Metastatic Gastrinoma in a Pediatric Patient With Zollinger-Ellison Syndrome

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Summary: Metastatic neuroendocrine tumors of childhood are extremely rare, and as such present diagnostic and therapeutic challenges. Here, we report a case of gastrinoma with extensive hepatic metastases in a pediatric patient with Zollinger-Ellison Syndrome who underwent orthotopic liver transplant followed by cytotoxic chemotherapy, somatostatin analog therapy, and immune modulation.

Key Words: gastrinoma, liver transplant, somatostatin analog, mTOR inhibitor

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ollinger-Ellison Syndrome (ZES) is characterized by Z gastric hypersecretion, peptic ulcer disease, and gastrinproducing pancreatic islet cell tumor or gastrinoma. The clinical presentation includes abdominal pain, diarrhea, heartburn, nausea, vomiting, and weight loss. The incidence of ZES is 1 per million population per year and is extremely rare in children, with only 1% of all cases occurring in pediatric patients.¹⁻³ Gastrinoma in children most often occur sporadically, as single pancreatic lesions with hepatic metastases, although nearly one fourth occur in association with autosomal dominant Multiple Endocrine Neoplasia type I as multifocal duodenal lesions.^{4,5} Experience with ZES and gastrinoma in the pediatric population is limited and thus a high index of suspicion is required to accurately diagnose these children and to provide appropriate surgical and medical management.

PATIENT PRESENTATION

An 11-year-old girl, with ZES and gastrinoma with extensive hepatic metastases was referred to our center for surgical management. The patient initially presented with a 3-year history of intermittent abdominal pain, vomiting, and diarrhea. Endoscopy, performed 2 months before diagnosis, revealed a duodenal ulcer. The patient's symptoms did not abate despite nearly 3 months of oral proton pump inhibitor therapy. Radiologic imaging obtained at the referring institute revealed a large mass in the tail of the pancreas and multiple liver lesions. At presentation to our center approximately 1 month after diagnosis, the patient

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had a distended abdomen; a large mass obscured splenic exam. Laboratory evaluation revealed a fasting serum gastrin level of > 100,000 pg/mL (normal < 125 pg/mL) and a serum chromogranin a level of 10,300 ng/mL(normal < 50 ng/mL). Aspartate Aminotransferase 42, alanine aminotransferase 21, alkaline phosphatase 98, lactate dehydrogenase 158, albumin 5.1, beta human chorionic gonadotrophin < 2, alphafetoprotein 3, ammonia 54, amylase 83, and lipase 11.4.

Magnetic resonance imaging (MRI) of the abdomen revealed a markedly enlarged nodular liver extending into the pelvis, with areas of T1 and T2 hyperintensity as well as enlargement of the tail of the pancreas (Fig. 1). An ultrasound and computed tomography (CT) scan of the abdomen revealed metastatic disease of the liver as previously described by MRI evaluation, normal left and right kidney anatomy, normal spleen, and a heterogeneous soft-tissue mass with minimal vascularity in the tail of the pancreas. A positron emission tomography CT scan found abnormal metabolic activity in the pancreatic tail mass, heterogeneous and patchy metabolism in the liver, and low grade but abnormal metabolic activity in the left axilla concerning for metastatic disease. An octreotide scan revealed increased uptake in the tail of the pancreas, diffuse hepatic uptake, and no definite uptake in the left axilla, where previous positron emission tomography CT scan had demonstrated fluorodeoxyglucose avidity. A bone scan was negative for skeletal metastases. Echocardiogram revealed mild mitral valve prolapse with trace regurgitation.

An ultrasound-guided liver biopsy confirmed metastatic gastrinoma; immunostains for chromogranin, synaptophysin, gastrin, and somatostatin receptor were strongly positive, stains for insulin and glucagon were negative. The Ki67 index was approximately 3%.

Evaluation for Multiple Endocrine Neoplasia type I was negative; family history was unremarkable, serum calcium, parathyroid hormone, prolactin, insulin-like growth factor-1, and thyroid function tests were normal. A CT scan of the head was normal.

The patient was started on omeprazole and octreotide 100 mcg/dose twice daily before transplant. She underwent a living related liver transplant with resection of the gallbladder, distal pancreas, and spleen. Pathology revealed disseminated intrahepatic metastases occupying approximately 80% of the liver parenchyma, Ki67 index of approximately 2%. Periportal lymph nodes (3 of 3) were positive for metastatic gastrinoma. Disease was documented in 4 of 6 peripancreatic lymph nodes, with a Ki67 index of 7%. Vascular invasion was identified although the pancreatic and radial surgical margins were negative. The patient's serum gastrin level decreased after transplant to < 1000 pg/mL. An octreotide scan obtained after transplant demonstrated 3 new foci in the abdomen located beneath the right hemidiaphragm, in the region of the epigastrium and medial to the

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FIGURE 1. Coronal HASTE (T2 weighted) magnetic resonance imaging image obtained at the time of presentation to the treating institution, demonstrates (A) massive hepatomegaly with abnormal heterogeneous signal in the liver, representing infiltrative metastases, and (B) enlarged pancreatic tail with abnormal T2 signal (arrow), representing the primary pancreatic gastrinoma.

lower pole of the right kidney, as well as focal uptake in the left suprarenal region. The patient began tacrolimus and sirolimus approximately 3 weeks after transplant.

