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CASE REPORT

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Hereditary Angioneurotic Edema: An Unusual Case of Maternal Mortality

Hereditary angioneurotic edema is an autosomal dominant, nonallergic disorder characterized by recurrent attacks of brawny edema of the extremities, face, larynx, and genitalia [*1*] and biochemically by a reduction in the serum protein C1 esterase inhibitor, a factor which prevents the activation of the first component of the complement system [*2*]. Although most attacks are precipitated by trauma [*3*], there have been no previously reported cases in pregnancy during delivery or in the immediate postpartum period, despite obvious traumatic injury during the birth process. This report describes a patient who, following delivery, developed localized perineal swelling, which over 72 h progressed to generalized edema, terminating in irreversible shock.

Case History

A 28-year-old, gravida II, Para 1, East Asian female presented in August 1977 with a normal full-term pregnancy, with no history of antenatal complications. She underwent an uneventful vaginal delivery, with the episiotomy repair requiring 5 ml of local Xylocaine® infiltration.

The patient had a history of edema of the face, tongue, and extremities when exposed to cold stimuli such as ice cream, ice water, or cold rain. Dental procedures had not precipitated any edematous attacks. There was no history of urticarial eruptions nor other atopic phenomena. A pregnancy three years previously had been uneventful. Her family history included a brother who developed urticaria after eating fish.

Forty-eight hours postpartum the patient began to complain of nonpruritic perineal swelling associated with a purulent discharge from the episiotomy site. Over the next 24 h the perineal region became markedly edematous with extension over the groin area. This was accompanied by mild edema of the eyelids. In view of the patient's history of edema related to cold, an ice cube was placed on the surface of one forearm; within a few moments a 3-cm-diameter area of induration appeared immediately beneath the ice cube. A diagnosis of hereditary angioneurotic edema was made. She was given Prednisone®, 25 mg at first and then 15 mg at bedtime and 20 mg each morning, and hydroxyzine (Atarax®), 20 mg orally four times a day. Early on the fourth postpartum day she became markedly diaphoretic with a blood pressure of 8/0 kPa (60/0 mm Hg) and a heart rate of 100/min. Laboratory investigation revealed a hemoglobin level of 22 g/100 ml, a hematocrit of

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60%, and a white blood cell count of 47 000 mm^{-3} (compared to admission values of 13.8 g/100 ml, 39%, and 11 800 mm^{-3}, respectively). The total serum protein was 3.3 g/100 ml. Qualitative assay for the serum C1 esterase inhibitor (C1 INH) by immunodiffusion technique revealed C1 INH to be absent. Quantitative radioimmunoassay for serum C4 showed the C4 to be 4 mg/100 ml (normal, 20 to 50 mg/100 ml).

Although the patient remained afebrile and all blood cultures were negative, she was given intravenous hydrocortisone (Solu-Cortef®), 1 g every 6 h; methylprednisolone (Solu-Medrol®), 4 g immediately; gentamicin, 80 mg every 8 h; clindamycin, 600 mg every 6 h; penicillin G, 5 000 000 units every 6 h; and dextran 40, 1000 ml. Despite therapy her blood pressure fell to 5/0 kPa (40/0 mm Hg) and she became oliguric. Arterial blood gases on an inspired oxygen concentration of 50% revealed a metabolic acidosis with a pH of 7.30, a pressure of oxygen of 9.2 kPa (69 mm Hg), a pressure of carbon dioxide of 3.2 kPa (24 mm Hg), and a bicarbonate level of 12 meq/litre. Serum lactate was 7.3 mg/100 ml (normal, <2 mg/100 ml). Serum amylase was 880 units (normal, <200 units). At this time the patient was intubated. Chest X-ray showed vascular congestion; auscultation revealed coarse bilateral rales throughout both lung fields. An electrocardiogram demonstrated small QRS complexes suggestive of a pericardial effusion. This was confirmed by echocardiography, and a pericardicentesis, which yielded 160 ml of straw-colored fluid, was performed. An emergency D & C ruled out retained placental fragments. In spite of treatment with intravenous bicarbonate, the metabolic acidosis increased; the patient developed ventricular tachycardia and died five days postpartum.

Pathology

Autopsy revealed diffuse brawny edema of the subcutaneous tissues most prominent in the faces and perineal region. There were serious effusions present within all body cavities: right pleural cavity, 150 ml; left pleural cavity, 100 ml; peritoneal cavity, 1000 ml; retroperitoneal space, 200 ml; and small and large bowel lumena, 1000 ml.

The tongue and laryngeal structures were edematous (Fig. 1). The lungs were heavily congested and white frothy fluid could be expressed from the bronchi. Microscopically, interstitial edema was present in all tissues examined. This was most striking in the laryngeal tissues and the pancreas (Figs. 2 and 3). In sections of the laryngeal tissues, granulated mast cells were identified by the Toluidine Blue stain; these showed no evidence of degranulation (Fig. 2). The pancreas showed focal fibrinoid necrosis of blood vessels and widespread recent fat necrosis (Fig. 3).

