Airway obstruction due to late-onset angioneurotic edema from angiotensin-converting enzyme inhibition

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Purpose: Angioneurotic edema is a well-documented complication of angiotensin-converting enzyme inhibitors (ACEI). We report a case of acute airway obstruction from a late-onset, probable ACEI-related angioneurotic edema and its subsequent management.

Clinical features: A 48-yr-old obese man presented for transurethral resection of a bladder tumour (TURBT). His past medical history included hypertension controlled with hydrochlorothiazide and quinapril which had been started 13 mo earlier. Previous surgery was uncomplicated. Midazolam was used for premedication and for intraoperative sedation together with fentanyl and propofol. After uneventful spinal anesthesia with bupivacaine, operation and recovery, he was transferred to the floor. Five hours later he developed severe edema of his face, tongue and neck, with drooling, that progressed into airway obstruction and respiratory arrest. Ventilation was restored *via* immediate cricothyroidotomy, and a subsequent tracheotomy was completed uneventfully in the operating room. His serum C1 esterase inhibitor levels at 1, 5 and 23 days later were normal. The angioneurotic edema was attributed to the ACEI treatment. The edema resolved after 48 hr, and further follow-up was unremarkable.

Conclusion: This observation is consistent with other reports that angioneurotic edema from ACEI can occur many months after the initiation of treatment. This can involve the airway and may produce life-threatening respiratory compromise. Physicians should be aware of this association and the possible need for immediate surgical intervention for the establishment of an airway in case of worsening edema or respiratory arrest.

Objectif : L'œdème angioneurotique est une complication bien documentée des inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA). Nous présentons un cas d'obstruction aiguë des voies aériennes causée par un œdème angioneurotique, probablement relié aux IECA, et son traitement subséquent.

Éléments cliniques : Un homme de 48 ans, obèse, s'est présenté pour une résection transurétrale d'une tumeur à la vessie (RTUTV). Ses antécédents incluaient de l'hypertension contrôlée depuis 13 mois par de l'hydrochlorothiazide et du quinapril. Une intervention chirurgicale antérieure s'était bien déroulée. Le midazolam avait été utilisé en prémédication et comme sédation peropératoire avec du fentanyl et du propofol. Après la rachianesthésie sans incident avec de la bupivacaïne, l'opération et la récupération, le patient a été transféré à sa chambre. Cinq heures plus tard, il a développé un important œdème du visage, de la langue et du cou, accompagné d'hypersalivation, qui a provoqué une obstruction des voies aériennes et un arrêt respiratoire. La ventilation a été restaurée par une cricothyroïdotomie immédiate, et une trachéotomie subséquente a été pratiquée sans incident dans la salle d'opération. Son niveau d'inhibiteur d'estérase C1, 1, 5 et 23 jours plus tard, était normal. La cause de l'œdème angioneurotique a été attribuée au traitement IECA. L'œdème est disparu après 48 h et le suivi a été sans particularité.

Conclusion : Ce cas confirme d'autres observations du fait que l'œdème angioneurotique causé par les IECA peut survenir de nombreux mois après le traitement initial. Cet œdème peut atteindre les voies aériennes et compromettre gravement la respiration. Les médecins doivent connaître l'association de ces conditions et la possibilité d'une intervention chirurgicale immédiate nécessaire au rétablissement de la liberté des voies aériennes en cas d'aggravation de l'œdème ou d'un arrêt respiratoire.

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ANGIONEUROTIC edema is a well-documented complication of antihypertensive therapy with angiotensin-converting enzyme inhibitors (ACEI), such as quinapril.[1] We report a case of life-threatening, acute airway obstruction from delayed onset ACEI-related angioneurotic edema 13 mo after initiation of therapy and its subsequent management.

