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A 55-YEAR-OLD MAN WITH RAPID ONSET RECTOSIGMOID MASS AND HEPATIC METASTASES WITH AN AFP OF > 3 MILLION NG/ML

Francis Kim, MD

Case

A 55-year-old male with a past medical history of ulcerative colitis diagnosed in 1999, Barrett's esophagus, hyperlipidemia, and diabetes mellitus presented with a 2-week duration of daily constant abdominal pain. He described the pain as a sharp, epigastric pain not worsened with food intake or bowel movements. He was unable to tolerate any oral intake for a week prior to admission secondary to increased epigastric pain. He stated an increase in bowel movements to 1 per day that was softer and less formed than usual. He also stated he had a near syncopal episode on the day of admission and reported dizziness. The patient denied any bright red blood per rectum or having dark stools. He states he also had some fevers, chills, and a sore throat for 3 days duration. He had tried some Pepto Bismol without any improvement.

Medications he was taking included 6-mercaptopurine 50mg daily, pantoprazole 40mg twice a day, levemir 10 Units nightly, and cholestyramine 4g daily. He denied any alcohol, smoking, or drug use. He worked as a storeowner without any recent travel history. On admission, his vitals were: temperature 101 degrees Fahrenheit, pulse rate 54 beats per minute, respiratory rate 20 per minute, oxygen saturation 99% on room air, and blood pressure of 111/65 mmHg. On physical exam, the only significant finding was right upper quadrant tenderness to palpation on abdominal exam. The rest of the exam was normal. He was noted to have a positive hemocult.

Lab work showed a white blood count of 10.5 B/L, Hemoglobin of 9 g/dL, and Platelets of 398 B/L. The chemistry 7 panel was within normal limits and his liver function tests showed slightly increased total bilirubin at 1.5 mg/dL and direct bilirubin at 0.6 mg/dL with an otherwise normal panel. The patient had imaging performed 2 months prior to admission performed for recent weight loss. The MRI abdomen 2 months prior to admission showed: "mild hepatic steatosis, multiple sub 5 mm T2 hyperintense foci throughout the liver which are most likely cysts. There is a 1.0 x 0.8 cm cyst in the right hepatic lobe. No evidence of malignancy in the abdomen. Specifically, the pancreas appears normal." The patient's most recent colonoscopy was performed 11 months prior to admission, which showed "few inflammatory appearing polyps in the rectum... There was mild colitis involving the rectum and sigmoid and some scars." The rest of the colon was stated to appear endoscopically normal. The biopsies from that colonoscopy did not show any malignancy.

Hospital Course

The patient was admitted with concern for an ulcerative colitis flare versus infectious colitis. He was started on antibiotics and was ordered for a CT abdomen and pelvis. This CT scan showed a circumferential mass involving the sigmoid colon, a

filling defect within the left main portal vein, extensive hepatic masses, largest seen in the right hepatic lobe measure 6.2 x 5.1 x 6.6 cm and retroperitoneal lymphadenopathy. At this point, the patient underwent ultrasound-guided biopsy of the liver and oncology was consulted. AFP (alpha fetoprotein), CEA (carcino embryonic antigen), and CA (carbohydrate antigen) 19-9 levels were sent. The CEA and CA 19-9 levels returned normal, but the AFP level came back elevated at 2.4 million ng/mL. Subsequent rechecks of his AFP level peaked at 3.5 million NG/mL. LDH (lactate dehydrogenase) was markedly elevated >600 units/L. Beta-HCG (human chorionic gonadotropin) was negative. The fine needle aspirate of the liver showed poorly differentiated carcinoma. The immunohistochemical profile stated that the primary site of the carcinoma could not be stated with certainty. A sigmoidoscopy was performed and revealed a partially obstructing colon mass located at the rectosigmoid junction, mild colitis, and external hemorrhoids. Biopsy of this mass showed poorly differentiated adenocarcinoma. Colorectal surgery did not see an emergent need for resection as there was no acute obstruction and he was managed medically. To further work-up this malignancy, a testicular ultrasound was performed which was negative for any masses. At this point, due to the markedly elevated AFP and LDH, it was determined that this malignancy was an extragonadal germ-cell tumor. He was started on chemotherapy of bleomycin, etoposide, and cisplatin. His AFP decreased to 28,000 with chemotherapy in the ensuing months with stabilization of his disease on repeat imaging. However, the patient decompensated and passed away 7 months after initial diagnosis.

