Angioedema is a pathologic condition first described by Quincke and Osler. It can be genetically determined or acquired, and it is caused by a vascular reaction induced by deficiency or functional alteration of the C1 inhibitor (C1-INH), an enzyme involved in the regulation of complement, contact, fibrinolytic, and coagulation systems.

Two forms of angioedema have been described in the literature: hereditary angioedema (HAE) and acquired or idiopathic angioedema (AAE).

HAE is characterized by dominant autosomal transmission, early onset, and a positive family history. It is caused by a mutation of the gene for C1-INH, localized on chromosome 11. Type 1 HAE is the most frequent form (85% of cases) and is associated with deficiency of functional C1-INH in plasma (10%-30% of normal values). Type 2 HAE is characterized by normal or elevated plasma levels of dysfunctional C1-INH. Type 3 HAE occurs mainly in women. Affected persons display the typical clinical features of C1-INH deficiency but have normal plasma levels and functionality of C1-INH. Mutations in the coagulation factor XII gene have been detected in some of these patients.

AAE is characterized by late onset, usually after the fourth decade, and is not associated with a positive family history. Type 1 AAE is caused by increased catabolism of C1-INH and is generally associated with a positive history of benign or malignant lymphoproliferative disorders. Type 2 AAE is associated with autoantibodies against C1-INH.

Deficiency or dysfunction of C1-INH can cause a deregulation of the fibrinolytic system, of the complement pathway, of the contact system, and of the coagulation cascade, resulting in release of vasoactive substances, an increase in vessel permeability, and development of diffuse edemas.

Hereditary and acquired forms of angioedema are clinically indistinguishable. Edemas develop gradually over a period of 12 to 36 hours and require 2 to 5 days to subside completely. The frequency and severity of edema attacks vary from patient to patient and even in the same individual. This variability can change significantly over a patient’s lifetime: symptoms may intensify dramatically after puberty, although some cases have been reported that had been asymptomatic until the second decade of life and later.

The diagnosis of angioedema can often be suspected from a positive family history associated with the typical symptoms. Nevertheless, the diagnosis needs to be confirmed by laboratory tests to assess the quantity and function of C1-INH.

The differential diagnosis of angioedema includes anaphylactic shock. Considering the potential risk of asphyxia, it is essential to obtain an accurate patient history to ensure that the most appropriate approach to emergency treatment is chosen, because cortico-
steroids, antihistamines, and epinephrine are ineffective in the treatment of acute attacks of angioedema.\textsuperscript{6,8,14} Although angioedema attacks can occur without any specific precipitating factor, in 50% of cases the precipitating cause is tissue trauma.\textsuperscript{6,8,9} Trigger factors include dental procedures, endotracheal intubation, surgical or diagnostic interventions in the cephalic or cervical region (such as oral or maxillofacial surgery and tonsillectomy), mental or physical stress, infection, hormonal changes (menstruation, pregnancy, intake of oral contraceptives), intake of specific drugs (such as estrogens or angiotensin-converting enzyme inhibitors) or foods containing histamine or able to induce histamine release, insect bites, and strong temperature variation.\textsuperscript{3,5,9,12,13,15}

At present, it is possible to intervene with a specific therapy according to the patient’s needs.

**Long-Term Prophylaxis**

Long-term prophylaxis aims to reduce the frequency and severity of attacks and is indicated in patients who have significant and/or frequent episodes (≥1 attack per month) of angioedema.\textsuperscript{14} The first-choice drugs are synthetic anabolic steroids, which increase the hepatic production of C1-INH.\textsuperscript{5,6,14,16,17} Interferon-\gamma or antifibrinolytic agents (such as e-aminocaproic acid and tranexamic acid) are recommended as alternative therapy, particularly in patients who do not tolerate anabolic steroids. Interferon-\gamma increases the production of C1-INH, and antifibrinolytic agents inhibit the activation of plasmin and factor C1.\textsuperscript{5,6,14}

**Short-Term Prophylaxis**

Short-term prophylaxis is recommended in patients undergoing invasive procedures such as dental treatment, oral or maxillofacial surgery, and endoscopic operations.\textsuperscript{14} Therapy is based on the administration of an increased dose of anabolic steroids for 5 to 7 days before surgery and 2 to 5 days after surgery.\textsuperscript{7,13,14,18} Alternatively, fresh-frozen plasma can be given the night preceding the operation and before the beginning of the operation.\textsuperscript{5,6,19,20} Other options include C1-INH concentrate or antifibrinolytic agents.\textsuperscript{5,13,18}

**Therapy for Acute Attacks**

Acute attacks are managed with intravenous infusion of narcotics and anti-inflammatory drugs, to maintain the patency of the respiratory tract and control pain and nausea.\textsuperscript{5,14} In case of dehydration and hypotension caused by abdominal involvement, rehydration therapy is required.\textsuperscript{14}

The resolution of acute episodes of angioedema can be obtained by increasing C1-INH levels in serum.\textsuperscript{20,21} C1-INH can be given in the form of plasma concentrate or intravenous infusion of fresh-frozen plasma, which is rich in this factor.\textsuperscript{5,8,13,14,18,20,21} Although both formulations have been used in emergency treatment, data showing proven clinical effectiveness are available only with regard to C1-INH concentrate.\textsuperscript{21} The exhibition of these preparations allows the resolution of acute episodes in a short period of time.\textsuperscript{5}

Anabolic steroids have limited indications in the treatment of acute attacks of angioedema because they require 1 to 2 days to be effective.\textsuperscript{14}

**Report of a Case**

In March 2006, a 38-year-old woman presented to the Dental Clinic of San Gerardo Hospital in Monza, Italy, for dental consultation because of gingival inflammation and increased dental mobility (Fig 1).

