"Is It Autoimmune Or Malignant?"

A Medically Managed Case of Obstructive Jaundice In A Bahamian Healthcare System

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Abstract*—Although it is not considered to be one of the most prevalent cancers, pancreatic cancer should always be highlighted for its fulminant disease progression and dismal rates of survival. Globally, it is known to be the eighth most common cause of cancer in women and the tenth in men in 2020. Regrettably, many are not aware of its rapid progression until its discovery in its terminal stages. This case magnifies a similar picture which took place at the Rand Memorial Hospital, which is a hospital located on Grand Bahama Island in The Bahamas. This patient was a 67- year- old female with a known history of morbid obesity, type 2 diabetes mellitus and a known social history of heavy alcohol consumption which are well displayed risk factors for pancreatic cancer. Despite presenting with such a stark picture of jaundice and icterus, her chief presenting complaint was chest pain. The patient's liver function tests painted a "flawless" picture of obstructive jaundice. The need arose for first line imaging with a CT scan of the abdomen which could not be completed due to the patient surpassing the maximum weight capacity for the machine to confirm the diagnosis. This led to the completion of an abdominal ultrasound which is unfortunately user dependent. Due to the bulky pannus, this affected the ability to identify the offending agent that led to the patient's clinical presentation. Therefore, this led to myriad differential diagnoses primarily being whether this case was autoimmune or malignant. Alas, the patient continued to be managed under Internal Medicine where CA 19-9, CEA, anti- smooth muscle antibodies, antinuclear antibodies and antimitochondrial antibodies were completed to determine the etiology of the obstructive jaundice. After being hospitalized for 10 days, she wished to sign out against medical advice as she accepted her fate that the inevitable was likely to happen. After she expired, her tumor markers and antibody screen returned indicating that her CA 19-9 was 23404 U/ML. In addition, her CEA was noted to be 314.0 ng/mL and a positive actin smooth muscle antibody of 40 units was also seen despite having a negative antinuclear antibody and antimitochondrial antibody. This then posed the question to determine if this patient truly had an autoimmune disease or a co-existing autoimmune disease with the pancreatic cancer. It was also important to determine the association of the positive actin smooth muscle antibodies with pancreatic cancer. Through research, it was discovered that actin smooth muscle increases in instances of fibrosis such as pancreatic cancer and can be documented on immunohistochemistry according to K. Winter et al in "Alpha Smooth Muscle Actin (αSMA) Immunohistochemistry Use in the Differentiation of Pancreatic Cancer from Chronic Pancreatitis". Therefore, this draws the most likely conclusion that this patient indeed suffered from pancreatic cancer as this proves the connection. Peculiarly, this patient did not have a post-mortem autopsy completed to determine the exact cause of death. However, despite being controversial for confirming a diagnosis as they are non-specific, these tumor markers support this diagnosis.

Keywords— Pancreatic cancer, global incidence rate of pancreatic cancer, association between pancreatic cancer and antismooth muscle antibodies, ugib and pancreatic cancer

I. INTRODUCTION

Pancreatic cancer is a widely recognized contributor to malignant obstructive jaundice, given its rapid disease progression, limited response to treatment, and dismal prognosis with an overall five-year survival rate of merely 10%. As per the American Society of Clinical Oncology, pancreatic cancer accounted for 495,775 cases in the year 2020, ranking it as the eighth most prevalent cancer in women and the tenth in men. The present case involves a morbidly obese female who presented with obstructive jaundice and failed to benefit from appropriate imaging modalities to establish the underlying cause. Prior to her unfortunate demise, her obstructive jaundice had no identifiable cause, leading to the performance of tumor markers and antibody screening tests. The patient was found to have elevated levels of CA 19-9 (23404 U/ML) and CEA (314 ng/mL), an anti-smooth muscle antibody of 40 units, and negative antinuclear antibodies and antimitochondrial antibodies. No post-mortem autopsy was conducted. Given these findings, it is crucial to ascertain whether pancreatic cancer or an autoimmune disorder was the sole cause of the obstructive jaundice. Additionally, it is essential to investigate the possible association between anti-smooth muscle antibodies and pancreatic cancer.

