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CLINICAL VIGNETTE

Idiopathic Anaphylaxis and Under-Recognition of Mast Cell Disorders

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Anaphylaxis is a systemic hypersensitivity reaction with a reported incidence of 1.6-5.1% of the US population.[1] Anaphylaxis is often under-recognized and under treated.[2] Patients with a known food, drug, and insect venom hypersensitivity are at higher risk of developing anaphylaxis, but many patients present to the ER or their physician without an identifiable cause. Approximately 5-8% of the population has a reported food allergy,[3] 10% worldwide has a reported drug allergy,[4] and 1-3% have a reported venom hypersensitivity.[5,6] Anaphylaxis can be a very scary experience for the patient and provider, and can be fatal. Fatal drug induced anaphylaxis is most likely to occur in older individuals (50-80 years old). Although food induced anaphylaxis is most common in young children, fatal food induced anaphylaxis is most likely to occur in the second and third decades.

A 74-year-old woman with history of squamous cell carcinoma status post Moh's surgery, and adverse reaction to naproxen, presented to the Allergy and Immunology clinic with episodic symptoms of flushing, nasal congestion, restlessness, tachycardia, bowel urgency, nausea, vomiting, dizziness and/or syncope. These episodes had been occurring for the past 6-7 years. These symptoms would occur in rapid succession and last for 2 hours. As soon as they would start she knew that she had to call her daughter and lie down in the bathroom or else she would faint. Symptoms were attenuated by oral diphenhydramine 25mg, but would sometimes recur 4 hours later. She was not sure how often these episodes were occurring, but had 3 episodes in the previous 3 months. Three of the prior episodes were associated with ingestion of salmon less than 1 hour prior, but she had been avoiding salmon and continued to have episodes.

Four years prior to presenting at our clinic, she had seen an outside Allergist who performed allergy skin prick testing to a panel of 60 foods, and was found to be sensitized to many foods (eggs, milk, wheat, salmon, lobster, oyster, kidney bean, mushroom, banana, cantaloupe, string bean, tomato, beef, lamb, pork, and turkey). She only avoided salmon and shellfish, as she had never noted an adverse reaction to the other foods. She was prescribed an epinephrine auto-injector at that time but had never used it. She denied chronic rhinitis or chronic conjunctivitis symptoms, but also underwent allergy skin testing to a panel of inhalants and was found to be sensitized tree pollen, weed pollen, grass pollen, molds, dust mites, and animal dander.

She had been worked up for a pheochromocytoma three years prior, which showed elevated plasma levels of norepinephrine/epinephrine but normal urinary metanephrine levels and negative abdominal CT scan.

She denied any other atopic history, such as asthma, eczema, or venom hypersensitivity. There was an isolated episode of shaking, syncope, and bowel incontinence 14 years ago, after taking naproxen 440mg. Since then she had avoided all non-steroidal anti-inflammatory medications. At the time of presentation, she did not take any medications regularly. She was taking homeopathic supplements containing calcium, iron, potassium, magnesium, sodium chloride, silica, and calcium sulphate. She did not know of any family members ever having similar symptoms. Her family history was significant only for a sister with allergic rhinitis and asthma. Her vital signs were normal and physical exam was unremarkable.

We were very suspicious for a mast cell disorder. Her labs from the initial visit were significant for a tryptase level of 359 ug/L (normal < 11ug/L) and a Vitamin B12 > 4000 pg/ml. Serum-specific IgE to salmon, crab, lobster, shrimp, clam, oyster, scallop, and mussel were negative (<0.10 kUA/L). CBC and CMP were normal. She was referred to Hematology/Oncology and bone marrow biopsy was significant for clusters and aggregates of atypical mast cells, + c-kit mutation, and CD2 presence on CD117 mast cells. She was diagnosed with indolent systemic mastocytosis and advised to follow up with Allergy/Immunology for management of mast cell mediated symptoms.

For all patients presenting with signs of anaphylaxis, a serum tryptase at the time of the reaction can be very helpful in establishing that the patient's symptoms are due to mast cell mediator release. Mast cells are the primary cell thought to be responsible for anaphylaxis[7] and tryptase is the most sensitive and specific marker of mast cell activation.[8] If the serum tryptase is elevated while symptomatic, it needs to be repeated when the patient is asymptomatic. If the serum tryptase is greater than 11ug/L, the patient should be referred to Allergy and Immunology for evaluation. In addition, if the serum tryptase is greater than 20ug/L while asymptomatic, the patient should be referred to Hematology/Oncology in addition to Allergy/ Immunology, so that a monoclonal mast cell disease can be ruled out.

Our patient with indolent systemic mastocytosis was initially prescribed fexofenadine 180mg once daily, but this caused

severe dizziness. Famotidine caused shakiness. She did report diphenhydramine 50mg was more effective than 25mg in decreasing the severity of symptoms during episodes. She was a petite woman so we recommended a trial of cetirizine 5mg once daily. If this or higher doses of cetirizine are ineffective, we will next try doxepin, as it is a potent inhibitor of histamine-1 and histamine-2 receptors. Oral cromolyn is a mast cell stabilizer and can be a helpful addition for reducing gastrointestinal symptoms.[9]

Patients with signs of anaphylaxis should receive immediate, intramuscular epinephrine, as a delay in epinephrine administration increases the risk for death.[10] Oral, intramuscular, or IV antihistamines can also be helpful, but there is little evidence that administration of systemic steroids is helpful in reducing acute or delayed symptoms of anaphylaxis.[11] Even though the tryptase level will not be available for a few days, it can help confirm the diagnosis of anaphylaxis, as well as alert the physician that there may be an underlying mast cell disorder that is contributing to recurrent symptoms.

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