Gastroduodenitis Associated With Yttrium 90–Microsphere Selective Internal Radiation
An Iatrogenic Complication in Need of Recognition

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Context.—Selective internal radiation (SIR) therapy (SIRT) with yttrium 90 microspheres is increasingly used as an alternative therapeutic modality for patients with inoperable liver tumors. During administration of microspheres via the hepatic artery branches, some may on occasion be misdirected and be caught in the capillary bed of the duodenal and/or stomach.

Objective.—To better characterize the histopathologic features of these complications.

Design.—We report herein our experience with 3 patients who received SIR and developed gastroduodenal complications.

Results.—SIR-microsphere–induced gastroduodenitis was diagnosed from 10 days to 5 months after treatment. In all 3 cases, purple particles measuring about 40 μm in diameter were observed. An array of changes ranging from mucosal ulceration to epithelial changes were seen. Fibropurulent exudate was admixed with granulation tissue and reactive stromal cells. Epithelial changes included apoptosis and mucin depletion. Glandular cystic dilatation and epithelial flattening were also common as well as focal vascular hyperplasia, suggestive of reparative changes in one case. Capillary ectasia and prominent plump endothelial cells were also present.

Conclusion.—The spectrum of the alterations is consistent with radiotherapy-induced changes. Given the recent approval by the US Food and Drug Administration for the use of SIRT, it is anticipated that more patients will be treated with this modality. Pathologists should become aware of the adverse effects associated with its use.

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Clinical Presentations

Patient 1

The first patient, a 53-year-old man, initially presented with abdominal cramping and a 15-kg weight loss during a 6-month period. He eventually had surgery for a 3-cm stenosing sigmoid colon adenocarcinoma. He also was diagnosed with multiple synchronous liver metastases, the largest measuring 13 cm and involving both the left and right lobes. Postoperatively, the tumor was staged pT4b N1 M1 and the patient was given systemic chemotherapy with FOLFIRI (a combination of 5-fluorouracil, leucovorin, and irinotecan) and bevacizumab (Avastin; Genentech, South San Francisco, Calif), later replaced by FOLFOX (a combination of 5-fluorouracil, leucovorin, and oxaliplatin) and Avastin. Twenty-six months after surgery, 1 course of SIRT was initiated to palliate persistent metastatic liver deposits. In short, 33.2 μCi (1.23 MBq) of 90Y-labeled SIR-Spheres (Sirtex Medical, Lane Cove, New South Wales, Australia) was administered via a hepatic artery catheter after the left gastric artery was embolized with a coil to prevent extrahepatic deposition of spheres. After the procedure, abdominal single photon emission computed tomography depicted the heterogeneous distribution of the tracer throughout the liver, with greatest intensity in the right lobe inferiorly and no definite demonstration of tracer activity outside the liver. Subsequently, the patient reported belching, heartburn, and nausea, which were initially considered to be related to the ongoing systemic chemotherapy. Eventually, after the symptoms waxed and waned for 5 months, an upper endoscopy was performed. It demonstrated a diffusely erythematous and friable duodenal bulb (Figure 1, A) and gastric antral mucosa (Figure 1, B).

Patient 2

Our second patient is a 34-year-old woman given a diagnosis of hepatic metastasis of a colonic adenocarcinoma, for which she received combination chemotherapy with FOLFOX and Avastin, with excellent clinical response. Eight months later, she presented with residual liver disease and was treated with 1 course of SIRT, with the methodology previously described. Soon after the procedure, persistent emesis and nausea developed, with a markedly decreased energy (caloric) intake associated with a 16-lb weight loss. A few weeks later, an upper endoscopy dem-
Our third patient, a 56-year-old woman, had received a diagnosis of right-sided colonic adenocarcinoma. At the time of presentation, the patient had multiple synchronous liver metastases and received combination chemotherapy with FOLFIRI and Avastin followed by FOLFIRI and cetuximab (Erbitux; ImClone Systems Incorporated, New York, NY). Six months later, a restaging positron emission tomography–computed tomography scan showed a persistent lesion in the right lobe of the liver, but no evidence of extrahepatic disease. Eight weeks later, pre-SIRT prophylactic coil embolization of the gastroduodenal and right gastric artery was performed, and selective infusion of SIRT in the common hepatic artery was performed for whole liver brachyembolization. The patient was given concurrently a proton pump inhibitor and ferrous sulfate. Ten days after treatment, nausea, diarrhea, and upper abdominal pain developed. An upper gastrointestinal endoscopy, performed soon after, demonstrated an erythematous gastric mucosa with superficial ulceration of the antrum.