Clinical Presentation and Patient Information

This is the case of a 67-year-old female with a known medical history of morbid obesity, congestive heart failure and visual impairment secondary to uncontrolled type 2 diabetes mellitus for more than 15 years. She presented to the Accident and Emergency Department at the Rand Memorial Hospital on September 28th, 2022, and was referred to the Internal Medicine specialty for further management. Her chief presenting complaint was a one-day history of isolated chest pain. She confirmed palpitations, shortness of breath, nausea, and vomiting, but denied diaphoresis or syncope. The patient denied any history of allergies. With regards to her drug history, she was unable to recall the names and dosages of her current medications. Her social history was significant for heavy alcohol consumption which ceased in 2018. Her family history was notable for type 2 diabetes mellitus and hypertension.

Lastly, her review of systems was significant for a one-week history of diarrhea and loss of appetite.

Upon examination, the patient was noted to have an increased body habitus (possibly >500lbs) with a heavy pannus and significant icterus and jaundice. The patient's foleys was notable for significant macroscopic bilirubinuria and hematuria with minimal urine output. In terms of pertinent examination findings, the patient was noted to have decreased air entry bilaterally on her respiratory exam. Abdominal examination noted a diffusely tender abdomen. Examination findings were limited due to the need for manpower to mobilize the patient.

Investigations

Initial Laboratory Investigations:
(Complete Blood Count, Basic Metabolic Profile and Liver Function Tests)

15.3	10.0 / 32.1	318	131 / 4.8	102 / 19.0	47 / 2.9	126		
ALT	AST	ALP	GGT	LDH	TB	DB	Alb	TP
58	N/A	**564**	N/A	**255**	N/A	N/A	**3.1**	7.7

Urinalysis noted large urinary bilirubin and a notable urine microscopy for 25-50 WBC's and 2+ bacteria.

Impression: The complete blood count was notable for a leukocytosis and a normocytic anemia as the MCV was 94. Chemistries indicated a hyponatremia and pre-renal azotemia. A complete liver panel and pancreatic enzymes were not completed due to the lack of reagents for the study. However, based on the patient's clinical picture with significant jaundice and an elevated ALP without the confirmatory GGT, this is likely obstructive jaundice.

Imaging Investigations

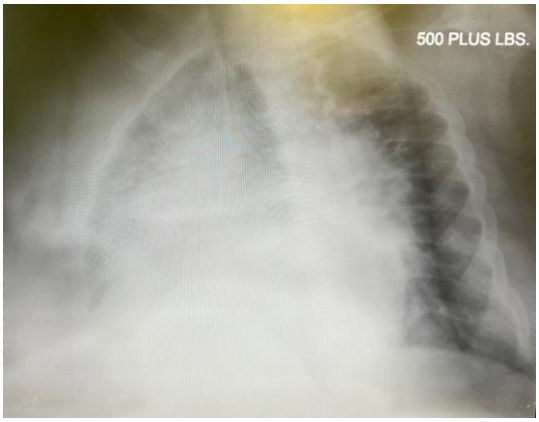

Image 1: Initial Chest X-Ray of Patient During Admission

The chest x-ray was an interesting radiograph and was sent to Radiology for a full report. Unfortunately, a CT scan was not completed due to the patient exceeding the maximum weight capacity.

Diagnosis and Assessment

The patient was assessed as rule out acute coronary syndrome due to her presentation of chest pain. Also, due to her initial chest x-ray, she was also assessed as rule out community acquired pneumonia versus malignant effusion. Other assessments included urinary tract infection, acute kidney injury, hematuria, obstructive jaundice (query occult malignancy versus autoimmune etiology) and type 2 diabetes mellitus.

