Differential Diagnosis of Upper Gastrointestinal Bleeding and Cancer

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This article is the third in a series on the Differential Diagnosis of Cancer. See the March/April 1977 issue of Ca-A Cancer Journal for Clinicians for "Anemia and Cancer" and the September/October 1977 issue for "Hypercalcemia and Cancer." Future issues of Ca will include other articles on the differential diagnosis of cancer, including "A Shadow in the Lung."

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Evaluation of the nature and location of upper gastrointestinal bleeding has been greatly facilitated by the development of fiberoptic endoscopy. Recent technical advances allowing for more flexibility and complete tip control have enabled examination of the entire esophagus, stomach, duodenal bulb and postbulbar region, from which virtually all upper gastrointestinal bleeding emanates. An open channel through the endoscope permits the introduction of biopsy forceps, cytology brushes and catheters for pulsatile lavage and aspiration of blood or fluid.

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I' ENDOSCOPIC DIAGNOSIS OF UPPER GASTROINTESTINAL BLEEDING

|                          | All Patients | Patients With Tumor |
|--------------------------|--------------|---------------------|
| Hemorrhagic Gastritis    | 38 (47%)     | 25 (43%)            |
| Exogenous Agents         | 25           | 12                  |
| Stress                   | 13           | 13                  |
| Peptic Ulcer             | 18 (22%)     | 13 (22%)            |
| Gastric                  | 8            | 6                   |
| Duodenal                 | 9            | 6                   |
| Stomal                   | 1            | 1                   |
| Tumor                    | 10 (12%)     | 10 (17%)            |
| Esophagitis              | 9 (11%)      | 6 (10%)             |
| Esophageal Varices       | 6 (7%)       | 4 (7%)              |
| Total                    | 81           | 58                  |

Patients without cancer, an observation made possible with the advent of a vigorous diagnostic approach using endoscopy. The second most frequent cause of bleeding in our reported group was peptic ulcer; only 12 percent of bleeding was attributed directly to cancer.

A prospective follow-up study also using endoscopy to establish the diagnosis confirmed that upper gastrointestinal bleeding originated most often in the gastric mucosa. Two causes of gastric mucosal bleeding, about equal in frequency, were noted: (1) bleeding associated with gastric irritants such as aspirin, Percodan, alcohol, adrenal steroids, indomethacin, phenylbutazone, chemotherapeutic agents and radiation therapy; and (2) bleeding associated with stress ulcers in patients who have undergone recent major surgery or those with sepsis, hypotension, hepatic renal or pulmonary failure, or advanced cancer. Lymphoma, leukemia, lung and breast cancers appear to predispose to the development of stress ulcers most frequently, however, a variety of other tumors may also cause this type of bleeding. Patients with stress ulcers often do not survive the massive bleeding. In contrast, patients with mucosal bleeding secondary to gastric irritants usually stop hemorrhaging when the irritant is discontinued.

Stress ulcers are superficial erosions in the gastric and occasionally esophageal and duodenal mucosa, usually extending to, but not through, the muscularis mucosa. They cannot be identified by X-ray, and endoscopy is necessary for accurate diagnosis. Patients with stress ulcers are extremely ill. In addition to an underlying cancer and organ failure, these patients have been subjected to a variety of diagnostic and therapeutic measures, which sometimes increase the stressful burden. Frequently, they have been treated with cytotoxic agents that alter DNA synthesis and otherwise reduce the host's ability to repair damage. It has been shown experimentally that altered DNA production is an important factor in the pathogenesis of stress erosions.

Human growth
hormone, a stimulant of DNA synthesis and therefore a potential treatment for bleeding from stress ulcers, is now being actively investigated at our institution.\textsuperscript{7,8} The use of this agent is based on our animal studies, which show that bovine growth hormone had a beneficial effect on the healing of restraint ulcers in rats.\textsuperscript{9} The mechanism of action is not yet known. However, it may be related to enhanced cellular repair or hemostasis, since growth hormone can stimulate the formation of new collagen fibrils to which platelets can adhere and begin clot formation.

Gastric erosions, whether from exogenous irritants or from stress ulcers, appear exactly the same on endoscopy—multiple superficial erosions in the gastric mucosa. (Fig. 2.) However, the distribution is different: hemorrhagic gastritis due to gastric irritants tends to be localized primarily to the antrum of the stomach while stress ulcers tend to be localized more to the proximal stomach, especially around the area of the cardio-esophageal junction.

Cancer

Extensive bleeding directly from a tumor in patients with known cancer is less common than gastric mucosal bleeding. In these patients the probability that the bleeding originates from a tumor is about 10 percent. However, if the tumor is located in the stomach, the probability that it is the source of bleeding rises to 50 percent; if the tumor is a primary gastric cancer or a gastric lymphoma, the probability increases to 75 percent.