Discussion

The differential diagnosis of this patient's fatal edema includes anaphylactic shock and angioneurotic edema. The clinical history of gradual onset with slow progression over 72 h and failure of all conventional treatment methods (fluids, dextran, antibiotics, and corticosteroids), the biochemical findings of an absent level of serum C1 esterase inhibitor and a markedly diminished level of serum C4, and the histologic features of capillary dilatation and interstitial and intracellular edema with normal granulation of the mast cells [*4*] all support the diagnosis of hereditary angioneurotic edema.

The clinical syndrome of hereditary angioneurotic edema, first described by Quincke (1882) [*5*] and Osler (1888) [*1*], is an autosomal dominant disorder which presents as episodic localized recurrences of brawny painless edema. The edema is biochemically related to an inherited deficiency of C1 esterase inhibitor, a serum α_2-globulin that not only inhibits the enzymatic activity of the first component of complement [*2*] but also affects the kinin-generating, clotting, and fibrinolytic systems.

In approximately 50% of cases, trauma is the factor that precipitates attacks of edema.

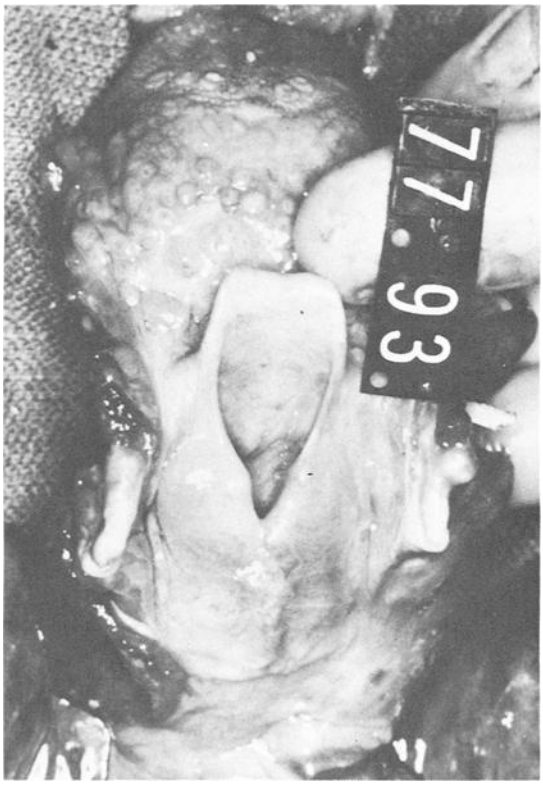

FIG. 1—*Photograph of tongue, epiglottis, and posterior laryngeal tissues. There is extensive edema of the tongue and the soft tissues about the larynx.*

Trauma exposes surface collagen, resulting in activation of the Hageman factor (factor XII), which leads to plasmin activation. Plasmin in turn activates C1, the initial component of the complement system. Activated C1 causes the activation of its substrates C4 and C2 into activated C42. A C2-kinin-like peptide, enzymatically cleaved from the activated C42, is the direct mediator of the vascular permeability [*6*], resulting in edema formation (Fig. 4). Since this process occurs within the blood and not on the cell surface, the remainder of the complement cascade is not activated [*7,8*]. In angioneurotic edema, absence of C1 esterase inhibitor allows the coagulation-fibrinolytic-complement cascade to proceed unchecked [*9,10*]. This results in a consumption of substrates such as C4 and an increase in the vasoactive peptides (C2-kinin) with increasing vascular permeability and edema. This process differs from anaphylactic shock, a type-1 allergic hypersensitivity phenomenon in which IgE binds with antigen on mast cells, resulting in their degranulation with the consequent release of vasoactive substances such as histamine.

The agonal serum amylase of 880 units and the autopsy findings of recent pancreatic edema and fat necrosis indicate a terminal pancreatitis related to ischemia. With the knowledge that pancreatic kallikreins can liberate vasoactive kinins [*11*], and that trypsin can activate C1 esterase [*12,13*], we can speculate that pancreatic enzyme release promoted the edema process in this patient.

Pregnancy has always appeared to provide a protective effect from attacks of hereditary angioneurotic edema, although the mechanism by which this occurs is obscure. In Gelfand's study [*4*], which included ten women with a total of 25 pregnancies, there were no attacks of angioedema following delivery despite the trauma to the birth canal. To our

