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CASE SET #23

An Immunology Case:

Hard to Swallow

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Clinical Laboratory Investigations

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LEARNING OBJECTIVES

Upon completion of reading the case, the learner will be able to:

1. Identify which type of hypersensitivity reaction(s) are associated with eosinophilic esophagitis (EoE).
2. Describe the symptoms most often associated with EoE.
3. Explain how laboratory tests are used to help confirm a diagnosis of EoE.
4. Describe the roles of the cytokines associated with the immune response in EoE.
5. Compare the different treatment options currently being used to treat EoE.
6. Describe the typical patient population with EoE.

Hard to Swallow

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Patient History:

An 11-year-old Caucasian male accompanied by his mother, presented in the pediatrician's office with complaints of lack of appetite and occasional vomiting. The most recent episode had occurred within the last 24 hours during the boy's baseball game. The mother reported that her son had eaten a small meal an hour prior to the game and had felt fine when he left for the game. During the baseball game the boy began coughing then vomited. He was taken home and later reported that his stomach hurt "a little bit". His temperature was normal and he had no other complaints.

Reflecting back over the last few months, the mother realized her son had gradually lost interest in eating. At the table, he had little appetite even for his favorite foods. He occasionally complained of a stomachache, but this was not a constant complaint and seemed to resolve without any additional intervention. She also noted that the vomiting had begun within the last 2 weeks and always occurred after her son had eaten. He often complained of a stomachache just before he vomited. No fever or diarrhea was associated with any of these episodes. The boy reported that he felt better after he vomited.

The pediatrician reviewed the boy's history. The boy was the youngest of three siblings, all boys. They lived in an upper-middle class suburban neighborhood. The child attended public schools where he earned good grades. He enjoyed participating in team sports. He was active in camping, hiking and other outdoor activities with his parents and siblings. He visited the pediatrician's office regularly for physicals, immunizations and typical childhood illnesses. He was diagnosed at age three with respiratory allergies and asthma. At that time, a standard daily oral asthma medication along with an inhaler was prescribed. His allergies and asthma were managed with the medication.

The pediatrician questioned the boy about his recent eating habits. He reported that he did get hungry, but found it difficult to swallow many foods and at times it felt like food was "stuck" in his throat. He also stated that at times this "stuck feeling" would lead to coughing and eventually vomiting. When asked if he felt any burning sensations in his stomach, the boy said yes. He also reported that he had trouble swallowing his allergy pill and multivitamin each morning.

Physical Exam:

Upon exam, the patient appeared pale and thin, but did not appear to be malnourished. At 58 inches tall, he was average height for his age (59th percentile). His weight was 71 pounds (17th percentile). The pediatrician noted that the child had lost 5 pounds since his last office visit six months earlier. The child's temperature was 37°C and his respiration rate and blood pressure were normal for his age. His throat was not inflamed nor were his tonsils swollen. There were no rashes or bruising noted on his back, abdomen or extremities.

At this point the pediatrician suspected the child might be suffering from gastro-esophageal reflux disease (GERD). He ordered base-line laboratory tests including a complete blood count (CBC) with differential, basic metabolic panel (BMP) and urinalysis (UA). In addition, he ordered a baseline total serum IgE level. The pediatrician prescribed a proton pump inhibitor (PPI) and referred the child to a gastroenterologist specializing in pediatric cases.

Laboratory Findings: (All reference ranges - Mayo Clinic)

Table I: Complete Blood Count with Differential

Test	Results	Reference Range
WBC	7.2	3.4-9.5 x 10^9/L (males 6-11 yrs.)
RBC	4.5	4.2-5.1 x 10^{12}/L (males 6-11 yrs.)
Hemoglobin	13.7	12.0-14.0 g/dL (males 6-11 yrs.)
Hematocrit	40	35.8-42.4% (males 6-11 yrs.)
Platelet count	280	150-400 x 10^9/L (>6 mo. or older)
Neutrophils	3.1	1.5-8.5 x 10^9/L (6-11 yrs.)
Lymphocytes	3.0	1.5-6.5 x 10^9/L (6-11 yrs.)
Monocytes	0.4	0.0-0.8 x 10^9/L (1-15 yrs.)
Eosinophils	0.6 (↑)	0.0-0.5 x 10^9/L (6-15 yrs.)
Basophils	0.1	0.0-0.2 x 10^9/L (6 mo.-15 yrs.)

Table II: Basic Metabolic Panel

Test	Result	Reference Range
Sodium	140	135-145 mmol/L (>1 yrs.)
Potassium	4.3	3.6-5.2 mmol/L (>2 yrs.)
Chloride	104	102-112 mmol/L (1-17 yrs.)
CO_2 venous	25	21-29 mmol/L (8-17 yrs.)
Glucose	100	70-140 mg/dL (>1 yrs.)
BUN	13	7-20 mg/dL (1-17 yrs)
Creatinine	0.5	0.3-0.7 mg/dL (10-11 yrs.)