Hospital Course and Management

Once the patient was admitted, a focused plan was completed. With regards to the obstructive jaundice, the medical team concluded that urgent imaging was necessary along with a complete liver panel to refer the patient to the surgical specialty. After consulting the lead radiologist, the team was informed that only an ultrasound of the abdomen could be completed due to the maximum weight capacity of CT and MRI machines. In the meantime, the patient's medical management continued. The chest x-ray was repeated after consulting the radiologist and was reported with minimally significant findings due to the patient's positioning during the time the radiograph was completed.

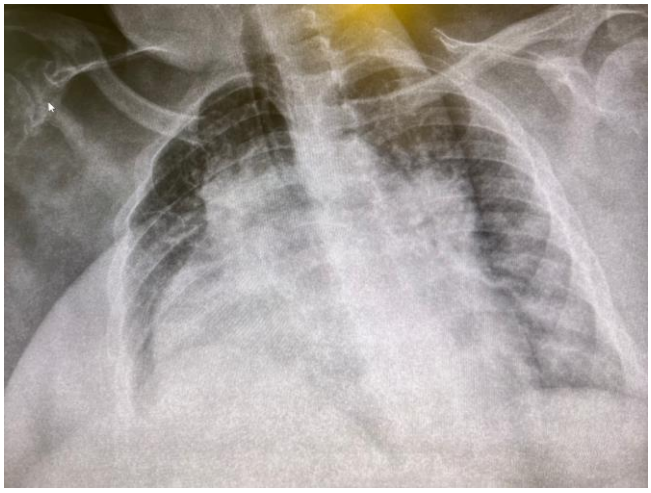

Image 2: Second Chest X-ray of Patient During Admission

Due to ACS being unlikely as cardiac enzymes were within normal limits and ECGs showed no further acute changes, it was concluded that a pulmonary embolism could be most likely especially due to the patient's risk factors. Once again, first line imaging was not completed with a CT-PA which led to the use of a d-Dimer. Due to the renal impairment, the patient was on strict urinary input and output charting and for fluid hydration. The urinary tract infection was managed with Zosyn 2.275g IV tid, which was renally adjusted. d-Dimer levels returned abnormal at 1.79 ug/ml (0.00-0.59) indicating a presumed PE. Clexane was then commenced and renally adjusted.

The complete liver function test panel returned as noted below:

AST	ALT	LDH	ALP	GGT	TB	DB	TP	Albumin	A:G	Glob
131	57	**445**	**545**	**447**	**32.0**	**24.0**	7.8	**3.0**	0.6	4.8

Pancreatic enzymes were noted to be within normal limits. The patient was referred once again to surgery who encouraged the team to complete tumor markers. However, surgical intervention was unlikely due to the likelihood of poor outcomes intraoperatively and postoperatively.

Image 3: Abdominal Ultrasound of Patient Indicating Minimal Pathologies

<u>Clinical impression</u>: The liver was normal in size. The common bile duct lumen measured 5.30mm in diameter and noted non- specific thickening of the common bile duct with no evidence of intra or extrahepatic biliary duct dilation consistent with ascending cholangitis. This is associated with a contracted gallbladder with the possibility of a gallstone. The pancreas could not be visualized. The other differential diagnosis: primary sclerosing cholangitis, ischemic cholangiopathy, infection, autoimmune cholangitis, and malignancy. The radiologist also suggested the medical team to correlate ultrasound findings with the patient's clinical parameters.

This report led to the medical team remaining as the primary consulting service due to the unimpressive ultrasound findings.

