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Gastrointestinal Stromal Tumor or Malignant Peripheral Nerve Sheath Tumor? An Enigmatic Mass

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INTRODUCTION

Neurofibromatosis type 1 (NF-1) frequently has been associated with sarcomas, leukemias, and lymphomas.[1] Benign or malignant, the expansive growth of these tumors is often one of the reasons why these patients have a shortened life expectancy.[2] Particularly, the incidence of gastrointestinal stromal tumor (GIST) and malignant peripheral nerve sheath tumor (MPNST) in patients with NF-1 tends to be higher than the general population.[1,3-5] Cases of NF-1 with cancer reported in the literature described patients who develop one of these tumors.[1,4,6] We present a patient with a perihilar hepatic mass with features of both GIST and MPNST concomitantly in the setting of NF-1.

CASE REPORT

The patient was a 39-year-old male with a history of NF-1 and known neurofibromas of the intra-medullary cervical region and along the cauda equina nerve roots, in addition to the muscle and subcutaneous tissues of the thorax. Given this extensive disease, he had chronic intractable shoulder pain, back pain, peripheral neuropathy, and headaches.

He presented to the emergency department with new-onset right upper quadrant abdominal pain, nausea, vomiting, and findings of obstructive jaundice. Computed tomography (CT) of the abdomen and magnetic resonance cholangiopancreatography (MRCP) showed intrahepatic bile duct dilatation with obstruction of the common bile duct (Figure 1). During endoscopic retrograde cholangio-pancreatography (ERCP), a localized biliary stricture was found, and a stent was placed. The upper third of the main bile duct, the left and right hepatic ducts, and all intrahepatic branches were dilated. Brush cytology was non-diagnostic. Subsequently, endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) was also non-diagnostic. The patient was advised to follow-up within four weeks for re-assessment.

Magnetic resonance imaging (MRI) of the abdomen was obtained one month later; a lesion measuring 25.40 mm x 35.66 mm compressing the porta hepatis was seen (Figure 2). The patient was referred to surgery for exploratory laparotomy during which two tumors were found: a perihilar mass (50 mm x 50 mm) involving the entire common bile duct and part of the left lobe of the liver and a mass in the small bowel (20 mm x 20 mm). The patient had a radical resection of the perihilar mass, small bowel, and common bile duct, Roux-en-Y hepaticojejunostomy to the intra-hepatic bile ducts, retroperitoneal and peri-portal lymphadenectomy, and left partial hepatectomy.

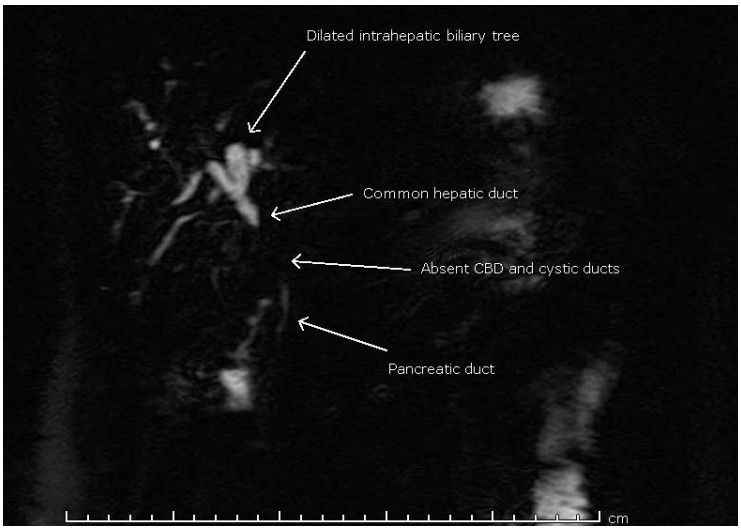

Figure 1. Magnetic resonance cholangiopancreatography showed intrahepatic bile duct dilatation with obstruction of the common bile duct.

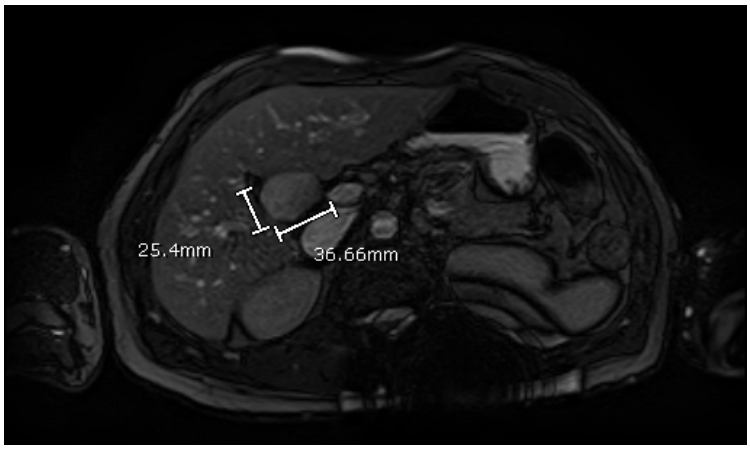

Figure 2. Magnetic resonance imaging of the abdomen showed a lesion measuring 25.40 mm x 35.66 mm compressing the porta hepatis.

