Case Report

Simultaneous Acute Pancreatitis and Angioedema Associated with Angiotensin-Converting Enzyme Inhibitor

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ABSTRACT. Angiotensin-converting enzyme inhibitors (ACEI) are commonly prescribed drugs for blood pressure (BP) control and renal protection. The use of ACEI is not associated with an increased risk of acute pancreatitis and ACEI-induced angioedema is rare. A 36-year-old woman presented with vomiting, headache, and aphasia. Her BP was 220/100 mm Hg. Urine analysis revealed proteinuria (2+), hematuria (3+). Serum creatinine level was at 1125 μmol/L. She had anemia with 6.1 g/dL of hemoglobin and thrombocytopenia (61,000/mm3). Renal histology revealed lesions of thrombotic microangiopathy. The diagnosis of atypical hemolytic uremic syndrome was made by the complement factor I deficiency. Plasma exchanges could not be done. She was placed on peritoneal dialysis for renal insufficiency. We introduced an ACE (captopril) for the treatment of high BP. Twelve-hours after taking the first dose, she experienced severe epigastric pain and two episodes of vomiting. Serum lipase was 560 IU/L, and abdominal computed tomography showed Stage B pancreatitis. Twenty-four hours later, the patient developed marked edema of the neck region without dyspnea or dysphonia. Cervical ultrasound revealed the infiltration of the subcutaneous tissues. Captopril was stopped with the progressive disappearance of the edema. Serum lipase was 350 IU/L and then normalized at the end of the 4th day. Clinicians should be careful about widely used drugs and their side effects. ACEI can cause potentially life-threatening complications such as angioedema and acute pancreatitis. Possibly, there could be a common mechanism for the onset of pancreatitis and angioedema under ACEI.

Introduction

Angiotensin-converting enzyme inhibitors (ACEI) are used worldwide and are a real advancement for the treatment of systemic hypertension and/or cardiac failure.
Visceral angioedema induced by ACEI is a rare, but well-established entity, described in some publications. The reported incidence of ACEI-induced angioedema ranges from 0.1% to 0.7% of all patients taking ACEI and accounts for up to 30% of all visits to the emergency department for angioedema. Angioedema is a localized swelling of deep dermis, subcutaneous, or submucosal tissue caused by the vascular extravasation of fluid into the interstitium. It may occur months or even years after the start of ACEI treatment.

Pancreatitis has already been described in association with ACEI, but it is even more uncommon than angioedema. Approximately 2% of pancreatitis in adults is drug-induced, but the use of ACEI is not associated with an increased risk of acute pancreatitis.

The action of angiotensin II is mediated through the interaction with two pharmacologically defined receptor subtypes, namely type 1 (AT1) and type 2 (AT2) that are distributed in numerous target tissues and organs.

The expression of renin-angiotensin system (RAS) components occurs in multiple tissues/organs. This tissue RAS is involved in the regulation of respective tissue/organ functions. The physiopathological mechanism may be related to effects on the kininogen-kinin (bradykinin) system since the breakdown of bradykinin is prevented by ACE inhibitors. A local accumulation of bradykinin may lead to both angioedema and acute pancreatitis.

We report a patient who experienced ACEI-induced angioedema and acute pancreatitis. The patient had a favorable outcome.

Case Report

Informed consent was obtained from the patient before presenting the report. A 36-year-old woman presented to our department with vomiting, headache associated with paresthesia of the upper right limb and aphasia. Her medical history included galactorrhea for one year. Results of a physical examination revealed a patient with mucocutaneous pallor and oliguria. Her blood pressure (BP) was 220/100 mm Hg and urine analysis revealed proteinuria (2+), hematuria (3+). Her serum creatinine level was 1125 μmol/L. She had anemia with 6.1 g/dL of hemoglobin, thrombocytopenia at 61,000/mm³, and lactate dehydrogenase at 3154 IU/L. Renal histology: appearance of thrombotic microangiopathy (H and E staining and silver staining).
ultrasound showed two normal-sized kidneys, with regular contours but with poor cortico-medullary differentiation. The cerebral scan was normal. Renal histology revealed lesions of thrombotic microangiopathy (Figure 1). We initiated the etiological assessment of hemolytic uremic syndrome (HUS) and measurement of serum complement components showed normal serum levels of C3, C4 and factor H but factor I deficiency (Table 1). The diagnosis of atypical HUS was made by the complement factor I deficiency: Plasma exchanges unfortunately could not be made. Eculizumab has not been introduced because of its unavailability in Tunisia. She was placed on peritoneal dialysis for renal insufficiency. The initial treatment of high BP was with nicardipin, methyldopa, and furosemide and subsequently we introduced an ACEI (captopril). Twelve hours after taking the first dose, she experienced severe epigastric pain with cramps. She had two episodes of vomiting and was unable to eat. The patient denied shortness of breath, wheezing, or rash. Significant physical findings included only moderate epigastric tenderness. The patient had an initial heart rate of 88 beats/min, a respiratory rate of 18 breaths/min with an SPO2 of 99% on room air, an oral temperature of 37°C, and a BP of 143/85 mm Hg. The serum lipase was 560 IU/L. Abdominal computed tomography showed a mildly edematous, inflamed pancreas reported as stage B pancreatitis.

