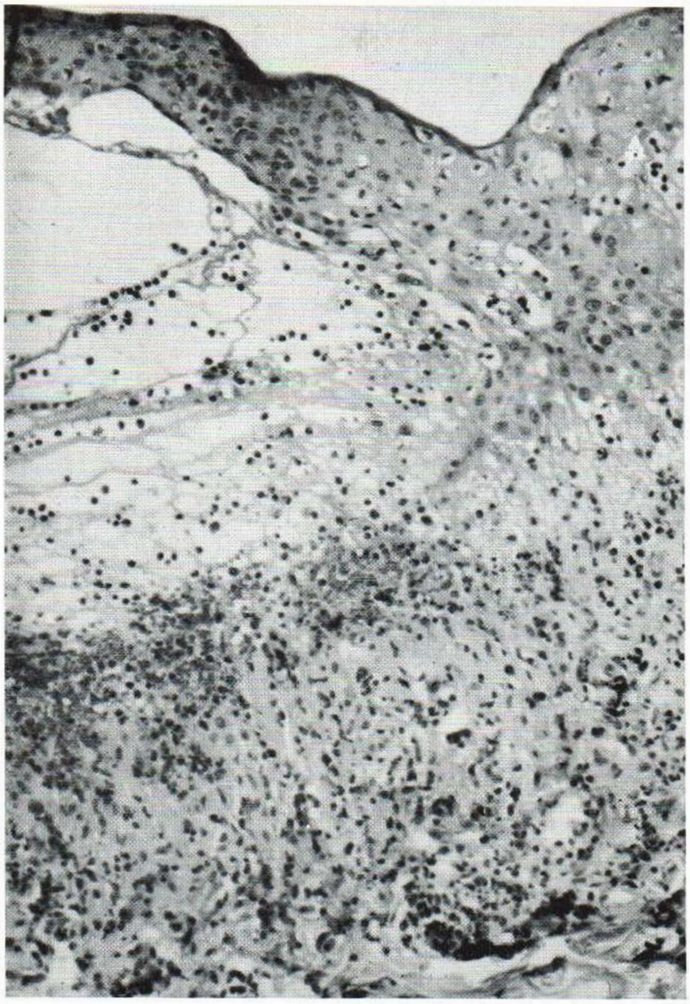

Fig. 2. Micrograph showing section of skin in the area of a bulla. It is clearly subepidermal. Dermal inflammatory perivascular reaction is clearly present.

these organelles were electron-opaque, and morphologically resembled lysosomes (Fig. 4). They were never observed in the middle or upper strata of the epidermis. The structural integrity of the basement lamina remained intact in the maculopapular eruption while in sections from the bullous lesion the basement lamina was never observed in the roof or floor of the bulla.

Study of sections taken from areas of bullous dermatitis revealed some similarities to the maculopapular eruption, but with some distinctive characteristics as well. In addition to the absence of a basement lamina in the bulla, these were: (*a*) The basal cells above the roof of the bulla were completely disorganized. (*b*) Arrangement of the tonofibrils remained linear, although without desmosomal attachments. No whorling of tonofilaments were seen. (*c*) The membrane-bounded bodies that were observed in sections from the maculopapular tissue were still present above the bulla roof. Red blood cells were also occasionally present. There was a very sparse amount of the usual cell organelles present in the disorganized basal cell stratum. This stratum above the bulla consisted mostly of tonofibrils (Fig. 5). The bulla itself contained an electron-light, amorphous material. The mid-to-upper-epidermal strata showed a normal morphologic pattern. Some of the epidermal cells immediately adjacent to the bulla contained cytoplasmic organelles that were membrane-bounded and electron-opaque (Fig. 6). Studies on the bullous tissue processed for acid phosphatase showed these bodies contained lead reaction product. In addi-

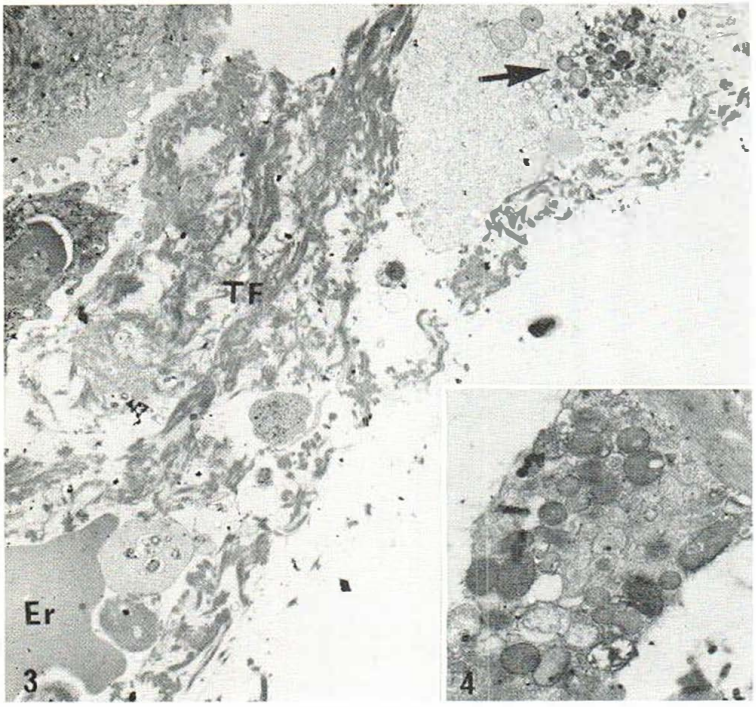

Fig. 3. An electron micrograph depicting the disorganization and loss of architecture of the basal cells in an early bullous lesion. Arrow points to membrane-bounded organelles resembling lysosomes. An erythrocyte is observed (*E*) near the tonofibrils (*TF*). × 5 000.

