Eosinophilic Cardiomyopathy with Endomyocardial Fibrosis

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Learning Objective 1: Recognize the clinical features of hypereosinophilic syndromes presenting with restrictive cardiomyopathy.

Case: A 70 year-old Korean female with no significant past medical history presented to the hospital after three months of generalized weakness and progressively worsening lower extremity edema. She denied any shortness of breath, chest pain, fevers, chills, rashes, arthralgias, orthopnea, paroxysmal nocturnal dyspnea, syncope, or any other constitutional symptoms.

She initially presented to her primary care physician one month prior to admission, and was started on a diuretic for her lower extremity edema. A CBC was checked, which showed a WBC of 20,000/mm3 with an absolute eosinophil count (AEC) of 19,000/mm3. At this point she was transferred to the National Institutes of Health for further evaluation of her hypereosinophilia.

A peripheral smear revealed the presence of dysplastic, hypogranular eosinophils. ProBNP was elevated at 2204 (normally 0-353 pg/ml). Troponin-I peaked at 0.024. An EKG showed a prolonged QTc of 480 milliseconds. A test for the FIP1-PDGFRa mutation came back negative.

Physical examination revealed a jugular venous pressure of 12, decreased breath sounds and 2+ lower extremity edema to her knees, bilaterally. On cardiac exam, she was found to have a normal rate and regular rhythm, with a 3/6 holosystolic murmur at the apex, radiating to the axilla.

A transthoracic echocardiogram was done, which showed an ejection fraction of 65%, moderate tricuspid regurgitation, severe mitral regurgitation, severe right ventricular (RV) dilatation with decreased RV function, as well as septal flattening consistent with RV overload. Her RV apex was described as thick and echodense.

A cardiac MRI was also done, which noted left ventricular (LV) apical thickening (in addition to RV thickening), suggesting bilateral apical thrombi vs. endomyocardial fibrosis, thought to be secondary to eosinophilic cardiomyopathy.

Treatment consisted of initiating imatinib and corticosteroids for her hypereosinophilic syndrome. Her diuretics were increased and she was started on anticoagulation for her apical thrombi, as well as an ACE-inhibitor for cardiomyopathy.

One month after discharge, the patient began to report increased energy and a significant reduction in her edema. Follow-up labs also showed resolution of her eosinophilia, with a WBC of 3,650/mm3 and an AEC of 1,380/mm3.

Discussion: This case illustrates eosinophilic cardiomyopathy as a rare, but clinically important, cause of restrictive heart failure. Eosinophil-mediated heart damage is characterized by three stages- 1) an acute necrotic stage, significant for direct endomyocardial infiltration and damage, 2) an intermediate phase, in which thrombi form along damaged endocardium and 3) a fibrotic stage, characterized by endomyocardial fibrosis, resulting in a restrictive cardiomyopathy. Clinicians must pay close attention to the cardiac physical examination for signs of heart failure and valvular disease, which is caused by fibrotic entrapment of chordae tendineae. Other organ systems are also frequently involved, including the skin, lungs and gastrointestinal tract, which are all characterized by eosinophilic infiltration.
Eosinophilic Pleural Effusion: A worm by another name?

Learning Objective 1: Recognize the different causes of eosinophilic pleural effusions

Learning Objective 2: Recognize the pulmonary manifestations of Strongyloides stercoralis infection and the dangers of misdiagnosis

Case: A 91 year old Korean man with history of hepatitis C and recurrent pneumonias presented with two days of fever, productive cough and hemoptysis. In the preceding year, he had two hospital admissions for bacterial pneumonia with a persistent left loculated pleural effusion of unclear etiology. On arrival, he had a temperature of 37.9°C, with a normal respiratory rate and oxygen saturation. He had decreased breath sounds in the left middle and lower lung fields. WBC count was 6,390 per µL with 21% eosinophils. His IgE level was 6103 IU/mL (normal <20 IU/mL). Mycobacterium tuberculosis (MTB) quantiferon gold ELISA test was positive. A single stool ova and parasite (O&P) test was negative. A chest CT identified a complex loculated left pleural effusion with ground-glass opacities in the right upper and middle lobes. A noncalcified granuloma was noted in the right apex. Bronchoalveolar lavage was performed, and acid fast culture, MTB PCR, and O&P testing were negative. A diagnostic thoracentesis yielded 44 WBCs per mL with 24% eosinophils, and an adenosine deaminase of 6.0 units per liter (consistent with transudative fluid). Wet prep of the pleural fluid was negative for ova and parasites. No malignant cells were identified. On the day of discharge, a second stool O&P test was obtained and eventually identified Strongyloides stercoralis larvae. Serum testing for strongyloides antibody also returned positive. He received ivermectin and had significant improvement in his symptoms and eosinophilia.