Case report

A 48-yr-old, 118 kg, 182 cm, moderately obese man with gross hematuria presented for transurethral resection of transitional cell carcinoma of the bladder. His recent history and review of systems were otherwise negative or unremarkable. His medical history was positive only for alcoholism in the remote past, depression, and hypertension currently controlled with 25 mg hydrochlorothiazide *po* and 10 mg quinapril *po* daily. Quinapril had been started 13 mo before the current admission and continued up to the day of surgery. Other medications included 100 mg sertraline *po* and 0.25 mg alprazolam *po* daily. Previous surgical procedures included a left nephrectomy three years ago under general anesthesia, and two TURBT three and one year ago under general and spinal anesthesia respectively. All were uneventful. Family history was unremarkable or non-contributory. Physical examination and laboratory findings were also unremarkable, with the exception of elevated BUN (34 $mg \cdot dL^{-1}$) and creatinine (1.7 $mg \cdot dL^{-1}$). Hematocrit was 42.9 % and sodium and potassium concentrations were 142 and 3.8 $mmol \cdot L^{-1}$, respectively.

Standard monitoring was applied, and 2 mg midazolam *iv* was administered as premedication. Spinal anesthesia was performed by injecting 13.5 mg hyperbaric bupivacaine *via* a 22 gauge Quincke needle at L_{3-4}. The surgical procedure included TURBT and right ureteroscopy and lasted 2.5 hr. The patient was sedated intraoperatively with 3 mg midazolam *iv* total, 100 µg fentanyl total, and 25 - 75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol. Three litres of sterile water were used to irrigate the bladder. Blood loss was difficult to estimate, and 2,100 ml saline were given *iv*. Throughout the procedure, the patient breathed 3 $L \cdot min^{-1}$ oxygen *via* a nasal cannula. He did not show any evidence of airway obstruction, respiratory distress, or hemodynamic instability. The immediate postoperative course in the postanesthesia care unit (PACU) was uneventful, and the patient was transferred to his room 2.5 hr later.

No medication was given to the patient in the PACU or after admission to the floor. Five hours after the completion of surgery, the patient was found sitting on the bed in respiratory distress. Considerable edema of the face and neck as well as drooling were noted. Repeated attempts were made to suction oral secretions and, because of worsening stridor, 0.5 mg epinephrine *sc* was given twice, along with 50 mg diphenhydramine *iv*. Within five minutes, symptoms and signs consistent with upper airway obstruction developed, cyanosis and respiratory arrest followed, and the emergency resuscitation procedures were initiated. The presence of severe purple edema of the face and neck and protrusion of a severely edematous tongue were noted. Direct laryngoscopy for tracheal intubation was not attempted. Instead, an immediate cricothyroidotomy *via* a horizontal incision was performed urgently and a 7.5 ID endotracheal tube was placed in the trachea. The lungs were ventilated with 1.0 FiO_2 through a resuscitation bag (AMBU), and bilateral breath sounds were noted. An initial hemoglobin saturation (SpO_2) reading of 78% was obtained. Then, 125 mg thiopental and 5 mg midazolam were given *iv*. The SpO_2 increased to 95%, and the patient was transferred to the operating room to complete a tracheotomy. Preoperative arterial blood analysis while breathing 1.0 FiO_2 showed pH of 7.2, $PaCO_2$ of 63 mmHg, PaO_2 of 92 mmHg, hemoglobin saturation of 95% and bicarbonate concentration of 25 $mmol \cdot L^{-1}$. Sodium and potassium concentrations were 139 $mmol \cdot L^{-1}$ and 3.5 $mmol \cdot L^{-1}$, respectively.

The intraoperative course was uneventful. The lungs were easily mechanically ventilated with an FiO_2 of 1.0 and an SpO_2 of 100% was maintained. Postoperatively, the patient was transferred to the Intensive Care Unit and treated with 50 mg diphenhydramine and 100 mg hydrocortisone *iv*. Angiotensin-converting enzyme inhibitor therapy was discontinued. The edema resolved completely over the next 48 hr; no adverse neurological or cardiac consequences were documented, and the patient was discharged home six days later. His C1 esterase inhibitor levels measured 1, 5 and 23 days later were found to be normal and qualitatively functional. The patient was doing well upon further follow-up two months later.

