CASE REPORT

A challenging case of bradykinin-mediated angioedema with airway obstruction: management and therapeutic strategies

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ABSTRACT

Angioedema is a potentially life-threatening condition that can have an allergic origin, usually mediated by histamine or a non-allergic origin, mediated by bradykinin. The distinction between these origins may present a clinical challenge at first approach, especially in cases that appear as an emergency and the outcome is time dependent. The authors describe a rare case of bradykinin angioedema associated with airway obstruction and discuss the right approach and therapeutic options. A 46-year-old patient under ACE inhibitor, renin-angiotensin-aldosterone blocker and beta blocker presented with difficulty swallowing, shortness of breath and angioedema, associated with inspiratory stridor, incapacity of talking, plantar pruritus and vomits minutes after ingestion of shrimp. The symptoms did not respond to epinephrine, anti-histamines or steroids. The airway quickly became an emergency and the authors discuss the importance of airway obstruction management and having a multi-disciplinary well-defined plan of approach with backup plans. Exuberant angioedema persisted leading to the suspicion of drug induced angioedema. Treatment with tranexamic acid 1g 6/6h and icatibant 30 mg 6/6h (3 doses) was started with resolution. In these cases, the rapid institution of the right pharmacological line will relate significantly to a better outcome. It is particularly important because, as their underlying physiopathologic mechanism differ, bradykinin mediated angioedema does not respond to drugs that histamine mediated angioedema does, like corticosteroids and antihistaminic. In severe and life-threatening cases icatibant and tranexamic acid have proven to be an effective therapy.

KEYWORDS: airway obstruction; angioedema; bradykinin; histamine; icatibant; tranexamic acid

INTRODUCTION

Angioedema may be histamine-mediated, dependent or non-dependent on immunoglobulin E or bradykinin-mediated. The most common cases are histaminergic and the clinical differential diagnosis between them remains a challenge [1].

Bradykinin-mediated angioedema is a rare condition that may compromise upper airways and present as a life-threatening emergency. It results from increased bradykinin production or inhibition of its degradation and consequent increased tissue permeability and vasodilation. It may be hereditary, acquired or drug induced [2-5].

Bradykinin (BK) is a peptide produced by Factor XII-triggered cleavage of kininogen by kallikrein. Plasmin may induce Factor XII activation and potentiate the production of BK.

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C1 esterase inhibitor (C1-INH) is an important regulatory protein of the complement system and fibrinolysis. It regulates the BK production acting as a blocker to its overproduction by inhibiting different molecules such as kallikrein and activated Factor XII (Figure 1). Mutations related to the C1-INH gene impairing its expression or function result in hereditary angioedema type I and II. Conditions that cause a C1-INH overconsumption, like autoimmune or lymphoproliferative diseases, result in non-hereditary angioedema. In drug induced angioedema, catabolic enzymes that are involved in the degradation of bradykinin, like angiotensin-converting enzyme (ACE), dipeptidyl peptidase 4, aminopeptidase, neutral endopeptidase and carboxypeptidase are blocked [6].

Antihistamines and corticoids are not an efficient treatment in bradykinin-mediated angioedema. The available treatments are based on C1-INH substitution, inhibition of the kallikrein-kinin pathway (ecallantide, tranexamic acid) and bradykinin type 2 receptors (B2R) antagonist (icatibant). In particular, tranexamic acid inhibits the activation of plasminogen to plasmin, essential to kallikrein activation and bradykinin formation [7-9].

