

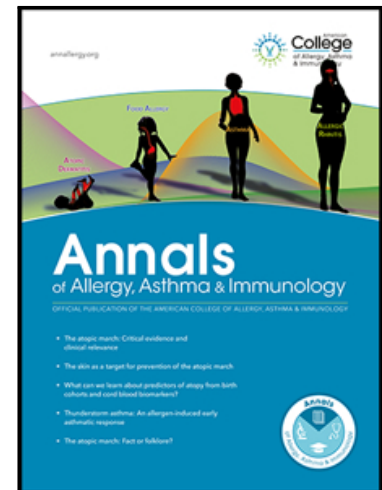
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Recurrent anaphylaxis due to chronic cholecystitis

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Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction, triggered by variable allergic and nonallergic exposures.¹ Here we report a case of recurrent anaphylaxis coinciding with flares of chronic cholecystitis. We hypothesize that in rare cases, inflammatory mediators released during episodes of cholecystitis can trigger anaphylaxis.

A 41-year-old woman with a past medical history of tree nut allergy initially presented for evaluation of idiopathic anaphylaxis occurring on 3 occasions over 3 months. Each episode consisted of urticaria, angioedema, nausea, vomiting, diarrhea, and generalized abdominal cramping. There was no hypotension with these initial episodes. She denied triggers related to temperature, exercise, infection, menstrual cycle, medication, food, or alcohol. The patient was a strict vegetarian and did not have mammalian meat exposure. There were no accidental nut ingestions, and there was no relationship between time of food ingestion and the onset of anaphylaxis. She was seen in the emergency department for each encounter, and was treated with antihistamines and steroids. She was not given epinephrine. Her labs in the emergency department were remarkable for elevated transaminase levels: AST of 207 U/L (13-40 U/L) and ALT of 66 U/L (5-35 U/L). Alkaline phosphatase, bilirubin, and lipase were within normal limits. No liver imaging was obtained during these initial ER encounters. No tryptase was obtained during these episodes. At her initial allergy clinic encounter, a baseline tryptase was established at 3.3 ug/L (<10.9 ug/L). Repeat lab testing demonstrated a normalization of AST and ALT. The patient was started on cetirizine 10 mg twice daily and famotidine 20 mg twice daily. After her initial clinical encounter, she was anaphylaxis free for approximately one month during which time her liver enzymes remained normal.

Her next episode of anaphylaxis was the most severe to date. The patient awoke in the night with generalized abdominal pain, vomiting, and diarrhea. Her last ingestion was several hours

before, and there were no suspicious food exposures. She subsequently developed urticaria, angioedema, hypotension, and loss of consciousness. She required 1 dose of epinephrine at home and received an additional dose in the ER. Vitals in the ER demonstrated an initial blood pressure of 95/36. She also received IV fluids, antihistamines and steroids. No tryptase was obtained during this ER course. The patient had an elevated white blood cell count of $13.2 \times 10^3/\mu\text{L}$ with left shift. Liver enzymes were again abnormal on admission including AST of 245 U/L and ALT of 90 U/L. Alkaline phosphatase, bilirubin, and lipase were again normal. A non-contrasted CT abdomen demonstrated thickening of the gastric wall. The appearance of the liver, gallbladder, and pancreas were normal.

Following this encounter, the patient was seen again in the outpatient clinic. She was asymptomatic at that time. Additional labs obtained during this encounter including a 24 hour 5-HIAA, N-methylhistamine and 2,3 Dinor-11 Beta-Prostaglandin F2 were unremarkable. The patient's suppressive antihistamines were increased to cetirizine 20 mg twice daily and famotidine 20 mg twice daily.

Despite this increase, the patient continued to have ongoing episodes of anaphylaxis, approximately every 2 weeks. On one such episode, she experienced urticaria, angioedema, abdominal pain, and hypotension to 79/53. She required multiple rounds of epinephrine. ER staff obtained a tryptase 3 hours after symptom onset which returned at 8.8 ug/L.

A break in the case occurred when the patient presented to the hospital with her typical urticaria, angioedema, and abdominal discomfort, except this time, her lipase was elevated at 1620 U/L (0-220 U/L). Bilirubin and alkaline phosphatase remained normal. In the work up for pancreatitis, an abdominal ultrasound was obtained, which demonstrated numerous gallstones and mild gallbladder wall thickening. The decision was made to perform cholecystectomy during the

hospitalization. Pathology from the gallbladder sample demonstrated chronic cholecystitis with cholelithiasis. Additional staining on the tissue including CD117/C-Kit, mast cell tryptase, and synaptophysin demonstrated normal tissue. There was no evidence for mastocytoma or carcinoid tumor. Over the following 12 months, the patient reported no additional anaphylactic episodes.

Although rare, there are case reports of patients with chronic urticaria triggered by chronic cholecystic disease.^{2,3,4,5} The clinical features of chronic cholecystitis can be minimal or vague which can lead to a protracted course before discovery.⁶ The link between cholecystitis and urticaria is generally made when symptoms of both disorders resolve upon cholecystectomy. Our patient shares a similar protracted course for several reasons. The skew of her liver enzymes that she demonstrated is more traditionally associated with hepatic injury rather than a biliary process. Additionally, the CT scan did not detect any liver or biliary abnormalities, although admittedly, CT is less sensitive for the diagnosis of cholecystitis. Our patient differs from prior case reports as she meets diagnostic criteria for anaphylaxis with symptoms of urticaria, abdominal pain, nausea, vomiting, and hypotension. Although it could be argued that her extracutaneous symptoms were caused by cholestatic disease, her acute rise in tryptase greater than 20% +2 of baseline is consistent with anaphylaxis.^{7,8} Additionally, the tryptase value was obtained about 3 hours after symptom onset. It is possible that more timely measurement would have resulted in greater tryptase values. To our knowledge, this is the first patient to have experienced anaphylaxis suspected to be triggered by chronic cholecystitis.

We hypothesize that these episodes of anaphylaxis were driven by non-allergic mast cell degranulation. Human mast cells can be activated through a variety of non-IgE dependent stimuli including cytokines (TNF- α , IFN- γ), complement, and Toll-like receptor ligands.¹

Immunohistochemical studies in chronic cholestatic disease suggest TNF- α plays a significant role in driving inflammation.⁹ It is possible that transient bile duct obstruction led to a cascade of systemic inflammation that triggered mast cell activation via TNF- α . In addition to TNF- α , it prostaglandins likely play a role in propagation of inflammation in gallbladder disease.¹⁰ It is unclear what role, if any, prostaglandins may have played in propagating the patient's anaphylaxis.

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