During her admission, routine laboratory investigations were completed to assess the patient's clinical course:

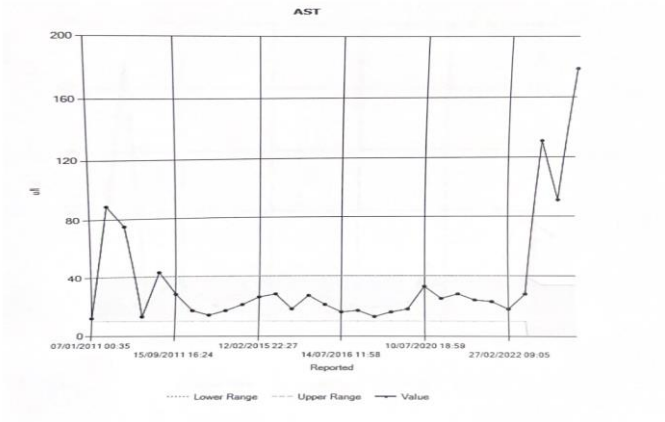

Image 4: AST trends throughout the patient's previous admissions and current admission

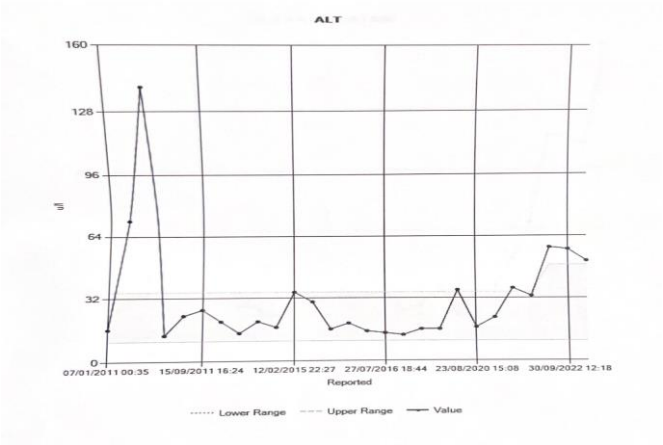

Image 5: ALT trends throughout the patient's previous admissions and current admission

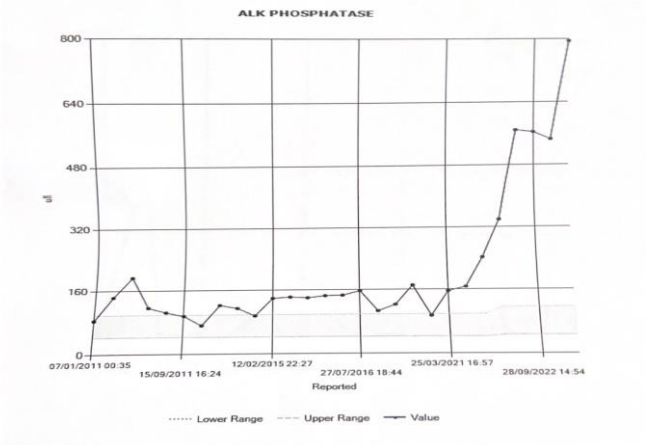

Image 6: ALP trends throughout the patient's previous admissions and current admission

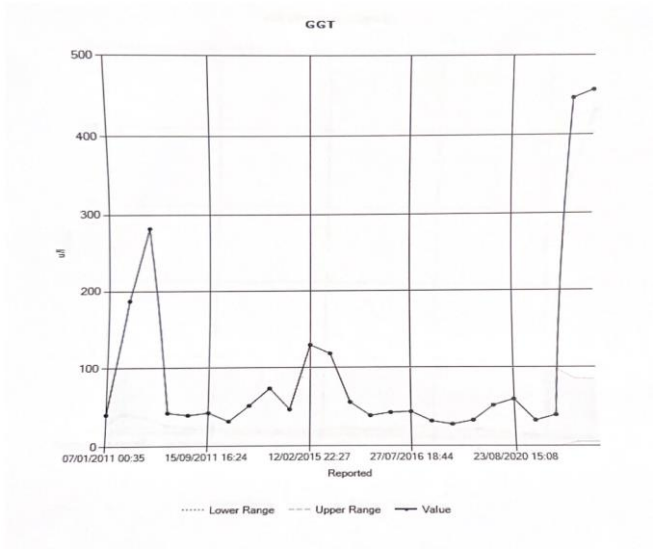

Image 7: GGT trends throughout the patient's previous admissions and current admission

