

Title: ACE inhibitor-associated intestinal angioedema in orthotopic heart transplantation

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Abstract

Angiotensin-converting enzyme inhibitor induced angioedema commonly involves the head and neck area. We report a case of angiotensin-converting enzyme inhibitor induced intestinal angioedema in a heart transplant recipient on mTOR immunosuppression. A 36 year-old Caucasian woman with history of heart transplantation on sirolimus, tacrolimus and prednisone presented to the Emergency Department with abdominal pain, one day following lisinopril initiation. A computer tomography scan demonstrated diffuse bowel wall thickening consistent with pancolitis and edema. She was subsequently diagnosed with angiotensin-converting enzyme inhibitor induced angioedema. Patients on mTOR immunosuppression are at higher risk for this potentially life-threatening side effect. Knowledge of this interaction is critical for providers prescribing mTOR agents.

Introduction

Angioedema is a swelling of the skin and mucous membranes which typically presents with swelling of the lips, tongue or face; however, it can manifest in any organ system. It is thought to be caused by increases in histamine and bradykinin that cause increased capillary leakage and edema. Angioedema associated with angiotensin-converting enzyme (ACE) inhibitors is a well-known phenomenon with incidence rates near **0.4%** (1).

We report a case of acute intestinal angioedema related to ACE inhibitor administration in an orthotopic heart transplant recipient.

Case Report

A 36 year-old Caucasian woman presented with severe diffuse abdominal pain one day following initiation of lisinopril for hypertension. She had a history of a tachycardia-induced cardiomyopathy requiring orthotopic heart transplantation in 2002, and was maintained on sirolimus, tacrolimus, and prednisone for immunosuppression. She was prescribed an ACE inhibitor the day prior to the admission for elevated blood pressures, a class of medications that she had never taken before. On presentation, she endorsed rapid onset of abdominal pain, dizziness, and sweating. She was without fevers, had a heart rate of 79 beats per minute, a blood pressure of 170/105 mm Hg that decreased to 74/52 mm Hg 8 hours after arrival and normalized with administration of intravenous fluids. She had diffuse tenderness to light palpation below the umbilicus and abdominal guarding on exam with clear lung fields notable for absence of bronchospasm and no urticaria or rash on skin exam. Initial laboratory analyses demonstrated a mild increase in white blood cells and liver tests.

A computer tomography (CT) of the abdomen and pelvis (Figure 1A and B) revealed diffuse wall thickening with enhancement affecting both small and large bowels and fat stranding consistent with pancolitis and edema. Given the time of onset and relationship with ACE inhibition, she was diagnosed with intestinal angioedema secondary to ACE inhibitor initiation. Alternative causes for diagnosis were considered; however, there was an absence of risk factors for other causative etiologies and further lab workup was unremarkable. **She was not evaluated for hereditary angioedema.** All oral medications were then held. She was monitored with serial abdominal exams and given opiates. All laboratory studies normalized, and home medications

including immunosuppressive agents were restarted the next day except for lisinopril. Over a 72-hour period, her pain resolved and she was discharged to home with the addition of amlodipine 2.5 mg daily for hypertension.

Discussion

Use of immunosuppressive medications with ACE inhibitors is a risk factor for angioedema among patients on immunosuppression, including the heart transplant population (2-7). Isolated involvement of the gastrointestinal tract is a rare presentation of ACE inhibitor induced angioedema. Although not definitively demonstrated in humans, one hypothesis is that immunosuppressive agents increase this risk by decreasing the activity of circulating dipeptidyl peptidase IV (both **dipeptidyl peptidase IV** and ACE inactivate vasodilatory **bradykinin and** substance P). This effect is seen with both calcineurin and mTOR inhibitors, but is greater with the latter (2, 8). Reports have demonstrated episodes of facial and sublingual angioedema in kidney transplant patients on mTOR inhibitors without concomitant use of an ACE-inhibitor (4, 9). In September 2015, the Food and Drug Administration (FDA) issued an update on the safety of ACE inhibitors stating that use in combination with mTOR inhibitors may increase the risk for angioedema (10). Despite this, our electronic medical record did not have this as a drug interaction.

In summary, this case and the relevant medical literature suggest that ACE inhibitor induced **angioedema** of the gastrointestinal tract must be considered in the differential diagnosis of both acute and recurrent abdominal pain in patients receiving concomitant ACE inhibitor and immunosuppression with an mTOR inhibitor. Despite the increasing incidence of ACE inhibitor induced **angioedema** in patients taking calcineurin inhibitors (2-9), extrapolation of basic science studies suggest mTOR inhibitors pose a greater risk to

interact with ACE inhibitors. Physicians prescribing mTOR inhibitors should have knowledge of the potential interaction.

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Figure 1A. Computed tomography imaging of intestinal angioedema in the coronal view. Arrow demonstrates profound small and large bowel wall edema and fat stranding.