The patient received adjuvant chemotherapy per Children's Oncology Group protocol AHEP0731 Regimen F, a therapeutic study designed for children with hepatoblastoma, with cisplatin, doxorubicin, 5-flurouracil, and vincristine, but did not receive subsequent weekly doses of vincristine secondary to toxicity. The patient was admitted secondary to dehydration, prerenal azotemia, and developed acute renal insufficiency, fever and neutropenia, cytomegalovirus viremia, mucositis with exacerbation of her peptic ulcer disease, and significant GI bleeding, requiring prolonged blood product support. Medical management included histamine blockers, proton pump inhibitors, and an octreotide drip, which was transitioned to subcutaneous injections and subsequently to octreotide long-acting repeatable depot. The patient continued to receive immune modulation therapy with tacrolimus and sirolimus.

MRI of the abdomen and pelvis did not demonstrate soft-tissue abnormalities beneath the hemidiaphragm, within the epigastric tissue or in the left suprarenal region as identified on previous octreotide scan. A high-signal lesion within the right transverse process of L1, correlating to the abnormality medial to the lower pole of the right kidney seen on octreotide scan, was identified. CT scan of the chest, abdomen, and pelvis revealed a sclerotic lesion in the right transverse process of L1 vertebral body corresponding to findings on MRI. Serum gastrin level was 188 pg/mL and chromogranin A level was 1154 ng/mL. The patient again received chemotherapy with cisplatin, doxorubicin, 5-flurouracil, and vincristine, followed by granulocyte colony stimulating factor rescue. Serum gastrin level was 295 pg/mL and chromogranin A level was 168 ng/mL.

MRI of abdomen and pelvis demonstrated stable enhancing focus of signal abnormality in the right LI transverse process. MRI of the spine also reveals abnormal signal involving the right transverse process of LI, differential diagnosis includes metastatic lesion versus an incidental lesion such as an osteoid osteoma. In addition a disc bulge at L4-L5 and L5-S1 without evidence of central spinal canal stenosis or neural foraminal narrowing was noted. Subsequent octreotide scan revealed interval resolution of the previously identified pentatreotide-avid foci.

The lesion in L1 transverse process likely represents a benign osteoid osteoma rather than persistent metastatic disease, as the lesion remains stable on repeat MRI to date; in addition, the patient remains asymptomatic > 2 years after transplant and chemotherapy. Since completion of chemotherapy, serum gastrin and chromogranin A levels remain < 200 and 150 ng/mL, respectively. The patient continues to receive octreotide 10 ng intramuscularly monthly, sirolimus and tacrolimus.

DISCUSSION

Surgical resection and adjuvant pharmacologic therapy are the mainstays of gastrinoma management. In approximately 50% of patients, tumors recur within 5 years after resection,³ necessitating careful long-term follow-up in pediatric patients with gastrinoma. The overall mortality rate among children is between 50% and 70%.⁶ Wilson⁷ reported 25- to 30-year survival among pediatric patients with gastrinoma following complete excision. Liver transplant in the setting of metastatic neuroendocrine tumor has been utilized in rare cases. Florman et al⁸ published a series of 11 adult patients who underwent liver transplantation; the 1- and 5-year survival among these patients was 76% and 36%, respectively, suggesting cure with transplantation alone is unlikely. Medical therapy for metastatic gastrinoma has historically included adjuvant chemotherapy with streptozotocin, 5-fluorouracil, and doxorubicin as second-line therapy for well-differentiated tumors and upfront etoposide plus cisplatin for poorly differentiated or anaplastic tumors.^{9,10} The Ki67 index was 2% to 7%; however, the disease was widely metastatic at the time of resection. We opted to administer 2 cycles of 5-fluoruracil, doxorubicin, and cisplatin plus vincristine. Rinke and collegues demonstrated the efficacy of long-acting somatostatin analog therapy in the management of neuroendocrine tumors. Octreotide LAR significantly prolonged the time to disease progression compared with placebo (66% risk reduction), and provided a more favorable antiproliferative response, in patients with metastatic gastrinoma.¹¹ Several studies have demonstrated the efficacy of mTOR inhibitors alone,12 and in combination with somatostatin analog therapy in the management of advanced neuroendocrine tumors associated with carcinoid syndrome¹³ and metastatic pancreatic neuroendocrine tumors.14 Immunosuppression with combined sirolimus and tacrolimus following orthotopic liver transplant is effective in the prevention of graft rejection.^{15,16} No increase in bone marrow suppression or nephrotoxicity and no new toxicities were observed when administered simultaneously.17 Studies evaluating the efficacy of small molecule multikinase inhibitors, such as sunitinib, ^{18,19} and the monoclonal antibody bevacizumab are promising.^{18,20} The patient presented here underwent tumor resection and orthotopic liver transplant followed by cytotoxic chemotherapy and adjuvant pharmacologic therapy with both a somatostatin analog and immune modulators. She received aggressive multispecialty care with the goal of achieving long-term remission.

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