Discussion

In the initial differential diagnosis of this patient with a new finding of a rectosigmoid mass with hepatic masses, colorectal cancer was considered. It is the most common GI tumor and also takes into account the patient's history of ulcerative colitis. The diagnosis of ulcerative colitis does increase the risk of colorectal cancer. In fact colorectal cancer accounts for around 15% of all inflammatory bowel disease deaths.¹ However in this case, the rapid development of this cancer in under a year (from his last colonoscopy which showed no malignancy) would be unusual as colon adenocarcinoma is typically slower progressing. Also, the tumor markers that are associated with colorectal cancer, such as carcinoembryonic antigen (CEA), and carbohydrate antigen (CA) 19-9 were within normal limits.² Hepatocellular carcinoma (HCC) is another tumor that has been shown to produce elevated AFP markers above 400ng per milliliter. The diagnosis of HCC is made by incorporating typical imaging (CT/MRI) features specific for HCC, AFP levels, and if needed, liver biopsy.³ For this patient, the liver biopsy did not reveal HCC. It was in the

evaluation of the alpha fetoprotein and LDH levels that the diagnosis of extragonadal germ cell tumor was considered.

AFP is a marker usually produced by the fetal yolk sac that becomes undetectable in normal men. However, elevations in AFP can be seen in germ cell tumors, specifically non-seminomatous germ cell tumors. Usually, AFP values greater than 10,000mg/L are found exclusively in non-seminomatous germ cell tumors or hepatocellular carcinoma. Opposed to non-seminomatous germ cell tumors, seminomatous germ cell tumors by definition do not produce AFP.⁴

Extragonadal germ cell tumors are germ cell tumors that do not originate in either the testes or the ovaries. As this patient had a normal testicular ultrasound, it was determined that his primary tumor was extragonadal in location. Extranodal germ cell tumors are relatively uncommon, accounting for only 1-5% of all germ cell tumors. They tend to arise in midline locations in adults with the most common sites including the anterior mediastinum, retroperitoneum, and the brain.⁵ A possible explanation of the extragonadal location is that there is a reverse migration of the transformed totipotent germ cells.⁶

In considering the diagnosis of extragonadal germ cell tumors, it is mandatory to check for testicular masses via physical exam and ultrasound. Up to one third of patients can have TIN (testicular intraepithelial neoplasia) in one or both testicles that appear to be normal on imaging and ultrasound. However, a testicular biopsy is not recommended due to the fact that all extragonadal germ cell tumors will most likely receive the cisplatin-based therapy, which will eliminate the majority of TIN. The diagnosis of germ cell tumors (GCT) is supported by elevated AFP or B-HCG levels. LDH is also an important prognostic marker of disease but is less sensitive and specific to GCT. Placental alkaline phosphatase (PLAP) staining in biopsy specimens can also be used to diagnose GCTs. The isochromosome i12p is also very specific for this tumor entity.⁷ The biopsy specimen from this case came back negative for both PLAP and i12p.

However, in cases in which there is unequivocal elevation of AFP or B-HCG levels, chemotherapy should be the first line treatment

without delay as germ cell tumors have been known to have curative potential with cisplatin based chemotherapy regimens. Markers of poor outcome include hepatic, osseous, and/or brain metastasis, and high serum levels of LDH, AFP, or HCG.⁶ Once the diagnosis of extragonadal germ cell tumor was made in this case, the patient was started on bleomycin, etoposide, and cisplatin therapy. In the ensuing months, repeat CT scans showed stabilization and some mild improvement in the size of his cancer. Repeat AFP levels also dropped precipitously from 3.5 million to 28,000 ng/mL. Despite some positive signs, he also had many poor prognostic indicators including his metastatic disease, high AFP levels, and high LDH levels.

In conclusion germ cell tumors, and more specifically non-seminomatous GCTs, should be considered in patients with greatly elevated AFP levels. In a male patient, a testicular ultrasound should be performed to rule out primary testicular cancer. Once a germ cell tumor has been diagnosed, due to the historically good response to chemotherapy the patient should be started on a cisplatin-based chemotherapy.

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"Florence"

photograph by Mitul Kanzaria, MD