Clinical examination and orthopantomography (Fig 2) confirmed the diagnosis of generalized chronic periodontitis, with evident horizontal bone resorption in both arches, as well as furcation involvement (degree 2) and mobility (degree 2) of the first and second maxillary and mandibular molars, bilaterally.

**FIGURE 1.** Extraoral presentation of the patient.

During the anamnestic data collection, the patient reported that she was affected by HAE, which had been diagnosed at 13 years of age and was treated initially with C4 and C1-INH. During adolescence, frequent abdominal colic caused by stress, trauma, and menstruation had been the only symptoms of HAE. At 30 years of age, after the patient’s first pregnancy, the clinical picture had been worsened by the onset of recurrent diffuse nonpruritic edemas involving the hands, feet, and face. However, she had no history of respiratory difficulties caused by the involvement of the airway mucosa.

The patient was being treated daily with antifibrinolytic agents (500 mg of tranexamic acid orally: 1 g in the morning and 1 g in the evening) as prophylactic therapy; in the case of invasive procedures, she took androgen derivatives (200 mg of danazol orally 3 times daily) from 5 days before surgery to 5 days after surgery.

The treatment plan for this patient included nonsurgical periodontal therapy and, subsequently, additional periodontal therapy with elevation of full-thickness flaps in the maxilla and mandible and extraction of compromised teeth.

Because of the necessity to carry out the specific prophylaxis before each dental procedure, we planned to perform the nonsurgical periodontal therapy in 1 session. For the same reason, surgery was scheduled in a single operation with the patient under general anesthesia with nasotracheal intubation.

Androgen derivatives (200 mg of danazol orally 3 times daily, from 5 days before surgery to 5 days after surgery) were used as preoperative prophylaxis.

A blood sample was taken from which autologous platelet-rich plasma (PRP) was prepared at the Transfusion Centre of San Gerardo Hospital: PRP was used in postextraction sites and surgically treated periodontal defects.

After the local infiltration of 2% Carbocaine (mepivacaine hydrochloride, Scandoest 2%; Saint-Maur-Des-Fosses Cedex, France) with 1:100,000 epinephrine, mucoperiosteal flaps were elevated and the extraction of the compromised teeth was performed. Granulation tissue was removed, and PRP was placed in the bone defects (Fig 3). Finally, No. 4-0 silk stitches were applied.

In the 24 hours after surgery, the postoperative course was characterized by severe edema involving the face and the oral cavity (Fig 4). No other region of the body was involved, and the patient showed no sign of dyspnea resulting from the involvement of the respiratory tract.

A constant ooze from the surgical sites occurred, with formation of voluminous clots. Therefore the patient’s hospitalization was extended 72 hours; the edema decreased gradually in the days after hospitalization (Fig 5). Periodic check-ups were scheduled 10 days, 1 month, and 2 months after surgery to monitor the state of recovery of the tissues.

Discussion

In certain cases microtrauma caused by dental treatment can trigger an angioedema attack involv-
ing the respiratory tract. Four cases of death caused by asphyxia from laryngeal edema after dental extractions have been reported in the literature. Moreover, in a review of the literature, the mortality rate from severe airway obstruction was reported to be 15% to 33% in patients with untreated angioedema.

For these reasons, obtaining an accurate history of patients with angioedema is essential: careful preoperative, intraoperative, and postoperative treatment can reduce or prevent the occurrence of complications. As a result, dental procedures can be carried out with relative safety, and appropriate treatment can be given in case an acute attack occurs.

This case report highlights the primary role of the dentist in identifying the patient with angioedema: the careful recording of a detailed and comprehensive medical history allowed the correct identification of this clinical case and the appropriate planning of the surgical procedure, avoiding intraoperative complications.

Although preoperative prophylaxis decreases the risk of acute attacks, this risk cannot be avoided completely. For this reason, it is important that both the patient and the dentist know the clinical features of acute episodes of angioedema, to identify the early signs and symptoms and permit prompt emergency intervention.

In addition, because the time interval between the occurrence of the first signs and symptoms and the onset of a clear clinical picture varies from 30 minutes to 3 days, it is important to inform the patient about the emergency procedures to be used in case an acute attack occurs.

Another aspect to be considered is the importance of a careful evaluation of treatment options and indications. When possible, conservative treatment should be preferred over more invasive procedures, such as dental extraction. For this reason, it is advised that patients with angioedema should be included in a dental prevention program with periodic check-ups.

Finally, it is important to perform surgery in a hospital facility to ensure, if necessary, prompt emergency intervention and supervision of possible complications. Performing surgery in a hospital facility such as San Gerardo Hospital allowed us to control the significant postoperative sequelae through the patient’s hospitalization in the days immediately after surgery.

References


Control of Life-Threatening Head and Neck Hemorrhage After Dental Extractions: A Case Report

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Report of a Case

A 54-year-old man presented to the North Central Bronx Hospital Dental Clinic (Bronx, NY) on October 30, 2007, with a complaint of pain in his right mandible. The patient’s vital signs were unremarkable on presentation with a blood pressure of 140/75 mm Hg and a pulse rate of 85 beats/min. The patient reported having a stroke 10 years previously that was managed with aspirin therapy for 7 years. The patient denied taking any medications. He had no known drug allergies but admitted to occasional alcohol use. He denied any drug or tobacco use on the medical intake questionnaire and during the initial consultation. He noted a history of bruising easily but reported having previous dental extractions without incident. A panoramic radiograph (Fig 1) showed multiple nonrestorable teeth (maxillary right third molar, maxillary right first premolar, maxillary right canine, maxillary left second premolar, maxillary left first molar, mandibular left second molar and mandibular right third molar, as well as a fractured crown and an exposed endodontic metal post in the

FIGURE 1. Preoperative panoramic radiograph (October 30, 2007).