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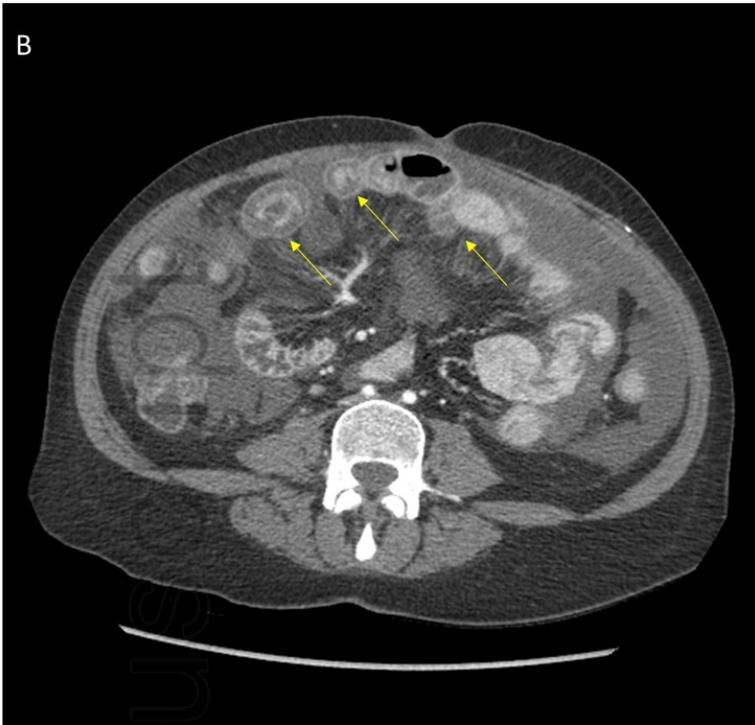
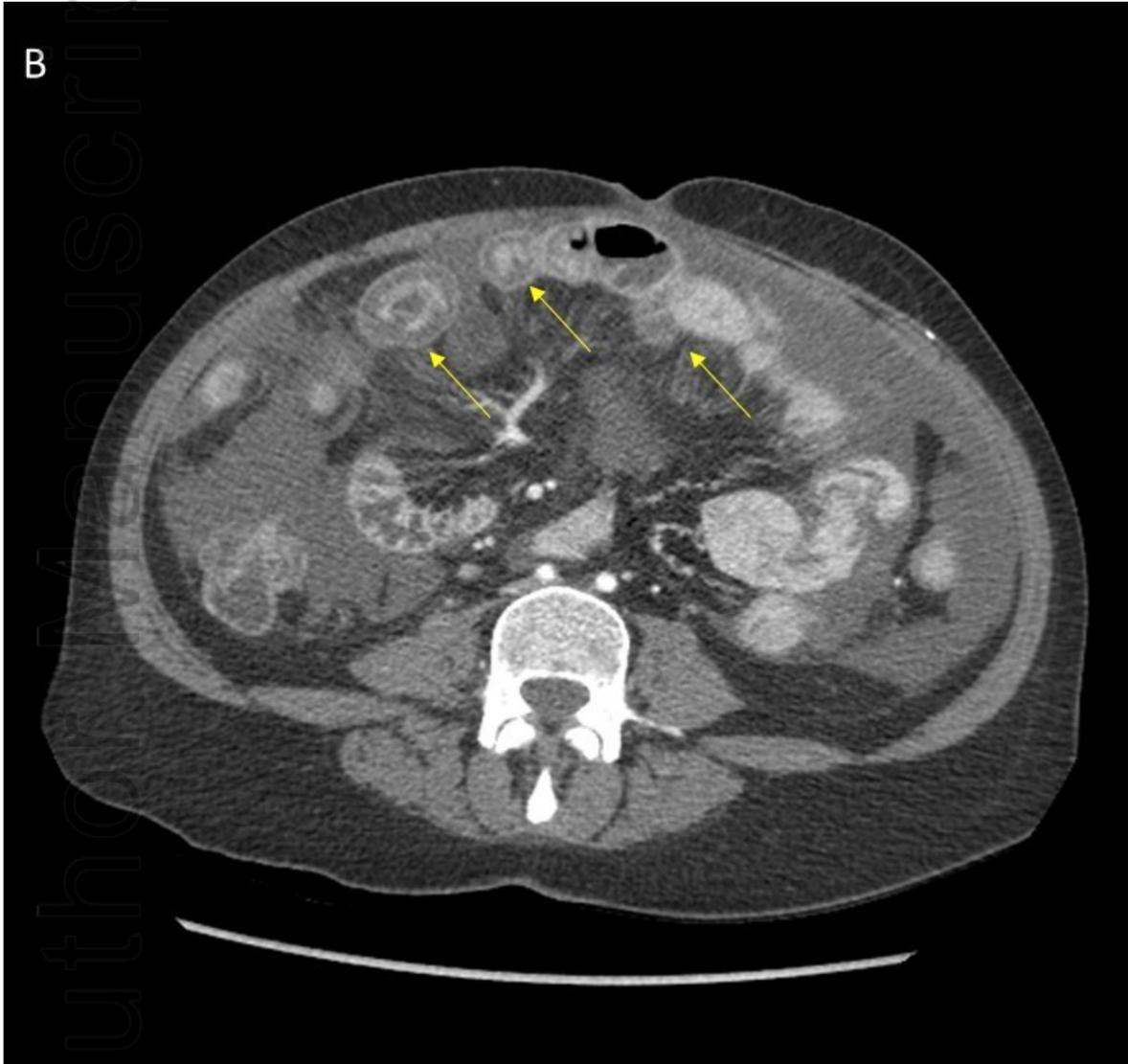


Figure 1B. Computed tomography imaging of intestinal angioedema in the transverse view. Arrow demonstrates profound small and large bowel wall edema and fat stranding.

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