Table III: Immunoglobulin Testing

Test	Result	Reference Range
Total Serum IgE	902 kU/L	< or = to 696kU/L

Table IV: Urinalysis

Test	Results	Reference Range
Color	Yellow	
Clarity	Clear	
pH	6.0	4.5-8.0
Specific gravity	1.018	1.002-1.035
Protein	Negative	
Glucose	Negative	
Ketones	Negative	
Nitrite	Negative	
Leukocyte esterase	Negative	

The patient was seen by a gastroenterologist specializing in pediatric cases 10 days later. The gastroenterologist inquired about the symptoms while the child had been on the PPI medication. The mother reported that he was still not eating well and that he continued to have episodes of stomach pain, coughing and vomiting. The gastroenterologist decided to continue the PPI medication for an additional 4 weeks and asked that the patient return for a follow-up visit at the end of that period. Additionally, he ordered a multiallergen IgE antibody panel.

When the patient returned for follow up, the mother reported there had been no improvement of symptoms since the last visit. By this time, the results of the multiallergen IgE antibody panel had been reported and were inconclusive. The gastroenterologist asked if there was a family history of stomach ailments or allergies. The mother reported no other family member had any complaints of stomach illnesses aside from an occasional bout of stomach upsets. The mother reported she suffered from asthma and eczema, but the father and older siblings had neither allergies nor asthma.

At this point, the gastroenterologist indicated that due to the increased eosinophils in the peripheral blood, an increased total IgE, an inconclusive results from

the multiallergen IgE antibody panel, along with the PPI having little effect, he strongly suspected that the child may be suffering from eosinophilic esophagitis (EoE). He further stated that the only way to confirm the diagnosis would be to perform an endoscopy of the boy's esophagus at which time he would collect a biopsy for histologic testing. The child had the biopsy performed at a local outpatient surgery center the following week. During the endoscopy, the gastroenterologist noted strictures in the esophagus. He collected several mucosal biopsy samples from various parts of the esophagus. Several days later the results of the histologic exam were reported. The results showed eosinophilic infiltration of the esophageal mucosa with greater than 20 eosinophils per high power field. The diagnosis of EoE was confirmed.

Discussion:

Eosinophilic esophagitis (EoE) is one of the emerging diseases included in the category of eosinophilic gastrointestinal diseases. Also included in this category are eosinophilic gastroenteritis and eosinophilic colitis. EoE has been rising in incidence over the last two decades[1].

EoE is primarily a chronic immune response and allergic reaction disorder of the esophagus, three times more common in males than females, and more common in Caucasians than other races. Its growing prevalence spans the globe, but is higher in socioeconomically developed countries, as well as in colder climates; and although it can present at any age, it typically presents in childhood[2,3]. It is uncertain if adult patients have a true late onset of symptoms or if they have suffered from years of subclinical chronic inflammation of the esophagus[4]. While there seems to be familial

clustering, it is as yet unclear how much is due to genetic factors versus common environments[2,3].

EOE in children causes symptoms of nausea, vomiting, abdominal pain, and failure to thrive, while adolescents and adults present with dysphagia, heartburn, gastro-esophageal reflux disease (GERD)-like symptoms, and food impaction. It can be difficult to distinguish EoE from GERD as their symptoms overlap and are not mutually exclusive[5].

The allergic reactions and chronic inflammation cause disturbances in the epithelial barrier of the esophagus, leading to chronic inflammation and fibrogenesis[5]. This can cause endoscopic abnormalities such as strictures, longitudinal furrows, nodules, corrugated rings, and “crepe-paper” mucosa caused by a decrease in mucosal elasticity. These abnormalities are typically seen in adult patients, while one-third of pediatric patients have a normal esophageal appearance upon endoscopy[6].

Specific to EoE, there is an accumulation of eosinophils in the esophageal tissue. Confirmatory diagnostic criteria for EoE includes observation of greater than 15 eosinophils per high power field in tissue with some specialists requiring as high as 20 or more eosinophils per high power field in esophageal tissue preparations taken during an esophageal biopsy[2].

In addition to the tissue specimen results, laboratory testing can help confirm the diagnosis of EoE. Protocols include those that can detect total IgE and allergen specific IgE. Total IgE is used as a screening tool to identify those with allergic tendencies. If total Ig E is elevated, allergen specific IgE testing may be performed. Historically the radioallergosorbent assay (RAST) was used but has been replaced by non-radioactive

testing protocols and microarray testing for specific allergens[3,4,7]. Additionally, laboratory testing for atopy and skin prick allergy testing can be used to help confirm a diagnosis of EoE[3].

For the patient with a normal immune reaction to the allergens, they usually respond with a Th1 response which triggers the production of interferon gamma, IL-12 and IL-18. These cytokines are produced by macrophages and may help suppress production of IgE antibodies[4].