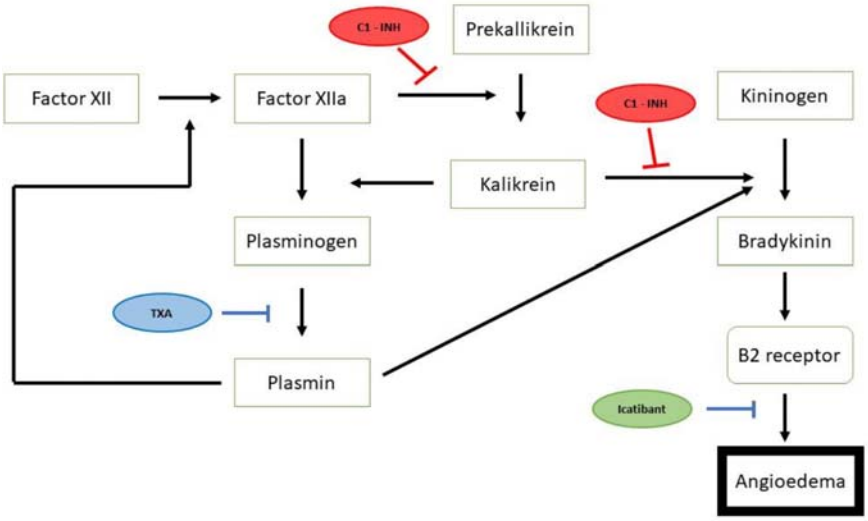

Fig. 1. Mechanism of bradykinin-mediated angioedema.

The choice of drug should consider that the efficacy of the treatment is time-dependent, so the sooner the better outcome. The first drugs of choice are icatibant (30 mg subcutaneous) or C1-INH concentrate (20 UI/Kg intravenous). Icatibant should be used with caution in patients with acute ischemic heart disease or unstable angina. Tranexamic acid is an alternative that has the advantage of availability with an associated low rate of adverse effects [10-13].

CASE PRESENTATION

A 46-year-old black male patient, with a history of hypertension controlled with ACE inhibitor, renin-angiotensin-aldosterone blocker, and beta blocker for several years, type 2 diabetes controlled with metformin and hyperuricemia controlled with alopurinol presented to the emergency room with difficulty swallowing, shortness of breath and angioedema of the face, lips, and tongue. These complaints associated a few minutes after installation with inspiratory stridor, incapacity of talking, plantar pruritus and vomits. The symptoms started while he was having lunch, 5 minutes after ingestion of shrimp. The medical prehospital team assisted the patient at the site 10 minutes after and administered sequentially epinephrine 0,5 mg IM twice, clemastine 2 mg IV, hydrocortisone 200 mg IV and epinephrine 100 mcg IV with little improvement.

On hospital admission he had a GCS 14, angioedema has described, superficial ventilation, spO2 100% with nasal cannula 4l/m, wheezes at auscultation, MAP>70 mmHg, HR 90 ppm. Progressively the patient deteriorated and the ICU was contacted admitting the patient to ensure airway patency.

Immediately delineated 3 plans of multidisciplinary approach with Anaesthesiology, Pneumology and Intensive care team. Plan A executed by Anaesthesiology consisted in awaked videolaringoscopy approach with sedation with dexmedetomidine and Ketamine which failed because of subglottic massive edema. Plan B which consisted in nasal intubation with bronchoscopy by Pneumologist also failed with impossibility to progress through the cornets. At this time the patient presented important desaturation. Plan C was then executed by the Intensive Care team and consisted in FONA (Front-of-neck airway) approach with cricothyrotomy. The patient had a BMI of 30 and a short neck. A horizontal incision was made in the cricothyroid membrane, followed by insertion of a Frova Stylet and a ETT 6 through it. After starting rescue ventilation quick recovery of oxygenation was accomplished. The patient was the submitted to a surgical tracheostomy. As a complication of the emergency procedure, he had pneumomediastinum and pneumothorax.

By this time, we were able to uncover the allergy history of the patient and he had 4 similar but less severe episodes after ingestion of sea food. Although he started on corticoids and antihistamines an exuberant angioedema persisted leading to the suspicion of other cause, namely drug induced angioedema (more likely ACE inhibitor or renin-angiotensin-aldosterone blocker). Treatment with tranexamic acid 1g 6/6h and icatibant 30 mg 6/6h (3 doses) was started with resolution of angioedema. The laboratory study showed normal values of Histamine, C1 INH, C3, C4, tryptase and IgE. Radioallergosorbent (RAST) test for *Pandalus borealis* (shrimp) was normal.

He had mechanical ventilation during 6 days and the tracheostomy was closed after 18 days. He returned to his normal life with renin-angiotensin-aldosterone system drugs eviction.

DISCUSSION

Angioedema with swelling of upper airway structures is a life-threatening time-dependent emergency. The approach starts with assuring a patent airway and it should consider several alternatives in case one fails, from less invasive to more invasive and with more complications associated. The FONA approach is the final lifesaving method in airway obstruction management [14,15].

