**TITLE OF CASE**  
Alpha-1 Antitrypsin Deficiency

**AUTHORS OF CASE**  
Please indicate corresponding author by *  
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**SUMMARY**  
Up to 150 words summarising the case presentation and outcome

H.R is a 36 yr old white female, follow up from the emergency department with esophageal candidiasis, persistent dysphagia and odynophagia. H.R. has a history of Alpha-1 antitrypsin deficiency. In 11/07 she presented to the office with an elevation of Alk phos, GGTP was normal. She was referred to the gastroenterologist who tested her for Alpha-1 antitrypsin. She was deficient at that time and was referred to a pulmonologist, where her Alpha-1 levels were tested again, phenotyped, chest x-ray, and PFT. Her levels and phenotype were not deficient enough to be put on replacement therapy. Her chest x-ray was normal and her PFT showed no response pre/post bronchodilator treatment. She was placed initially on Advair 250/50 and before the ER visit the dosing was increased to 500/50. She was give Diflucan and told to stop Advair. The gastroenterologist will be performing an EGD to determine reason for ER visit.

**BACKGROUND**  
Why you think this case is important – why you decided to write it up

I really decided to write up this case because in our Clinical Medicine course Dr. Hakemi said don’t forget about Alpha-1 antitrypsin deficiency. Then in my 4th day of clinicals presents a patient with a hx of Alpha-1. So I started doing some more research on Alpha-1 and found some pretty daunting stats. Alpha-1 presents as the COPD characteristic emphysema. COPD is the 4th leading cause of death in the US and up to 5% of all people with COPD have Alpha-1 deficiency. It is the #1 cause of liver failure and transplant in the pediatric population. It also is equally as frequent as Cystic Fibrosis. I thought that CF was discussed a little bit more so I thought Alpha1-antitrypsin deficiency would be something nice to touch on.

**CASE PRESENTATION**  
Presenting features, medical/social/family history

**HPI**
H.R was a F/U from the ER with esophageal candidiasis, dysphagia and odynophagia. She stated she was feeling much better but still has some trouble swallowing and some white exudate on the tongue  
In 11/07 she presented with some trouble breathing, Alk phos elevation, and history of alpha1-antitrypsin deficiency.

**PMH:**  
Alpha-1 antitrypsin deficiency, Fibromyalgia, pseudotumor cerebri, asthma, COPD, IBS, Obstructive Sleep Apnea,

**FH:**  
M-HTN, Bipolar  F- n/a  MGP- stroke, cancer, diabetes, PGP- stroke, cancer, glaucoma, diabetes

**Meds:**
Advair 500/50, Trazodone 150mg prn, Wellbutrin 150mg, Premarin 1.25, Miralax, Protonix, Singulair 10mg, Albuterol inhaler prn, albuterol nebulizer

**Allergies:**
Codeine and Morphine

**PSH:**
TAH w/ BSO in 2003
Cholecystectomy in 2005

**Social:** works at Family Video, non-smoker, occasional alcohol, daily coffee 2-3 cups

**INVESTIGATIONS** *If relevant*
Initially (11/07): Alk Phos- 150  GGTP-36  Alpha-1 level- 59  CRP-.8
(2/08):  Alpha-1 level- 87   Phenotype: SZ   CXR: WNL  PFT: 97% pre/ 103% post
Bronchodilator treatment

**DIFFERENTIAL DIAGNOSIS** *If relevant*
Asthma, COPD, Chronic Bronchitis, Bronchiectasis , monitor for future lung infections

**TREATMENT** *If relevant*
The treatment for H.R. for Alpha-1 antitrypsin deficiency was Advair 250/50, Albuterol nebulizer as well as inhaler for the emphysema symptoms. Her dose was later increased to 500/50. Her esophageal candidiasis was treated with Diflucan in the ER. In the office she was asked to finish her Diflucan and introduce soft foods and plenty of liquids. If her symptoms worsened she was to return.

**OUTCOME AND FOLLOW-UP**
H.R. was feeling much better at presentation to the office. She was still having some trouble breathing and swallowing and was following up with both the pulmonologist as well as the gastroenterologist to do a scope to see if there something other than the medicine causing the esophagitis

**DISCUSSION** *including very brief review of similar published cases (how many similar cases have been published?)*
Alpha-1 Antitrypsin Deficiency (AAT def) is an autosomal recessive disorder that causes a deficit in the amount of AAT produced in the body. AAT def usually leads to a pulmonary disorder, a liver disorder or both. In rare occasions AAT def can cause hepatocellular carcinoma or panniculitis. AAT def should be suspected in patients who smoke and have COPD symptoms at a young age or a person with COPD symptoms that does not smoke 2, 8.