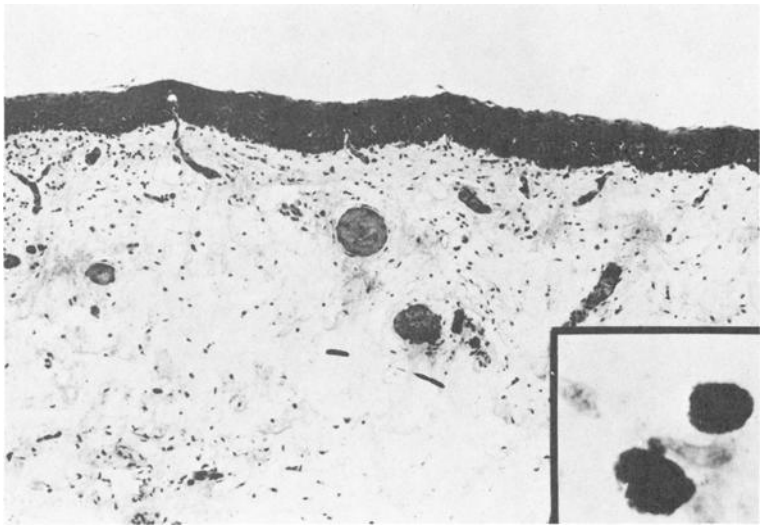

FIG. 2—*Photograph of laryngeal tissues. Massive edema of the soft tissues and vascular congestion are seen. The inset shows a high-powered view of mast cells which remain granulated (hematoxylin and eosin; magnification, approximately ×10; inset: Toluidine Blue; magnification, approximately ×150).*

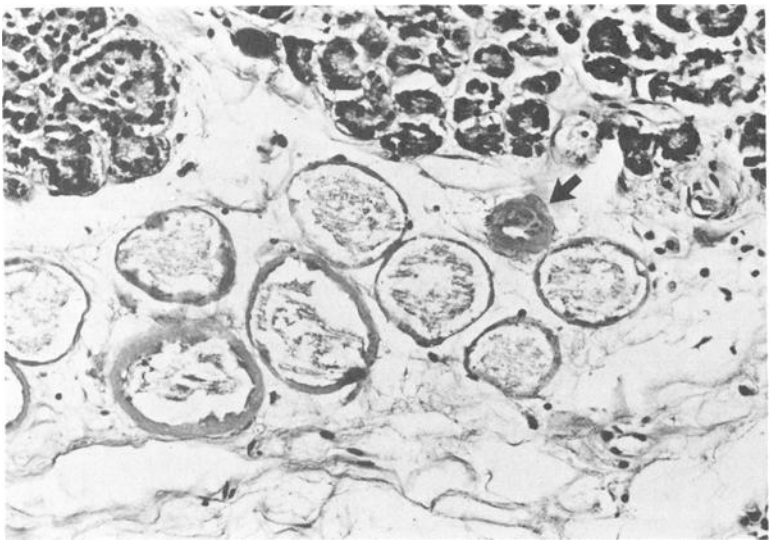

FIG. 3—*Photomicrograph of pancreas. There is extensive interstitial edema and fat necrosis. The arrow shows a blood vessel with fibrinoid necrosis (hematoxylin and eosin; magnification, approximately ×38).*

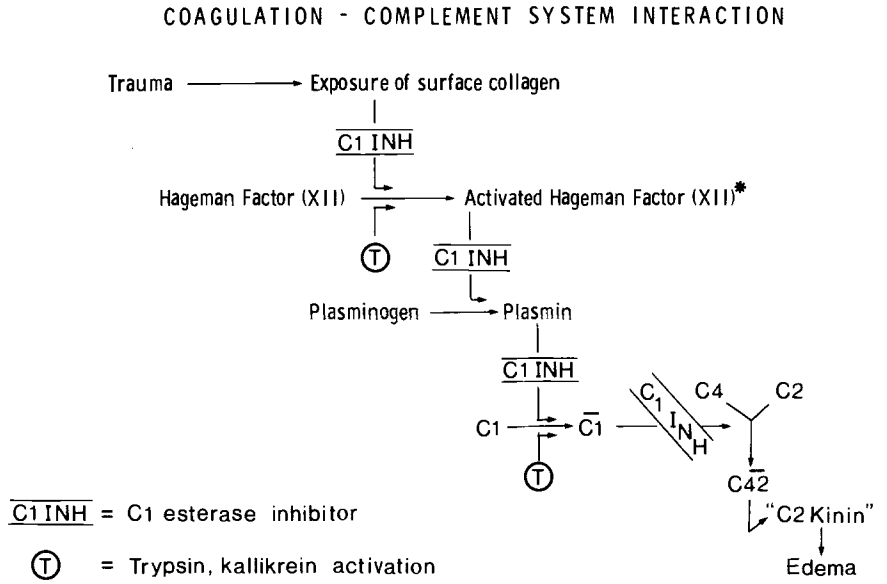

FIG. 4—*Diagram of coagulation-complement system interaction. Note that C1 esterase inhibitor blocks the sequence at several steps. The sequence may be activated nonspecifically by the enzymes trypsin and kallikrein.*

knowledge, this is the first report of a fatal case of hereditary angioneurotic edema in the postpartum period. Why the first pregnancy was uneventful and why the second pregnancy in this patient failed to be protective remain unknown.

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