

Histopathological and ultrastructural observations on tissues from patients with hereditary angioneurotic edema

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Tissues from 10 patients with clinical and biochemical evidence of hereditary angioneurotic edema were reviewed. Skin changes consisted of subcutaneous edema and capillary and venular dilatation. By electron microscopy, gaps appeared in the postcapillary venule endothelial cells of the patients' skin during attacks. Upper respiratory tract involvement always revealed laryngeal edema caused by a non-inflammatory submucosal edema. Jejunal tissue demonstrated edema of the lamina propria, submucosa, and serosa. These mucocutaneous and visceral tissue findings in hereditary angioedema can be distinguished from those of fatal systemic anaphylaxis, wherein the involved organs contain an inflammatory infiltrate with eosinophils. Death in hereditary angioedema appears consequent to asphyxiation from submucosal edema of the larynx, while the edema of the lamina propria of the small bowel may account for the abdominal colic.

Griffith¹ in 1902 first called attention to the marked edema of the upper respiratory tract mucous membranes from a patient with hereditary angioneurotic edema (HAE) who asphyxiated consequent to laryngeal edema. Shortly thereafter, Morris² reported noninflammatory edema of gastric mucosa obtained during an abdominal crisis caused by hereditary angioneurotic edema. More recently, Biering³ described submucosal thickening and edema of the muscularis occurring in an involved area of the colon. Various observations of affected respiratory or gastrointestinal tract tissues have confirmed the early observation⁴⁻⁸ of extensive edema without the presence of inflammatory cells. The present study was undertaken to re-examine gross and ultrastructural changes in tissues of patients with the biochemically proved diagnosis of hereditary angioneurotic edema.

MATERIALS AND METHODS

The diagnosis of hereditary angioedema was established by estimation of the C₁ inhibitor in serum of affected individuals. This assessment was carried out by three methods: (1) inhibition of esterolytic activity with the use of N-acetyl-L-tyrosine ethyl ester as

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FIG. 1. A section of skin biopsied during an attack of angioneurotic edema stained with hematoxylin and eosin. (Original magnification X400.) Note separation of collagen bundles by edema, prominent venules, and perivenular around cells.

substrate and partially purified $\bar{\text{C}}\text{I}^{9-11}$ electroimmunodiffusion¹² with a goat antiserum to highly purified $\bar{\text{C}}\text{I}$ inhibitor¹³; and (3) inhibition of immune hemolysis in an assay in which $\bar{\text{C}}\text{I}$ inhibitor is measured by its ability to inhibit sites on sensitized red cells carrying CI (EAC1 cells).¹⁴

Skin biopsies were performed by the punch technique with xylocaine anesthesia injected intracutaneously 5 cm. proximal to the biopsy site. All tissues, following fixation in Bouin's solution, were paraffin embedded, cut at 6 microns, and stained with hematoxylin and eosin. Mast cells were demonstrated with toluidine blue dye. Tissues for electron microscopy were fixed in 2.5 per cent glutaraldehyde in 0.067M cacodylate buffer at pH 4, postfixed in osmium collidine, and embedded in Epon 812. Thin sections were prepared on an LKB II ultratome, stained with uranyl acetate and lead citrate, and examined with a Philips 200 electron microscope.¹⁵

Tissues were available from 10 patients. The concentration of $\bar{\text{C}}\text{I}$ inhibitor protein of 9 patients from 6 kindreds was significantly reduced, ranging from 0.075 to 3.15 mg. per 100 ml. (normal 18 ± 4 mg. per 100 ml.), whereas the serum of one patient contained a normal serum protein concentration of $\bar{\text{C}}\text{I}$ inhibitor but reduced activity by inhibition of N-acetyl tyrosine ethyl ester hydrolysis.

RESULTS

Gross anatomic and microscopic changes were recognized in the skin, respiratory tract, appendix, and jejunum. Histologic features revealed prominent subcutaneous edema, as evidenced by the separation of the collagen bundles. Marked venular dilatation with perivascular accumulation of mononuclear cells was apparent (Fig. 1). Mast cells appeared somewhat degranulated by light microscopy in all three biopsies obtained during attacks of angioneurotic edema and by electron microscopy when this technique was also carried out (Fig. 2). Edema was not present in biopsies obtained early in the development of attacks or between attacks.

Laparotomy, in three instances, revealed well-demarcated edema involving

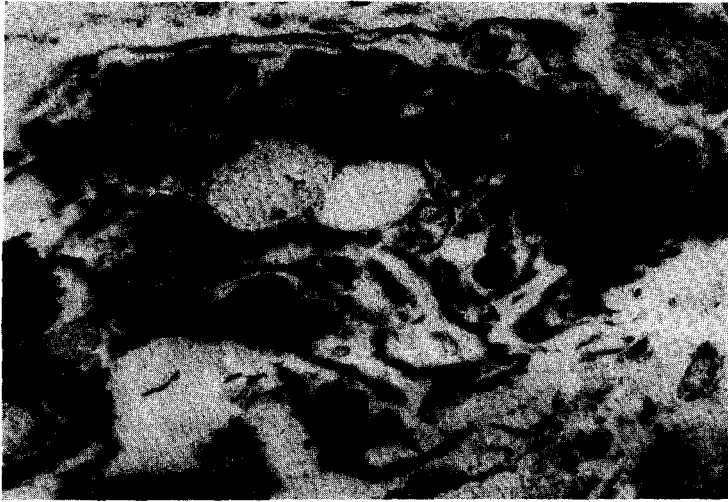


FIG. 2. Mast cell in the dermis from an area involved with angioneurotic edema. (Original magnification X19,000.) Note partial degranulation of the cytoplasmic granules.

the entire jejunum. In microscopic sections, edema of the superficial portion of the villi with widening of the lamina propria was noted. The villi appeared club shaped as a result of the edema. The submucosa and subserosa were also markedly edematous (Figs. 3 and 4).