Twenty-four hours later, the patient developed marked edema of the neck region without dyspnea or dysphonia. Cervical ultrasound revealed infiltration of the subcutaneous tissues. ACEI-induced angioedema was suspected. Captopril was stopped with progressive disappearance of the edema. Serum lipase came down to 350 and then normalized at the end of the 4th day.

### Discussion

ACEI are one of the most prescribed medications worldwide. Angioedema is a well-recognized adverse effect of this class of medications, with a reported incidence of ACEI-induced angioedema ranging from 0.1% to 1.0%.

ACEI angioedema is a class effect and is not dose-dependent, and thus, symptoms can occur any time from a few hours up to 10 years after the initial dose. It occurs more commonly in African-American patients and tends to be particularly severe in elderly African-American women. African Americans have a 4.5-fold higher rate of ACEI angioedema as compared to Caucasians.

The pathophysiology of ACEI angioedema remains controversial. The mechanism is thought to be related to its effect on the kallikrein-kinin system. Kallikrein is a protease that converts high-molecular-weight kininogens into kinins, primarily bradykinin. ACEI prevent the breakdown of bradykinin. Decreased degradation of bradykinin, a potent vasodilator that increases vascular permeability, is thought to be the main cause of ACEI-associated angioedema.

ACEI have been associated with pancreatitis. The presence of a local RAS in the pancreas, which play a role in the regulation of pancreatic microcirculation, affect islet hormonal secretion. The mechanism of ACEI to cause acute pancreatitis is also caused by angioedema in the pancreatic ducts due to bradykinins. Pancreas contains a local RAS that is involved in the physiological regulation of digestive enzyme secretion and appears to be upregulated during pancreatic inflammation.

**Table 1. Measurement of serum complement components.**

| Complement components | Results | Normal values |
|-----------------------|---------|---------------|
| C3                    | 0.762   | 0.743–1.62 g/L |
| C4                    | 0.439   | 0.162–0.53 g/L |
| CH50                  | 122     | 75%–138%      |
| Factor H              | 125%    | 70%–120%      |
| Factor I              | 49%     | 70%–120%      |
Pancreatic RAS was subject to regulation by chronic hypoxia and by acute pancreatitis.\textsuperscript{20,21} Furthermore, ACEI may alter the Kallikrein-kinin system and the accumulation of Kallikrein appears to be an important trigger of pancreatic inflammation during treatment with ACEI.\textsuperscript{22}

The trigger of pancreatic damage induced by ACEI is attributed to hypersensitivity or a metabolic idiosyncratic reaction in almost all cases.\textsuperscript{23} Our patient had no fever, rash, or eosinophilia. We found no alternative pancreatic causes for our patient, such as biliary stones or sludge, alcohol use, hypertriglyceridemia, hypercalcemia, or active viral infection, to explain the onset of acute pancreatitis in this case.

Treatment must be stopped immediately when medication is suspected to cause these adverse events and to avoid any rechallenge because of the high risk of inducing a life-threatening situation.\textsuperscript{24} Institution of supportive measures such as airway management, fluids, and vital sign monitoring is very important.

