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 foveal 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. (Arch Pathol Lab Med. 2008;132:1734–1738)
Figure 1. Endoscopic image showing diffuse erythematous, friable mucosa with contact bleeding in the duodenal bulb (A) and stomach (B).

Figure 2. Endoscopic appearance of the ulcerated gastric mucosa in the second patient (arrowhead).

Figure 3. Ulcerated duodenal biopsy specimen showing fibrinopurulent exudate admixed with atypical reactive stromal cells and scattered purple yttrium 90 selective internal radiation microspheres (inset) (hematoxylin-eosin, original magnifications ×200 and ×400 [inset]).

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 to-

mography 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,
metastases of CRC, with liver deposits developing in near-
ally controlled after discontinuation of capecitabine (fluor-
ropyridimine given orally), which might have exacerbated
friability, and granularity of the entire mucosa and several
repeated gastric endoscopy showed persistent erythema,
nausea, abdominal pain, dehydration, and weight l oss. A
pump inhibitor therapy and fluids, the patient eventually
was not performed.
metastases and died 40 months postsurgery. An autopsy
for the worse as he subsequently developed lung and bone
changes and the presence of the microspheres were sug-
peristaltic hepatic CRC after failure of standard systemic che-
ment of hepatocellular carcinoma and metastatic neuro-
endocrine 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 ap-
proximately 30 to 40 μm in diameter, is a pure β-emitter
with average and maximum penetration of 2.5 and 11 mm,
respectively. The physical half-life of 90Y is about 2½ days
day 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 clin-
cal trials that enrolled patients with progressive meta-
static hepatic CRC after failure of standard systemic che-
motherapy regimens. However, the risk of radiation-in-
duced toxicity may hamper the use of this novel modality.
Before initiating treatment, the risk of radiation pneumo-
nitis 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 gland-
ular 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 pro-
pria would seem to exclude, at least partially, that an is-
chemic mechanism is at play, and again, favor radiation-
induced damage. In addition, the chronology of the ap-
pearance of symptoms, as well as the physical half-life of
90Y and maximum penetration of the radiation, is co nsis-
tent 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, pancre-
atitis, hepatitis with reported mortality, and cholecystitis
have been observed. These adverse effects have been
reported with an incidence ranging from 0% to 13%, gen-
erally within the first 2 months after the proce-
dure. Furthermore, in a recent series of 21 pa-
gients, a much higher rate of gastrointestinal toxicity was
reported, with gastric ulceration in 29% of patients. No-
tably, erratic migration of the microspheres is not imme-
diately recognized, despite sensitive radionuclide imaging
(single photon emission computed tomography in our
case) to look for extrahepatic deployment. Given the non-
specific gastrointestinal manifestations, biopsies are likely
to be more efficient than endoscopy in diagnosing SIRT-
associated gastroduodenal complication because the mi-
crospheres can be identified under the microscope. Pa-
thologists should be aware of this type of therapy and

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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