In individuals who asphyxiated from laryngeal edema, involvement of the entire upper respiratory tract was seen. Labial, lingual, and posterolateral pharyngeal edema with marked swelling of the uvula occurred. Histologically, marked spongiosis of the epithelial cells lining the mucous membrane was observed with vacuolar formation in the cytoplasm. Extensive edema involving the submucosa obliterated the fibrous structures of the larynx (Fig. 5). The lingual epithelium similarly demonstrated spongiosis but without accompanying submucosal alterations. The basement membrane lining the respiratory epithelium was thickened; diffuse, extensive edema and some hemorrhage of the lungs were observed.

Depletion of Malpighian follicles (germinal) and absent secondary centers with depletion of splenic red pulp were observed. Eosinophilic infiltration was not noted. These changes were seen in accessory splenic tissues removed during attacks of gastrointestinal crisis, as well as from the patient who died from a myocardial infarction.

DISCUSSION

Tissues from patients with hereditary angioneurotic edema revealed the presence of capillary and venular dilatation, marked edema, moderate degranulation of mast cells, and minimal diapedesis of inflammatory cells. Presumably, these findings are a consequence of the activation of the first component of complement in the blood of patients during attacks of angioneurotic edema; the findings resemble the histopathologic changes induced by highly purified ac-



FIG. 3. Jejunum biopsied during an attack of angioneurotic edema exhibiting marked edema of the submucosa. (Hematoxylin and eosin. Original magnification X400.)

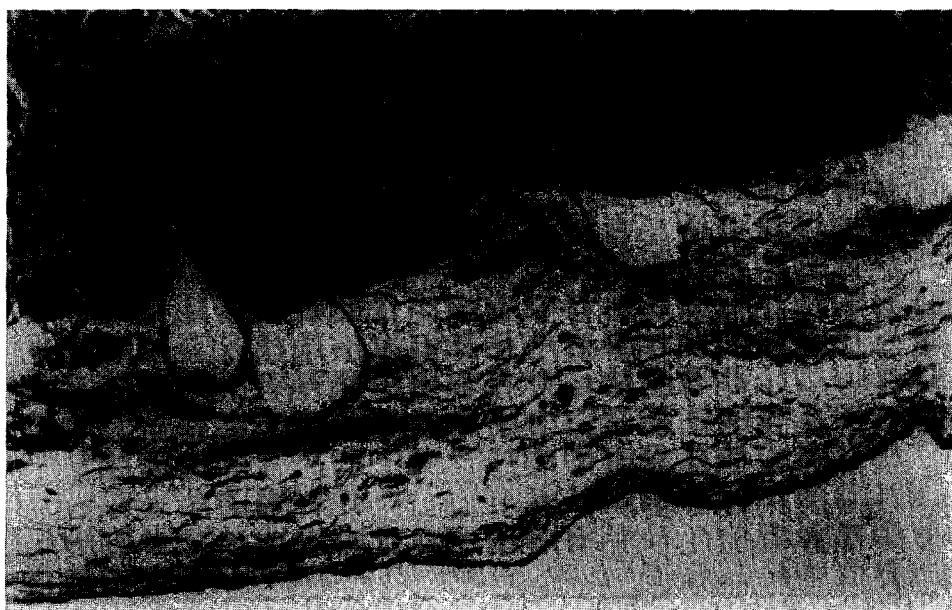


FIG. 4. Jejunum biopsied during an attack of angioneurotic edema exhibiting marked edema of the serosa. (Hematoxylin and eosin. Original magnification X400.)



FIG. 5. Larynx at postmortem examination from patient who died consequent to laryngeal edema. (Hematoxylin and eosin. Original magnification X400.)

tivated C1 injected into human or guinea pig skin.^{16, 17} Wide endothelial gaps in postcapillary venules, extravasation of vascular elements, and moderate degranulation of mast cells have been observed in these experimental lesions.¹⁸ The mediator of these vascular changes appears to be a kinin-like peptide which can be detected in the plasma of patients with HAE or can be generated in their plasma *in vitro* when they are asymptomatic.¹⁹ It is chemically and pharmacologically distinct from bradykinin and the anaphylatoxin derived from C3 (C3a).

The paucity of inflammatory cells in areas involved with angioneurotic edema is in marked contrast to what is observed in acute anaphylactic reactions in which eosinophilia is prominent in the involved parts.²⁰ Although chemotactic factors are generated by the late-acting components of complement, mainly, C3, C5, C6, and C7, evidence has been cited that the pertinent interactions of complement activation occurring in hereditary angioneurotic edema involve only the early complement components.^{21, 22}

The extensive pulmonary edema observed in the lungs of patients with HAE who have died from laryngeal edema cannot be distinguished from the changes observed in the lungs of those who die from upper airway obstruction or other causation. The depletion of red pulp and the small size of the spleen which is persistently observed in all patients with HAE may be a consequence of the contracted vascular volume.

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