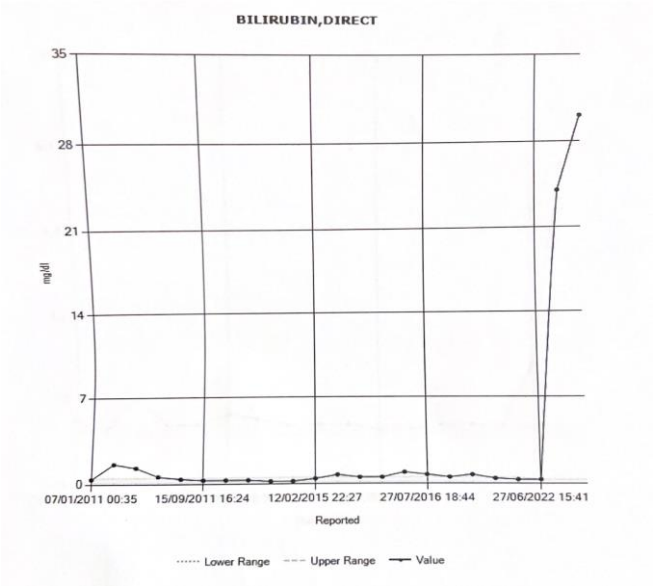

Image 8: Direct Bilirubin trends throughout the patient's previous admissions and current admission

At this time, liver enzymes and bilirubin levels also continued to elevate. The patient's renal impairment continued to worsen noting that bile cast nephropathy was the offending etiology. The possibility of infectious hepatitis and non- alcoholic fatty liver disease were also entertained due to the rapid increase in the liver enzymes. Upon assisting the nursing staff with a diaper change and changing the patient's urinary catheter, it was further confirmed of the presence of an obstructive jaundice picture due to cement appearing stools, leading to the surgical specialty being reconsulted. Tumor markers were then completed along with an autoimmune screen because of the ultrasound findings. Due to the patient being in consistent excruciating pain, she wished to sign a Do Not Resuscitate order. After being admitting for 10 days, she decided to sign out against medical advice. A family conference was held prior to updating the family on the patient's prognosis. The patient presented two days after signing out and expired after going into cardiac arrest. Several days after the patient expired, results of the tumor markers and antibody screen indicated that her tumor markers showed marked elevations. CA 19-9 was elevated at 23404 U/ML (0-35) and CEA was noted to be 314.0 ng/mL (0.0-4.7). Despite most of the antibody screen being non conclusive, it was interesting to note that her anti smooth muscle antibodies were strongly positive. Actin/ smooth muscle antibodies were 40 units (0-19), ANA was negative and mitochondria antibodies were <20 units (0.0-20.0).