Histamine-mediated angioedema (HMA) is caused by a release in histamine from mast cells and basophils. The more frequent triggers are allergens such as specific foods, like shellfish or nuts, drugs, and insect stings. The onset of symptoms is usually rapid, occurring within minutes to an hour after exposure. The duration is generally shorter, from a few hours to a day. Swelling often affects the skin and

mucous membranes, including the face, lips, eyes and hands. Urticaria is commonly associated. Antihistamines are the first-line treatment and in severe cases corticosteroids are required to reduce inflammation and suppress the immune response. In case of anaphylaxis epinephrine is used to act on alpha adrenergic receptors as a vasoconstrictor and in beta 2 adrenergic receptors as a bronchodilator. It also stimulates beta 1 adrenergic receptors in the heart leading to an increase in heart rate and cardiac output. And can also modulate the release of inflammatory mediators such as histamine, reducing the response that led to the onset of angioedema. The most important laboratory tests to consider are made to identify triggers for allergic reactions such as Allergen-specific IgE testing or skin Prick test to identify specific allergens. Serum Tryptase can also be measured as elevated levels can suggest mast cell activation [16].

Bradykinin-mediated angioedema is caused by an elevation in bradykinin which leads to increased vascular permeability. It may be hereditary, acquired or drug induced. The onset of symptoms is often slower taking several hours to develop and usually last longer, for about 48-72h. Swelling includes skin, mucous membranes, and deeper tissues. Commonly involves the face, lips, tongue, throat, and extremities. This type of angioedema does not respond to antihistamines or steroids. It responds to C1-INH replacement therapy, inhibition of the kallikrein-kinin pathway and bradykinin type 2 receptors (B2R) antagonist. Important laboratory testing includes the C1-INH functional assay, C4 and C1q complement levels [4].

Several independent risk factors associated to ACEI – induced angioedema have been described, namely black-skin, female sex, or age older than 65 years. Although the occurrence of angioedema after initiating treatment is more common, there are reports of patients with a latency period of more than 10 years from the beginning of ACEI therapy. Angiotensin receptor blockers (ARBs) are also implied, less commonly in the occurrence of angioedema [17].

The etiology of angioedema should be considered from start since the pathophysiologic mechanism may vary in different cases and in subsequence so does the treatment. Bradykinin-mediated angioedema does not respond to treatment with corticoids or antihistamines since it is not histamine-mediated. Distinguishing between a bradykinin or histamine mediated angioedema proves to be very difficult in some cases, such as in the present case where the clinical features and the history of the patient could lead the differential diagnosis impression both ways.

In this particular case, the initial diagnosis approach was of HMA regarding the patient had a confounding clinical history. HMA triggers generally involve allergens, such as sea food, and the onset of symptoms is usually rapid as it was described. However, HMA respond to treatment with antihistamines and corticosteroids. Later, the laboratory study showed normal values of histamine, tryptase and IgE. specific test for shrimp.

This patient was also on ACE inhibitor, renin-angiotensin-aldosterone blocker, and beta blocker medication. These drugs are often associated with BK-mediated angioedema, and although the onset is usually slower the symptoms tend to last longer, usually for 48-72h. Gastrointestinal involvement is frequent as is in HMA [17].

Often the clinical history and presentation of this entities overlaps and the failure to respond to therapeutic should incite the search of another pathophysiologic mechanism. The laboratory study did not find any abnormalities, and the clinical response only after the institution of icatibant and tranexamic acid was evident associated with failure of antihistaminics and corticosteroids which points to the diagnosis of BK-mediated angioedema [17,18]. Tranexamic acid is an easily available and effective treatment and may prove to be important while waiting for more specific and less accessible treatment as icatibant and C1INH concentrate [19].

CONCLUSION

This case brings out the requirement to a rapid assessment to angioedema as it can become a life-threatening condition if associated with airway compromise. It shows a systematic and multidisciplinary approach that should be implemented in emergency teams.

It also highlights the importance of considering bradykinin-mediated angioedema in differential diagnosis as it does not respond to steroids and antihistamines and requires a specific treatment like with icatibant and tranexamic acid that have proven to be an effective therapy.

Declaration of interest

The authors declare no conflict of interests.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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