Fig. 4. Micrograph shows electron-opaque organelles which resemble lysosomes and are found in the maculopapular basal cells. × 16 130.

tion, there were occasional autophagic vacuoles within these cells.

Study of 1-micron-thick sections revealed an inflammatory infiltrate in the dermis in sections taken from the maculopapular area. Very little morphologic change of actual collagen fibers appeared in the dermis. Dense perivascular infiltrates were present as described under the section on light microscopy.

DISCUSSION

Knowledge of erythema multiforme, particularly its morphologic pattern observed by electron microscopy, is scanty. Caulfield & Wilgram (4) stated that the sequence of events which initiates erythema multiforme appears to begin in the dermis. We have observed morphologic changes in the dermis consisting of inflammatory and perivascular infiltrates similar to theirs. However,

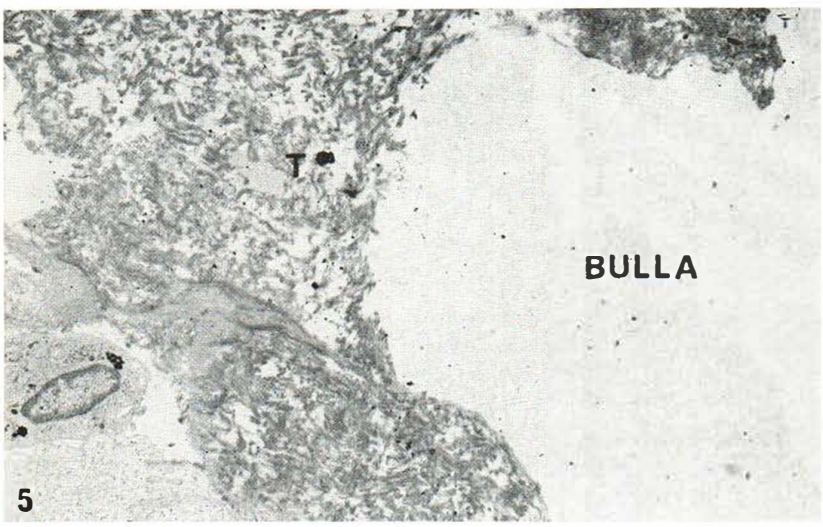

Fig. 5. Micrograph shows bulla and tonofibrils (*T*) above the bulla. × 5 130.

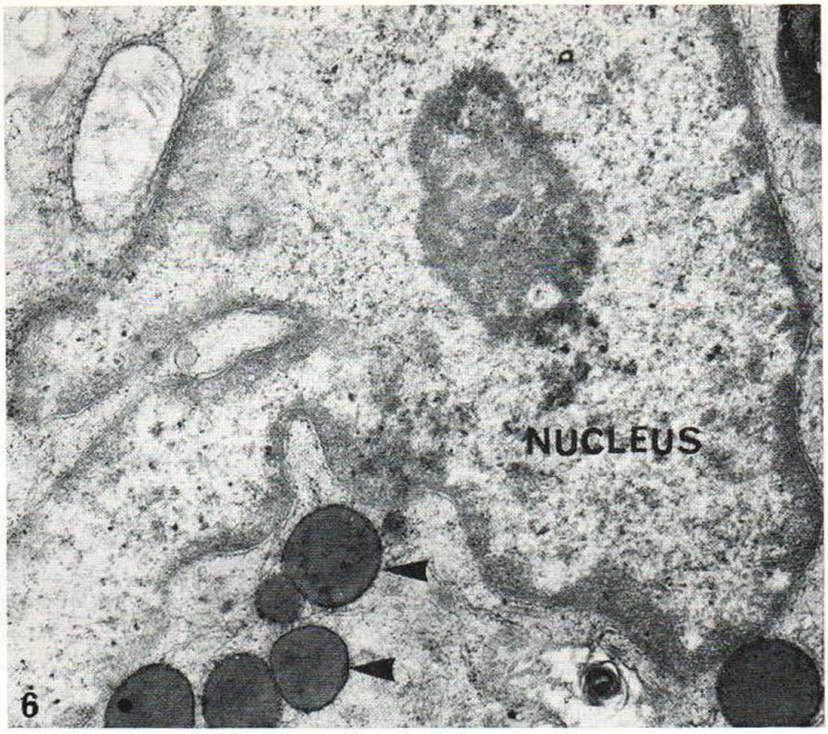

Fig. 6. Arrows point to lysosome-like organelles in a peribullous basal cell. × 18 425.

our study also revealed striking epidermal edema in the early lesion. This was notable intercellularly, and slightly, intracellularly, in the lower strata of the epidermis. The loss of architecture of the basal cells and most of the organelles within these cells, accompanied by the presence of lysosomal forms in this basal cell site, may all predispose to blister formation. It has been reported by several investigators that lysosomes are normally present in the stratum granulosum and stratum corneum of the epidermis (2, 7, 9). These lysosomes play a role in keratinization and are responsible for the dissolution of the cell organelles. deDuve (5, 6) has suggested that lysosomes participate in cell degradation when they rupture and release their hydrolases. In an electron microscopic study of oral mucosal lesions in erythema multiforme, the investigators reported that they never found changes in the connective tissue, but did find intracellular and intercellular edema (3).

A number of drugs, infectious agents and theories have been implicated in the pathogenesis of erythema multiforme (10). Recently we demonstrated the presence of anti-epithelial antibodies in maculopapular eruptions following penicillin (8). In this case, such tests were negative.

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