Discussion: Eosinophilic pleural effusions are commonly encountered by general internists. While the most common etiologies are malignancy, idiopathic, and parapneumonic effusions, other causes including tuberculosis (TB), collagen-vascular diseases, and parasitic infections – namely Strongyloides stercoralis – must be considered in the appropriate demographics. In this case, our suspicion for active TB was high. Without acquiring a repeat O&P stool sample, more invasive diagnostic procedures for TB may have been performed. This highlights the importance of testing numerous stool samples, as the sensitivity does not approach 100% until obtaining 7 samples. The pulmonary manifestations of Strongyloides stercoralis can include eosinophilic pleural effusions, asthma and acute respiratory failure. If undiagnosed, hyper-infection can occur, with high worm burden and disseminated disease. Specific to pulmonary disease, there have been at least three documented fatalities in patients with undiagnosed strongyloides who received corticosteroids for presumed asthma. Considering strongyloides infection is therefore critical in patients with eosinophilic pleural effusions.
Breast Malignancy Masquerading Under the Cloak of Acute Urticaria

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**Learning Objective 1:** Recognize the potential association between urticaria and underlying systemic disease, including malignancy.

**Case:** Presenting in more than 20 percent of the general population, urticaria is a common disorder characterized by intensely pruritic, erythematous, raised plaques with or without associated angioedema. Common triggers of new onset urticaria include infection, allergic reactions, or medications. Although often idiopathic, the presence of urticaria can be associated with underlying systemic disease.

A 58-year-old woman presented with a flat, erythematous, pruritic rash involving her palmar surfaces bilaterally. Within days, the rash progressed to generalized edematous annular plaques located on her forearms, lower extremities, upper abdomen, suprapubic area, and buttocks. She then developed deep dermal swelling of her hands, lip and face prompting initiation of systemic steroid treatment, resolving the eruption. Skin biopsies were consistent with urticaria showing dermal edema with mixed dermal and panniculitis with abundant eosinophils. Due to unknown etiology, a thorough workup was pursued. Laboratory studies including thyroid function, serum protein electrophoresis, complement, anti-nuclear antibody, autoimmune blistering disease studies, flow cytometry, and Lyme disease serology were normal as was a chest x-ray and urinalysis. Routine age-appropriate cancer screening was ordered. Mammography revealed four lesions in her left breast. Ultrasound-guided core needle biopsies revealed that three of the four lesions demonstrated grade 1 invasive ductal carcinoma. Mastectomy was performed with clear margins and negative sentinel node biopsy. Following surgery, steroids were gradually tapered off and no recurrence of rash had occurred at four weeks post operation.

**Discussion:** This case demonstrates the atypical association between breast malignancy and acute urticaria and emphasizes the importance of age-appropriate cancer screening in patients presenting with urticaria of unknown etiopathogenesis. Acute urticaria is a clinical diagnosis based on history and physical exam findings and confirmed by skin biopsy. Careful history focused on typical triggers of urticaria, including ingestion, infection, travel, medication, endocrinopathies, physical triggers, and systemic symptoms should be reviewed. Importantly, many systemic diseases may initially present as urticaria.

To date, only two cases have been reported connecting breast cancer with chronic or acute urticaria. Although more commonly associated with paraproteinemias, other investigations have shown the association between urticaria and solid tumors of the lung, brain, ovary, thyroid, colon or rectum. The case we described supports a possible association between breast malignancy and urticaria. Thus, symptoms and signs of urticaria with unknown cause should prompt a thorough history, physical examination, and review of age-appropriate cancer screening.
**Beware of Doxies: Targeting the Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome**

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**Learning Objective 1:** Recognize and appropriately manage the DRESS syndrome

**Learning Objective 2:** Risk-stratify patients with drug reactions

**Case:** A 64 year-old man presented five days after developing a pruritic rash on his hands, which rapidly spread to involve his entire body despite a 4 day course of topical and oral steroids. He also noted shortness of breath, lower extremity edema, and two days of fever. He had returned from sub-Saharan Africa approximately 4 weeks prior and was taking doxycycline for malarial prophylaxis; other medications included hydrochlorothiazide and lisinopril for hypertension, and meloxicam for osteoarthritis.

On physical exam, he had a violaceous, non-blanching targetoid rash on his limbs and trunk. A single buccal ulcer was noted; his oropharynx was otherwise normal. There was non-painful cervical lymphadenopathy but no other lymph node involvement. No obvious ulcers were noted on examination of his ocular membranes but golden-colored crusting of his eyelids was present. His penile exam was negative for ulcers and examination of his joints was unremarkable. No hepatosplenomegaly was noted on physical exam.