This is not an immunoglobulin E-mediated allergic reaction. Conventional treatment with regimens used to control allergic angioedema: epinephrine, corticosteroids, or antihistamines will not reverse the pathology.\textsuperscript{25}

There are no agents approved by the Food and Drug Administration to target ACEI angioedema and to prevent intubation. C1 inhibitors are approved for hereditary angioedema but may show promise in alleviating inflammation associated with ACEI angioedema.\textsuperscript{26} Reduced C1 inhibitor activity is correlated with increased bradykinin levels secondary to activation of the kallikrein-kinin system in patients with hereditary angioedema.\textsuperscript{27}

According to the 2013 French guidelines for treating ACEI angioedema, the use of specific bradykinin antagonists or C1 inhibitors is justified.\textsuperscript{28} Some authors reported the successful use of C1 inhibitor therapy to alleviate asphyxia from ACEI angioedema when bradykinin antagonists were not available.\textsuperscript{29} Airway protection is essential in ACEI angioedema, and because of their ability to control serum concentration of bradykinin, C1 inhibitors have been shown to be effective in preventing airway compromise in these patients.\textsuperscript{30,31} The guidelines suggest an intravenous dose of C1 inhibitor 20 IU/kg to be an effective treatment strategy. However, the overall cost of C1 inhibitors is high. Of the novel agents conventionally used for hereditary angioedema, icatibant (Selective Bradykinin B2 Receptor Antagonists) has the highest level of evidence and has been reported to be successful in limiting the progression of angioedema.\textsuperscript{32,33}

**Conclusion**

High incidence of serious ACEI angioedema appears largely unappreciated and under reported and requires further investigation.

Some ACEI, alone or in combination with hydrochlorothiazide, can cause potentially life-threatening complications such as angioneurotic edema and acute pancreatitis, not only at the beginning of treatment but also after long-term therapy.

The diagnosis is often challenging and time consuming, requiring careful evaluation of the patient’s medication and their side effects.

We must stop treatment immediately when medication is suspected to cause these adverse events. Medication recently developed, icatibant, a selective and specific antagonist of bradykinin B2 receptors, has been used to treat ACEI angioedema with some success.

**Conflict of interest:** None declared.

**References**

1. Korniyenko A, Alviar CL, Cordova JP, Messerli FH. Visceral angioedema due to angiotensin-converting enzyme inhibitor therapy. Cleve Clin J Med 2011;78:297-304.
2. Frutuoso B, Esteves J, Silva M, Gil P, Carneiro AC, Vale S. Visceral angioedema induced by angiotensin converting enzyme inhibitor: Case report. GE Port J Gastroenterol 2016;23:166-9.
3. Benson BC, Smith C, Laczek JT. Angiotensin converting enzyme inhibitor-induced gastrointestinal angioedema: A case series and literature review. J Clin Gastroenterol 2013;
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47:844-9.

4. Brown T, Gonzalez J, Monteleone C. Angiotensin-converting enzyme inhibitor-induced angioedema: A review of the literature. J Clin Hypertens (Greenwich) 2017; 19:1377-82.

5. Cheng RM, Mamdani M, Jackevicius CA, Tu K. Association between ACE inhibitors and acute pancreatitis in the elderly. Ann Pharmacother 2003;37:994-8.

6. de Gasparo M, Catt KJ, Inagami T, Wright JW, Unger T. International union of pharmacology. XXIII. The angiotensin II receptors. Pharmacol Rev 2000;52:415-72.

7. Leung PS, Sernia C. The renin-angiotensin system and male reproduction: New functions for old hormones. J Mol Endocrinol 2003;30:263-70.

8. Winters ME, Rosenbaum S, Vilke GM, Almazroua FY. Emergency department management of patients with ACE-inhibitor angioedema. J Emerg Med 2013;45:775-80.

9. Howes LG, Tran D. Can angiotensin receptor antagonists be used safely in patients with previous ACE inhibitor-induced angioedema? Drug Saf 2002;25:73-6.

10. Kaplan AP, Gravens MW. Angioedema. J Am Acad Dermatol 2005;53:373-88.

11. Maier C. Life-threatening postoperative angioedema following treatment with an angiotensin converting enzyme inhibitor. Anaesthestist 1995;44:875-9.

12. Pillans PI, Coulter DM, Black P. Angioedema and urticaria with angiotensin converting enzyme inhibitors. Eur J Clin Pharmacol 1996; 51:123-6.

13. Kupfer Y, Ramachandran K, Tessler S. ACE inhibitor-induced angioedema in elderly African American females requiring tracheostomy. J Natl Med Assoc 2010;102:529-30.

14. Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. Clin Pharmacol Ther 1996;60:8-13.

15. Javau N, Karami A, Stirnemann J, et al. Bradykinin-mediated angioedema: Factors prompting ED visits. Am J Emerg Med 2013; 31:124-9.

16. Ip SP, Kwan PC, Williams CH, Pang S, Hooper NM, Leung PS. Changes of angiotensin-converting enzyme activity in the pancreas of chronic hypoxia and acute pancreatitis. Int J Biochem Cell Biol 2003;35:944-54.

17. Maringhini A, Termini A, Patti R, Ciambra M, Biffarella P, Pagliaro L. Enalapril-associated acute pancreatitis: Recurrence after rechallenge. Am J Gastroenterol 1997;92:166-7.

18. Kuoppala J, Enlund H, Puikkonen J, Kastarinen H, Jyrkkä J, Happonen P, et al. ACE inhibitors and the risk of acute pancreatitis—a population-based case-control study. Pharmacoepidemiol Drug Saf 2017;26:853-7.

19. Tsang SW, Ip SP, Leung PS. Prophylactic and therapeutic treatments with AT 1 and AT 2 receptor antagonists and their effects on changes in the severity of pancreatitis. Int J Biochem Cell Biol 2004;36:330-9.

20. Chan WP, Fung ML, Nobiling R, Leung PS. Activation of local renin-angiotensin system by chronic hypoxia in rat pancreas. Mol Cell Endocrinol 2000;160:107-14.

21. Leung PS, Chan WP, Nobiling R. Regulated expression of pancreatic renin-angiotensin system in experimental pancreatitis. Mol Cell Endocrinol 2000;166:121-8.

22. Griesbacher T, Lembek F. Effects of the bradykinin antagonist, HOE 140, in experimental acute pancreatitis. Br J Pharmacol 1992;107:356-60.

23. Urmoski E, Grillo A, Rosini JM. Use of C1 inhibitor for angiotensin-converting Enzyme (ACE) inhibitor-induced angioedema decreases mechanical Ventilation Time. J Emerg Med 2015;49:e173-5.

24. Bexelius TS, Ljung R, Mattsson F, Lu Y, Lindblad M. Angiotensin II receptor blockers and risk of acute pancreatitis – A population based case-control study in Sweden. BMC Gastroenterol 2017;17:36.

25. Roberts JR, Lee JJ, Marthers DA. Angiotensin-converting enzyme (ACE) inhibitor-induced angioedema: The silent epidemic. Am J Cardiol 2012;109:774-5.

26. Gallego-Rojo FI, Gonzalez-Calvin JL, Guilarte J, Casado-Caballero FJ, Bellot V. Perindopril-induced acute pancreatitis. Dig Dis Sci 1997; 42:1789-91.

27. Banerji A. Hereditary angioedema: Classification, pathogenesis, and diagnosis. Allergy Asthma Proc 2011;32:403-7.

28. Nosbaum A, Bouillet L, Flochard B, Javau N, Launay D, Boccon-Gibod I, et al. Management of angiotensin-converting enzyme inhibitor-related angioedema: Recommendations from the French National Center for Angioedema. Rev Med Interne 2013;34:209-13.

29. Rasmussen ER, Bygum A. ACE-inhibitor
induced angio-oedema treated with complement C1-inhibitor concentrate. BMJ Case Rep 2013;2013. pii: bcr2013200652.
30. Lewis LM. Angioedema: Etiology, pathophysiology, current and emerging therapies. J Emerg Med 2013;45:789-96.
31. Wilkerson RG, Martinelli AN, Oliver WD. Treatment of angioedema induced by angiotensin-converting enzyme inhibitor. J Emerg Med 2018;55:132-3.
32. Sinert R, Levy P, Bernstein JA, Body R, Sivilotti ML, Moellman J, et al. Randomized trial of icatibant for angiotensin-converting enzyme inhibitor-induced upper airway angioedema. J Allergy Clin Immunol Pract 2017;5:1402-9000.
33. Riha HM, Summers BB, Rivera JV, van Berkel MA. Novel therapies for angiotensin-converting enzyme inhibitor-induced angioedema: A systematic review of current evidence. J Emerg Med 2017;53:662-79.

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