Discussion

As previously stated, pancreatic cancer carries the stigma of being one of the most aggressive types of cancers due to its fulminant disease progression and dismal survival rates. Typically, the age of onset of pancreatic cancer varies between the ages of 60-80 and are commonly seen between the Black and Jewish populations. Its etiology varies depending on many risk factors. Some instances can be genetically associated with various syndromes such as Von- Hippel Lindau Syndrome, Multiple Endocrine Neoplasia Type 1, BRCA1 and 2 mutations, etc. However, majority of other cases are associated with risk factors such as alcohol, chronic pancreatitis, a history of type 2 diabetes mellitus, obesity and a known history of smoking which appears to be the most associated etiology of pancreatic cancer. Notably, this patient was exposed to majority of the previously mentioned risk factors. The clinical presentation of pancreatic cancer varies considerably. Unfortunately, symptoms may not present until the disease has progressed into its later stages. However, patients can have symptoms such as epigastric pain, weight loss, diarrhea, and signs of obstructive jaundice such as pale stools and dark urine. Thrombosis is also a known presenting feature which was depicted when the patient developed a pulmonary embolism. Due to the patient's clinical presentation, her previous records were investigated to determine the rate of disease progression. Her records primarily indicated several episodes of acute cholecystitis, episodes of decompensated congestive heart failure and immunological complications of diabetes such as cellulitis and fournier's gangrene. Her records also indicated a previous history of an upper gastrointestinal bleed with an unknown etiology. According to L. Munoz et al (2020) in "Gastrointestinal Bleeding in Patients with Pancreatic Cancer: Causes and Hemostatic Treatments" of the United European Gastroenterology Journal, it was discovered that upper gastrointestinal bleeding can occur in cases of pancreatic cancer which may be seldom. However, it occurs due to portal hypertension which can cause esophageal varices and possible rupture. Causes of the upper gastrointestinal bleed were not confirmed. Previous lab investigations (seen in images 4-8) indicated a previous history of elevated liver transaminases in a prior admission, but they resolved overtime and is likely associated with her previous history of alcohol use. Her previous admission noted earlier in the year of 2022 also showed no indications of the disease as her clinical presentation was contrary to her current presentation.

The antibody screen was initially completed due to the ultrasound report indicating minimal pathologies. However, as previously stated, ultrasounds are user dependent especially if body habitus is a limiting factor. Differentials at the time included primary biliary cholangitis and autoimmune hepatitis. However, the patient's clinical picture was not consistent with the aforementioned. As it pertains to the autoimmune screen and a positive anti smooth muscle antibody, the primary concerns were if this case was indeed secondary to an autoimmune cause or a co-existing incidental finding. Anti-smooth muscle antibodies are used

in the diagnosis of autoimmune hepatitis. Despite being in acute liver failure, autoimmune hepatitis primarily occurs in patients with a pre-existing autoimmune disease. This patient's anti-nuclear antibody screen was also negative which decreases the likelihood of this possibility but cannot be completely ruled out. According to the Journal of Clinical Medicine, a publication entitled "Alpha Smooth Muscle Actin (αSMA) Immunohistochemistry Use in the Differentiation of Pancreatic Cancer from Chronic Pancreatitis" by K. Winter et al (2021) discussed this correlation. This study discovered that actin smooth muscles are typically activated in cases of fibrosis such as chronic pancreatitis, liver cirrhosis and ductal pancreatic adenocarcinoma. This activation occurs due to pancreatic stellate cells and were noted upon immunohistochemistry biopsy results. Therefore, this concludes that these antibodies produced are associated with this finding on immunohistochemistry. It further substantiates that this indeed was a case of pancreatic cancer given that this patient's CA 19-9 was 23 times the upper limit. Unfortunately, there was no imaging or post- mortem results to confirm the existence and location of the malignancy.

Conclusion

To summarize, the patient was believed to have had pancreatic cancer based on laboratory investigations and studies on fibrosis and its relationship with actin smooth muscle in immunohistochemistry. An autoimmune etiology is unlikely given these findings. Pancreatic cancer is a condition that can progress rapidly and often remains asymptomatic until advanced stages, particularly in patients with risk factors such as smoking, high alcohol consumption, obesity, and type 2 diabetes. It is difficult to predict the patient's likelihood of survival if the cancer had been detected earlier due to its aggressive nature and the limitations posed by the patient's morbid obesity, which made both surgical and medical management challenging.

A CT scan was crucial for both specialties in this case as it was necessary to confirm the malignancy, determine its location, and stage the cancer for further management. Unfortunately, the patient's weight posed a challenge in terms of accessing the necessary diagnostic tools, highlighting the need for CT scans without weight restrictions worldwide. This also underscores the importance of overall health and wellness to ensure that weight limitations do not prevent the use of necessary diagnostic tests.

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