Research is ongoing to determine if EoE is an immediate hypersensitivity reaction or a delayed type hypersensitivity (DTH) due to a Th2 host response or a combination of both types of hypersensitivity reactions[8]. The immune reaction in some pediatric and adult patients who are prone to allergies, may not be a Th1 reaction but rather a Th2 reaction. This Th2 reaction increases production of cytokines IL-3, IL-4, IL-5, IL-9 and IL-13. IL-5 promotes proliferation in the bone marrow and primes eosinophils for cytokine stimulation[3]. IL-4 and IL-13 are responsible for the final differentiation that occurs in B cells which can lead to the production of IgE. IL-5 and IL-9 promote development of mast cells. Increased production in eotaxin chemokines, CCL11 (eotaxin-1), CCL24 (eotaxin-2) and CCL26 (eotaxin-3) which specifically attract eosinophils[2], can also occur in Th2 reactions. Research continues to investigate the roles of other components of the immune system as well, such as leukotrienes and tumor necrosis factor-alpha, and their role in EoE[3].

Treatment can be complex depending upon severity of the inflammation process and symptoms involved. Endoscopic abnormalities can be controlled or reversed and symptoms alleviated with appropriate treatment. However, due to the chronic nature of

EoE, treatment needs to be prolonged or life-long, since symptoms tend to reoccur if treatment is discontinued[6]. Currently, treatments consist mainly of the "3Ds": drugs, diet, and dilation[2,9].

Treatments for EoE can include prescribing proton pump inhibitors (PPI) alone or in combination with corticosteroids, restricted diets, or some combination of the above[3]. PPIs are usually the initial treatment, as reduction of acid secretions may reduce the inflammation as well as aid patients with concurrent GERD[6,9]. Thirty to forty percent of patients may respond to PPI therapy[6].

Systemic corticosteroids may be used initially to reduce inflammation but is followed by maintenance therapy of topical steroids[9]. Topical steroids can be administered by inhalers, where patients are instructed to swallow, not inhale, the aerosolized drug. Viscous liquids can also be used to deliver steroids, with the drug mixed into a sucralose mixture, but various foods have been used as well, such as honey and applesauce[5].

Three forms of dietary treatment are used to treat EoE are elemental, directed elimination, and empiric elimination diets. The elemental diet, consisting of an amino acid-based liquid, has been shown to achieve a high rate of success. However, it is expensive, and not well tolerated by patients since it lacks food variety and has an unpleasant taste[3,9]. Directed elimination diets have also been shown to achieve a high rate of success and rely on allergy testing, such as skin-prick and patch testing to identify food triggers. However, allergy testing can be expensive and time consuming, while patch tests are not standardized. Further, skin-prick tests can have a high rate of both false-positive and false-negative results. Empiric elimination diets exclude the

most common food allergens: cow milk, egg, wheat, soy, nuts, and fish. Foods are then reintroduced one at a time until the allergen is isolated. This can result in relapse of symptoms and requires multiple endoscopy procedures for follow-up[3,5,6].

In addition to these therapies, there are some patients who require esophageal dilation but this comes with risks and may be contraindicated for certain individuals with EoE[1]. While dilation can alleviate strictures, it does not address the underlying causes of inflammation which will require other afore-mentioned treatment anyway, and may require repeated dilation procedures[5,9].

There is no consensus protocol currently on how best to treat a pediatric or adult patient with EoE. The most recent survey indicates that oral corticosteroids (swallowed) along with PPI was the most widely used first line treatment. Surveys of treatment options indicate that even though dietary options are very effective, they were not the first option implemented due to compliance issues, particularly with the pediatric patients[1]. Administering antibodies to IL-5 has been explored, but results of those studies found no statistically significant improvement in patients when compared to the placebo control group[3].

Conclusion:

Following diagnosis, the gastroenterologist recommended a multi-pronged approach treatment. He continued the PPI initially to reduce the acid secretions. He prescribed a viscous corticosteroid twice daily to reduce symptoms of dysphagia. This treatment reduces the infiltration of eosinophils in the esophageal mucosa. He also recommended an elimination diet. The mother was told to remove all wheat, dairy, eggs, soy, peanuts, tree nuts, fish and shell fish from the child's diet. Although the child

found the diet difficult at first, he did experience symptom relief and began to gain weight over the next three months. He began to eat with enthusiasm at meal time. A decision about possibly reintroducing some of these foods will be made at a later date. The PPIs were eventually discontinued due to the success of the diet. Finally, because strictures of the esophagus were noted on the endoscopy, dilation of the esophagus was performed. A second dilation was performed three months later and will be repeated if the gastroenterologist deems it necessary. Twelve months after beginning treatment, the patient continues to do well in school and remains involved in sports and outdoor activities. He aspires to become a chef and prepare foods for those with similar dietary restrictions.

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