Histology of the small bowel tumor was consistent with a typical GIST morphology and immunophenotype with expression of CD-117 and DOG-1. The tumor had a low mitotic rate, negative epithelial membrane antigen, rare expression of SOX-10, and retention of the gene transcription repressor H3-K27-me3.

The perihilar tumor's histology showed mitotically active malignant-appearing spindle cell neoplasm with necrosis infiltrating into the liver. This tumor's morphology is seen in MPNST. However, its immunophenotype was not concordant with its morphologic features. There was complete loss of expression of H3-K27-me3 as would be expected in MPNST but CD-117, DOG-1, and SOX-10 were positive, which are diagnostic for GIST.

Three months following the Whipple procedure, MRI of the abdomen showed three hepatic lesions with high grade spindle cell neoplasm on histology. He was initiated on gemcitabine and taxotere to treat MPNST. However, the patient's disease progressed on chemotherapy. He was switched to ifosfamide and etoposide. Despite current treatment, his malignancy has metastasized further.

DISCUSSION

Our patient presented with a mass that had features of both GIST and MPNST, making the diagnosis difficult and rendering its management uncertain. While rare in the general population, these tumors have a greater prevalence among patients with NF-1.[1,3-5]

GIST is the most common NF-associated gastrointestinal tumor, its incidence in NF-1 is significantly higher than that of the general population.[1,7] While cases of GIST have been reported in all age groups, they are diagnosed most commonly in the 6th decade of life.[6] These tumors are found predominantly in the stomach (60%) followed by the small intestine (20 - 30%). However, in patients with NF-1, GIST is found predominantly in the small intestine and diagnosed at a younger age, as seen in our patient.[4,8] The diagnosis of GIST usually is established with immunohistochemistry that demonstrates a gain-of-function mutation of the receptor tyrosine kinase protein, KIT, also known as CD-117.[9] DOG-1, a transmembrane protein, is sensitive and specific to GIST and more sensitive than CD-117 for gastric GIST, while CD-117 is more sensitive than DOG-1 in intestinal GIST.[10,11]

MPNST is an aggressive spindle cell neoplasm associated with NF-1; 50 - 60% of MPNST cases have a known diagnosis of NF-1.[12] Approximately 2 - 5% of patients with NF-1 develop MPNST in the second or third decade of life.[3] These tumors commonly arise from pre-existing plexiform neurofibromas, which are prevelant in patients with NF-1.[3,5] The diagnosis of MPNST involves nonspecific histologic features; no pathognomonic immunohistochemical stain has been defined for MPNST.[13] Since it is difficult to distinguish MPNST from plexiform neurofibromas, loss of H3-K27-me3 has been studied as a possible diagnostic marker for MPNST.[14] Loss of H3-K27-me3 has a high specificity for the diagnosis of MPNST, particularly NF1-associated MPNST.[14-16] However, studies have reported variable sensitivity levels for this test.[15,16] Consequently, loss of H3-K27-me3 should be considered in the setting of a spindle-cell neoplasm.[16]

Our patient was found to have two tumors, both expressing DOG-1 and CD-117, which are diagnostic for GIST.[8] However, the perihilar tumor exhibited loss of H3-K27-me3 in addition to spindle cell morphology. Since this marker is specific for MPNST, the possibility that the second tumor had two simultaneous NF-associated malignancies cannot be ruled out.[15,16]

The hilar mass could represent a NF-associated GIST with loss of H3-K27-me3 due to high mitotic activity. However, no previous studies were found discussing such an occurrence. Loss of H3-K27-me3 could serve as a marker of an aggressive variant of GIST as well, however, no prior cases were described in the literature.

GIST and MPNST carry devastating prognoses. Malignant GIST has a median five year relative survival rate of 45% and is resistant to conventional radiation and chemotherapy.[9,17] This has made surgery the primary treatment modality for localized tumors, with a cure rate of 60%.[9,17] The tyrosine kinase inhibitor imatinib has been used prior to surgery to decrease tumor size and as adjuvant chemotherapy with a response rate of 82%.[9] MPNST's five-year survival rate is 35 - 50% and decreases to 10% in patients with NF-1.[18] To the best of our knowledge, this is the first case of NF-1 presenting with a tumor carrying features of both GIST and MPNST.

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