Eosinophilia (peaking at 5,000 cells/ul) with leukocytosis (without atypical lymphocytes), mild transaminitis, and acute kidney injury were found on laboratory testing. Testing for the presence of tick-born, parasitic, bacterial, treponemal, and viral infection was negative; imaging did not suggest malignancy. A skin biopsy one week after presentation demonstrated changes consistent with a drug reaction. His RegiSCAR score was calculated at 6 (definite case of the DRESS syndrome). With discontinuation of his doxycycline and treatment with high-dose corticosteroids, the patient’s symptoms resolved and did not return.

**Discussion:** Drug reactions are a common challenge in the general physician’s practice. A systematic approach is needed to assess the severity of the illness; awareness of less common manifestations is critical to appropriate triage. The presence of a targetoid rash and involvement of mucosa triggered concern for potential Stevens Johnson Syndrome (SJS) spectrum disease and led to hospitalization in the ICU. However, in this case, the lack of epidermal sloughing, high fever, and evidence of organ involvement did not suggest this diagnosis, but rather erythema multiforme (EM), an uncommon initial presentation of the DRESS syndrome. Other diagnostically confounding infectious, inflammatory, and malignant conditions were ruled out before a diagnosis of DRESS syndrome was made.

The DRESS syndrome is a clinical diagnosis supported by tissue pathology. The use of the RegiSCAR score helps categorize the likelihood of DRESS and allows development of a growing body of literature on this rare condition. Many medications have been associated with DRESS, but doxycycline is a rare cause, with only 4 cases reported.

Supportive treatment with recognition of the DRESS syndrome may make the difference between a positive outcome and multi-organ failure. As our medical pharmacopeia grows, the general internist will increasingly be depended upon for early detection and coordination of care in these complex drug reactions.
Satisfying an Itch From The Inside Out

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Learning Objective 1: Review the diagnoses associated with chronic urticaria.

Learning Objective 2: Recognize the association between Helicobacter pylori infection and chronic urticaria and the potential for improved patient comfort with Helicobacter pylori eradication.

Case: A 34 year-old woman with a 4 year history of intermittent chronic hives and gastroesophageal reflux disease (GERD) presented with a 4 day history of worsening urticaria. She had undergone multiple non-revealing skin and allergen tests, and described a typical outbreak as a sudden appearance of itchy and burning red marks across her chest, abdomen and bilateral thighs and buttocks. The outbreaks occurred several times a month. She was unable to identify exacerbating factors and had tried multiple over the counter topical creams and ointments without relief. She also had a 3 year history of acid reflux and abdominal discomfort. Home medications included hydroxyzine and esomeprazole. Family history was notable for systemic lupus erythematosus (SLE) in her mother. Despite persistent itching and burning, physical exam failed to detect any skin lesions. She had pictures of an outbreak from the previous day, revealing multiple round, circumscribed, raised erythematous plaques across her abdomen and thighs. Baseline laboratory testing was unremarkable and an extensive panel of autoimmune tests was negative; skin biopsy was not performed due to lack of visible lesions. Helicobacter pylori (H. pylori) IgG and IgM serology were both positive. Subsequent upper endoscopy showed multiple superficial erosions in the gastric body and antrum. Biopsy of these erosions revealed the presence of H. pylori. Patient was started on twice daily 600 mg Clarithromycin and 1 g Amoxicillin in addition to twice daily 20 mg omeprazole for 14 days. Three months following completion of therapy the patient has noted complete resolution of urticarial symptoms; her longest symptom-free interval since her initial onset 4 years ago.

Discussion: Affecting up to 1% of the population, chronic urticaria (CU) is a common and frustrating condition for patients and physicians. Despite being typically managed by dermatologists, general internists are confronted with the task of identifying potential exogenous causes of CU. While finding an underlying cause of CU is daunting (successful in 20% of cases), unmasking an underlying systemic disease may improve CU-associated symptoms and prevent future morbidity and mortality. Common associated conditions include H. pylori, Sjogrens syndrome, SLE, rheumatoid arthritis, cryoglobulinemia and hypothyroidism. Due to the ubiquitous occurrence of H. Pylori, (25% of the population in industrialized countries and higher in developing areas), the link between H. pylori and CU is of particular interest. Due to a lack of large clinical trials, the association between CU and H. pylori is still controversial. H. pylori has been found to occur 2-3 times more frequently in patients with CU and subsequent eradication has demonstrated a 2-fold increase in remission, compared to untreated H. pylori positive patients. The most commonly speculated mechanism of H. pylori-associated CU is chronic infection leading to increased gastric acid and pepsin release; this prompts recruitment of inflammatory cells (mainly lymphocytes and neutrophils), subsequently inducing mast cell degranulation and histamine release. Recognition of H.pylori-associated urticaria may lead to improved urticarial symptoms and earlier identification and eradication of H.pylori.