HISTOPATHOLOGIC FINDINGS

The duodenal biopsy specimens of the first patient demonstrated the presence of mucosal ulceration with fibrinopurulent exudate admixed with granulation tissue and reactive stromal cells (Figure 3). The gastric mucosa was less damaged and revealed a moderate amount of chronic inflammation of the lamina propria.

The gastric biopsy specimens of the second and third patients demonstrated multiple ulcerations, as well as a spectrum of epithelial and stromal changes. The biopsies of patient 2 were performed within weeks of SIRT, and the specimens obtained showed epithelial apoptosis and mucin depletion in addition to the superficial mucosal erosion. Cystic dilatation of the glands and epithelial flattening were also common. In the stroma, prominent eosinophilia was observed (Figure 4). The gastric biopsy specimens of the third patient were less inflamed, although patchy aggregates of neutrophils were seen. Foveolar hyperplasia was noted, suggestive of architectural reparative changes. Atypical regenerative epithelial changes were obvious, along with capillary ectasia and prominent plump endothelial cells (Figure 5).

In all 3 sets of biopsy specimens, foreign particles measuring about 40 μm in diameter were observed. They were formed of a purple material with a lighter peripheral halo,
yet.

metastases of CRC, with liver deposits developing in near-
ally controlled after discontinuation of capecitabine (fluoro-
pump inhibitor therapy as well. No follow-up is avail-
repeated gastric endoscopy showed persistent erythema,
was readmitted 4 months post-SIRT because of persistent
for the worse as he subsequently developed lung and bone
changes and the presence of the microspheres were sug-
Figure 6. Evidence of microsphere extrusion into the lamina propria with foreign body giant cell reaction (hematoxylin-eosin, original magnification ×600).

reminiscent of psammoma bodies, but without concentric lamellation. Of note, a microsphere was lodged in the lamina propria and elicited a foreign body giant cell reaction (Figures 3 through 6). Tests with immunohistochemical stains for cytomegalovirus and herpes simplex virus were performed on the biopsy specimens of the second patient and were negative. Overall, the spectrum of characteristic changes and the presence of the microspheres were suggestive of radiotherapy-induced changes.

FOLLOW-UP

Patient 1: The gastrointestinal symptoms were eventually controlled after discontinuation of capecitabine (fluoropyridimine given orally), which might have exacerbated the symptoms. However, the patient’s course took a turn for the worse as he subsequently developed lung and bone metastases and died 40 months postsurgery. An autopsy was not performed.

Patient 2: Treated first as an outpatient with proton pump inhibitor therapy and fluids, the patient eventually was readmitted 4 months post-SIRT because of persistent nausea, abdominal pain, dehydration, and weight loss. A repeated gastric endoscopy showed persistent erythema, friability, and granularity of the entire mucosa and several large ulcers.

Patient 3: The patient was discharged and given proton pump inhibitor therapy as well. No follow-up is available yet.

COMMENT

The liver represents the most common site of distant metastases of CRC, with liver deposits developing in nearly 50% of patients during the course of the disease. Over-all, metastases from CRC claim the lives of about 80,000 patients annually. Although surgical resection of solitary liver metastases can result in long-term survival, only about 25% of patients are candidates for surgery. For those with unresectable liver metastases, systemic chemotherapy and other modalities, such as external beam radiation therapy, stereotactic body radiation therapy, and radiofrequency ablation of individual hepatic lesions, have been applied. However, these methods are plagued with various limitations, including either poor tolerance of normal hepatic parenchyma (ie, radiation hepatitis) or lack of efficacy because the metastases are too numerous.