AAT is a protease inhibitor that is responsible for balancing out neutrophil elastase and allowing a person to breath normally. A significant decrease in the amount of AAT in the body can lead to clinical manifestations of emphysema, one of three characteristic forms of
COPD. A lot of research has been done to locate where in the body AAT comes from. AAT can be found on the SERPINA1 gene on Chromosome 14. Knowing this location is important in allowing patients to be phenotyped/genotyped to predict outcome\textsuperscript{3, 7}.

Individuals affected with AAT def causing pulmonary symptoms usually has those commonly seen in a patient with emphysema. In emphysema there is an enlargement and destruction of the alveoli in the lungs. Elastin, which allows the lungs to expand during inspiration, is permanently destructed. Emphysema is progressive and the symptoms do not usually improve with time. The clinical symptoms of emphysema include dyspnea on exertion, sputum production, chronic cough and respiratory wheezing. A patient then undergoes tests that are commonly used to diagnosis COPD starting with a chest x-ray or a CT scan. Each test has their own advantages but a CT scan is thought to be a more sensitive test. On a CXR there will be hyperinflation of the lungs, and flattening of the hemidiaphragms. The CT scan will show a decrease in fine peripheral vascular markings\textsuperscript{3, 8}. It will also show that AAT def traditionally occurs at the lung bases. PFT is utilized to determine the degree of airway obstruction as well as monitor treatment. The PFT usually shows an obstructive type pattern with FEV1 and FEV1/FVC ratio decreased as well as an increase in RV and TLC\textsuperscript{3}.

A patient having AAT def with liver complications most often presents as a pediatric patient. However, about 1/3 of adults presenting with AAT def can experience liver problems\textsuperscript{11}. In the pediatric population the most common finding for AAT is prolonged jaundice\textsuperscript{10}. Findings in an adult can vary but an abnormal elevation of liver enzymes is common, as well as symptoms of pruritis, jaundice, fatigue and weight loss may also be seen\textsuperscript{4}. In a study done in Sweden where 122 infants were screened for AAT def, 50 % presented with an elevation in liver enzymes. These patients were followed until age 18 and it was concluded that most patients did not show any signs of liver disease (less than 10%), giving patients a good prognosis\textsuperscript{11}. The most worrisome component of liver disease is the progression to hepatocellular carcinoma, a rare but real complication. One study stated that being of male sex, an increased BMI and having AAT def can cause liver cirrhosis, possibly leading to hepatocellular carcinoma\textsuperscript{11}.

It is important to determine both the amount of AAT in the body as well as the phenotype/genotype a patient may be. The phenotype is most clinically discussed. The phenotypes range from most likely to cause lung and liver problems, to less likely to cause problems. A phenotype of MM, MS or SS usually has a good outcome. Phenotypes that involve a Z decrease the prognosis (MZ or SZ). Finally patients with a ZZ or a null, clinically written as PiZZ, have the worst prognosis\textsuperscript{3}. The patients with PiZZ are the focal point of research and treatment options. One study stated that SZ is the beginning of worry for development of emphysema with it happening in 20-50% of patients. A patient with a ZZ makeup developed emphysma in 50-80% of cases and a patient with Null/Null ended up having it 100% of the time\textsuperscript{11}. Patients that have PiZZ usually have 2 defective AAT genes and cannot produce any AAT to combat the neutrophil elastase thus destroying alveoli.

The bulk of the research surrounding the AAT def continues to be in finding a cure. There is no definitive cure for AAT, only treatments directed at managing the symptoms. Most of the treatments have been studied surrounding the pulmonary aspect of AAT def. Due to the fact AAT def presents like COPD, the treatment is the same as COPD. The two most important treatments for COPD as stated by GOLD is smoking cessation and oxygen. The Alpha-1 foundation and Alpha1 association are quick to point out that any person that is still smoking should be encouraged to quit. Those that quit smoking may be able to limit that amount of damage the smoke does to the elastin. Oxygen therapy is essential in maintaining adequate ventilation and systemic perfusion.