Discussion

Angioneurotic edema is a demarcated, painless, non-pruritic, non-pitting edema of the deep dermis and subcutaneous tissue, usually involving the face, upper airway, gastrointestinal tract and extremities. It can be hereditary and secondary to C1 esterase inhibitor deficiency; but most commonly it occurs in sporadic, idiopathic forms which affect up to 10% of the population. Angioneurotic edema can be precipitated by a variety of environmental or pharmacological factors.[1]

Angiotensin-converting enzyme inhibitors (ACEI) commonly used for the treatment of hypertension and

congestive heart failure are associated with an incidence of angioneurotic edema from 0.1 to 2%.[1] Although a retrospective study of 36,000 patients showed that 60 - 70% of the incidences occurred in the first week of administration,[1] other publications have shown that late onset (up to one year after initiation of therapy) is also possible.[2,3]

Angioneurotic edema crisis is believed to occur as a result of inhibition of angiotensin-converting enzyme (ACE), and the subsequent block of metabolism of bradykinin and substance P, which are also metabolized by the same enzyme.[4,5] Both of these substances can mediate the reactions of vasodilatation, increased capillary permeability and edema formation.[6] Angioneurotic edema in conjunction with ACEI can produce severe airway obstruction,[7] respiratory distress,[8] and death.[9]

We attributed the upper airway obstruction in our patient to a late-onset attack of angioneurotic edema resulting from ACEI treatment initiated 13 mo before the incident. Other possible etiological associations were ruled out from the negative family and past medical history, as well as the negative testing for C1 esterase inhibitor deficiency. The presentation of symptoms and signs such as dyspnea, tongue swelling, drooling, and purple facial edema are recognized manifestations of the disease.[1,2] However, the events and the exact etiological associations which precipitated the crisis are unclear. Jain *et al.* recognized obesity, a history of previous face and neck surgery, and prior intubation as risk factors.[3] The interaction of the above factors and edema from bradykinin activation can result in a relatively narrowed airway that can evolve into severe obstruction. Of these risk factors, only obesity was present in our patient. However, we do not believe that obesity solely contributed to the angioneurotic edema in the absence of prior facial surgery or tracheal intubation. The association of airway instrumentation and precipitation of angioneurotic edema has been documented.[10] In our patient, it is possible that attempts to suction secretions from the oropharynx may have precipitated a severe attack on the basis of a subclinical mild degree of airway soft tissue edema. This might have resulted from excessive absorption of water from irrigation of the bladder, so this constitutes a remote possibility.

Codeine can lead to generation of tissue bradykinin from mast cell degranulation,[6] constituting thus another risk factor. However, in reviewing the patient's profile, no codeine or postoperative analgesics were administered to him.

Regardless of the etiological speculations, the urgent management of the airway was the most appropriate task under the clinical circumstances. It was considered that attempts at laryngoscopy and oral intubation of the trachea would have been too risky. Although medical management (epinephrine and diphenhydramine) had been tried previously, it was the emergency cricothyroidotomy that proved to be life-saving. Available literature indicates that our action was the most appropriate for the most severe cases of angioneurotic edema when respiratory arrest ensues.[2,7] Further management included observation in the ICU and treatment with antihistamine drugs and corticosteroids, which has also been reported.[2,7,10]

No other angioneurotic edema crisis has been reported to occur 13 mo after the initiation of ACEI therapy. This presentation, typical for a late-onset angioneurotic edema from ACEI, indicates the need for physicians to be aware of the potential for such complications in patients treated with ACEI. Angioneurotic edema may occur many months after initiation of treatment, but it may be difficult to recognize because of a lack of a definite temporal correlation. Events such as airway instrumentation and codeine administration can be precipitating factors. Immediate surgical intervention may be necessary to restore ventilation in the situation of worsening edema or respiratory compromise.

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