Recently, a microbrachytherapy strategy, SIRT, using resin-based microspheres impregnated with $^{90}$Y and administered through a catheter inserted in the hepatic artery, has been introduced for the treatment of CRC hepatic metastases. It is also under investigation for the treatment of hepatocellular carcinoma and metastatic neuroendocrine tumors. Since the overwhelming majority of the tumor blood supply is derived from the hepatic artery, while the normal parenchyma is largely supplied by the portal vein, this allows selective delivery of effective doses of radiation to liver lesions without compromising normal liver tissue. Yttrium 90, impregnated in microspheres approximately 30 to 40 μm in diameter, is a pure $\beta$-emitter with average and maximum penetration of 2.5 and 11 mm, respectively. The physical half-life of $^{90}$Y is about 2½ days and continual radiation emission lasts for approximately 14 days, destroying the tumor once the microspheres are trapped in the vascular bed. The therapeutic efficacy of this novel modality has been demonstrated in several clinical trials that enrolled patients with progressive metastatic hepatic CRC after failure of standard systemic chemotherapy regimens. However, the risk of radiation-induced toxicity may hamper the use of this novel modality. Before initiating treatment, the risk of radiation pneumonitis should be evaluated by measuring the percentage of microspheres that pass through the hepatic circulation and eventually lodge in the pulmonary parenchyma. The histologic appearance of the cases reported herein, ranging from apoptosis, epithelial flattening, and glandular cystic dilatation to nuclear atypia, capillary ectasia, and prominent endothelial cells, were consistent with acute and chronic radiation-induced gastroduodenitis. Furthermore, the extrusion of spheres into the lamina propria would seem to exclude, at least partially, that an ischemic mechanism is at play, and again, favor radiation-induced damage. In addition, the chronology of the appearance of symptoms, as well as the physical half-life of $^{90}$Y and maximum penetration of the radiation, is consistent with our findings. Whether the apparent clustering in the distribution of microspheres—as seen in our cases—plays a role in this process is unclear. It is obvious, as in our cases, that although embolization of the gastroduodenal artery and/or gastric arteries is common practice to avoid the migration of spheres, the retrograde migration of microspheres into the gastric or duodenal circulation can be observed. Examples of gastric and/or duodenal ulceration but also esophagitis, pancreatitis, hepatitis with reported mortality, and cholecystitis have been observed. These adverse effect have been reported with an incidence ranging from 0% to 13%, generally within the first 2 months after the procedure. Furthermore, in a recent series of 21 patients, a much higher rate of gastrointestinal toxicity was reported, with gastric ulceration in 29% of patients. Notably, erratic migration of the microspheres is not immediately recognized, despite sensitive radionuclide imaging (single photon emission computed tomography in our case) to look for extrahepatic deployment. Given the nonspecific gastrointestinal manifestations, biopsies are likely to be more efficient than endoscopy in diagnosis SIRT-associated gastroduodenal complication because the microspheres can be identified under the microscope. Pathologists should be aware of this type of therapy and...
complication, especially because their diagnosis can guide clinicians to the best supportive care, including proton pump inhibitors, for these patients. The microspheres are so characteristic in shape that potential differential diagnoses such as calcified egg shells of *Schistosoma japonicum*, pulse granulomas, and sodium polystyrene sulfonate crystals (Kayexalate; sanofi-aventis US, LLC, Bridgewater, NJ) embedded in gastrointestinal ulcer are unlikely to be mistaken for them. Importantly, regenerative stromal and epithelial cells may exhibit marked cellular atypia due to radiation effect, especially in the acute/subacute phase after SIRT. As is common in this type of situation, SIRT toxicity may be misinterpreted as primary malignant tumors of the stomach, duodenum, and other involved organs; however, the detection of characteristic microspheres and the clinical information should help avoid misdiagnosis.

In conclusion, because of the anticipated increase in use of SIRT for the treatment of hepatic malignancies, adverse effects such as gastric and/or duodenal ulceration secondary to misplacement of SIR microspheres may be seen more commonly. Awareness of this complication and the recognition of characteristic microspheres is cardinal for guiding appropriate management.

References