Other treatments for COPD include anticholinergics such as tiotropium (Spiriva) or ipratropium (Atrovent). These are the first line treatments for COPD. Other treatments include corticosteroids, such as fluticasone (Flovent), which help open up the airways by decreasing inflammation in the lungs. Also important are long and short-acting beta-2 agonists that bronchodilate the lungs, such as salmeterol (Serevent) and albuterol (Ventolin), respectively. In most cases of COPD it is important to have multiple drugs to help limit acute exacerbations. There are many combination medications that combine the
different drug classes utilized in COPD management. One such example being Advair, a combination of the corticosteroid fluticasone and the beta-2 agonist salmeterol. Pulmonary rehab made be tried to help the lungs gain some strength back. Pulmonary rehab is similar to the idea of physical therapy to strengthen a knee or back.

Two other treatments exist for AAT def of emphysema type. The first treatment is a surgery approach called Lung Volume Reduction Surgery (LVRS). In this case, a surgeon will remove the most damaged part of the affected lung. Removal of the affected lung is thought to make the lung act in a more efficient manner. The National Emphysema Treatment Trial group did an extensive study on the advantages and disadvantages of LVRS. The trial consisted of over 1200 patients which were classified as either candidates for surgery or candidates for continued medical therapy. The group stated that better surgical candidates included those with upper lobe emphysema as well as decreased exercise capacity. In these candidates the benefits outweighed the risks involved in surgery. A patient with lower lobe emphysema and increased exercise capacity was at greater pre-surgical risk, thus was a poor surgical candidate and did not undergo surgery. The trial concluded that over two years, exercise capacity initially increased, lung function increased, and quality of life was better, yet ultimately returned back to their pre-surgery baseline. Thus, certain individuals mentioned above, may benefit from the surgery.

The last treatment in fighting AAT def emphysema is called augmentation therapy. This type of treatment is probably the most beneficial but can only be used in certain situations. Augmentation therapy is a weekly infusion of IV human derived AAT into the body. In order to receive such therapy a patient must meet certain guidelines, including a phenotype of PiZZ and a level of AAT of less than 35% of the normal values, among others. There have been several studies concluding that augmentation therapy (60mg/kg) has raised levels of AAT into a protective threshold. The therapy has also been thought to decrease mortality for patients. The Alpha1 foundation is also very vocal about the benefits of augmentation therapy but provided some negatives for therapy as well. According to the Alpha-1 foundation and association this is the only FDA approved treatment for AAT def emphysema. There is no long term research to see if the treatment actually delayed lung problems and for how long. Some adverse problems associated with the therapy may include H/A, pain at infusion site and fatigue. A patient should be tested for IgA because it could cause a hypersensitivity reaction. Some products that are commonly used include Prolatsin, Aralast, and Zemaira.

In liver disease the treatment options are really very limited. Unlike in the emphysema type AAT there are limited drug options with many side effects to treat liver disease. The treatments are aimed at treating complications of chronic liver disease. Other trial treatments include Cyclosporin A helping to decreases hepatic mitochondrial injury. Phenylbutyric acid has been shown to be beneficial in animal studies but in a 14 day trial did not help levels and had some problematic side effects. While both glucosidase inhibitors and mannosidase inhibitors are useful to help stimulate a release of the available AAT the mannosidae inhibitors can cause degradation of AAT. The only real definitive treatment is to have a liver transplant. This option is reserved for patients with end stage cirrhosis. AAT def is the second most common cause of liver transplant behind biliary atresia in the pediatric population.

The patient in this case presentation had previously been tested for serum levels as well as phenotyped. Her phenotype was SZ which occurs in 0.3% of all people with AAT def. Her AAT serum level was 87 mg/dl with a normal being over 90. So, according to the research my patient had an increased risk of developing both liver and lung disease but was not eligible to receive augmentation therapy. The pulmonologist and gastroenterologist have been monitoring her treatment for lung and liver disease. Her COPD treatment initially included her use of Advair 250/50, but her symptoms were getting worse. The dose was increased to Advair 500/50 and soon after is when she presented to the hospital with esophageal candidiasis, dysphagia and odynophagia. I am a little curious if the patient was being compliant when she was taking her Advair. It is hard to say if she was rinsing her mouth and spitting it out. Was she swallowing the medicine and exposing her esophagus to corticosteroids, thus causing the candidiasis? Hopefully, her follow up with the gastroenterologist will give some answers. When our patient goes to see the pulmonologist it may be necessary that she begin to follow standard COPD treatments.
**LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points**

COPD like symptoms at a younger age, especially emphysema, consider Alpha-1 antitrypsin deficiency

Alpha-1 antitrypsin commonly has two components: lung disease and liver disease

In the pediatric population Alpha-1 antitrypsin is the one of the leading causes of liver transplant

Treat lung disease like COPD and liver disease with a transplant

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