Carcinomas of the stomach and esophagus frequently bleed in an occult manner. Extensive bleeding is rare. On the other hand, leiomyosarcomas, which frequently ulcerate, and lymphomas involving the gastrointestinal tract may be associated with massive hemorrhage. (Fig. 3.) The stomach is a frequent location of secondary lymphoma with multiple malignant ulcerations\textsuperscript{10,11} and bleeding. A more unusual cause of massive gastrointestinal bleeding in patients with lymphoma is caused by diffuse involvement of the spleen, resulting in adherence to the greater curvature of the stomach and erosion through the wall. Laparotomy has been required in these patients to control intractable bleeding.\textsuperscript{12}

The leukemias may also involve the gastrointestinal tract and cause bleeding. In one series of 148 patients with leukemia, the incidence of gross lesions in the gastrointestinal tract was 25 percent.\textsuperscript{13} Severe gastrointestinal hemorrhage occurred in 27 patients (18 percent) and was the cause of death in eight. Of course, the platelet abnormalities seen in patients with either leukemia or lymphoma, and the thrombocytopenic effects of chemotherapy in these patients, or in those with solid tumors, may predispose to gastrointestinal hemorrhage from any source.

Metastases to the gastrointestinal tract are unusual except in patients with breast carcinoma, melanoma and testicular tumors. However, direct invasion of the stomach and/or duodenum by pancreatic cancer is common, resulting in extensive upper gastrointestinal hemorrhage. In a review from our institution, 204 patients who died of metastatic breast cancer were found to have gastroduodenal mucosal or submucosal metastases. Only two of the group of 68 patients not treated with adrenal steroids had this type of metastatic involvement. Twenty-four of these 26 patients had been using adrenal steroids as treatment for metastatic breast cancer. Since gastroduodenal metastases were six times more frequent in patients receiving adrenal steroids than in patients with breast cancer in the control group, it appears that the use of adrenal steroids predisposes to the development of gastroduodenal metastases. Secondary ulceration from metastatic sites occurred in one-

\begin{quote}
"...leiomyosarcomas, which frequently ulcerate, and lymphomas involving the gastrointestinal tract may be associated with massive hemorrhage."
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Fig. 1 Histologic section through experimentally produced gastric stress ulcer demonstrating its superficial character extending to but not through the muscularis mucosa.

Fig. 2 Endoscopic view of a superficial gastric erosion with surrounding erythema.

half of the patients treated with adrenal steroids and in none of the controls; one-half of the patients with metastatic ulceration died as a result of massive gastrointestinal bleeding.\(^4\) (Fig. 4.)

The presumptive diagnosis of cancer can certainly be suggested by radiologic studies, but a definitive diagnosis depends on histologic and/or cytologic confirmation. Brush cytology is superior to biopsy in both the esophagus and the stomach, however the two techniques are complementary. Tumors that are primarily exophytic or mass-like usually yield a positive tissue diagnosis, whereas tumors that are primarily infiltrative are less often diagnostic.\(^5,6\) Lesions that measure less than three cm. or those localized at the cardia or lesser curvature beyond the angularis of the stomach, or lesions that are recurrent, may be difficult to diagnose; lavage cytology using a dental irrigating machine can be combined with brush cytology and biopsy to increase the diagnostic accuracy.\(^7,8\) (Fig. 5.) In patients with gastric ulcers it is necessary to take six or more biopsy specimens from the rim of the ulcer in order to assess its nature. Biopsies obtained from the necrotic ulcer base are often unsatisfactory. This, of course, does not apply to duodenal ulcers since the risk of cancer in the duodenal bulb is almost absent. Gastric lymphoma can be diagnosed by endoscopic brush and biopsy techniques with a high degree of accuracy.\(^9\) When lymphoma is confirmed by tissue diagnosis, the management of the patient may be drastically altered.

Peptic Ulcer

Benign gastric and duodenal ulcers occur in patients with cancer and may cause massive gastrointestinal bleeding. (Fig. 6.) In our prospective study these conditions were second only to multiple gastric erosions as the cause of bleeding. Although duodenal ulcers are more common in the general population than gastric ulcers, an equal frequency was seen in our series. Peptic ulcers associated with the use of adrenal steroids for the treatment of can-
Cancer occur more often in the stomach and may exhibit less surrounding inflammatory reaction than the usual peptic ulcer. Anastomotic ulcers following subtotal gastrectomy are almost non-existent in patients who have undergone the procedure for carcinoma, as compared to those who have had gastrectomy for peptic ulcer.

Gastrinomas arising from the non-beta cell portion of the islets of Langerhans in the pancreas are associated with hypergastrinemia, hypersecretion of gastric acid and peptic ulcers primarily of the duodenum but also of the stomach, esophagus and jejunum (Zollinger-Ellison syndrome). Repeated episodes of massive gastrointestinal hemorrhage have developed with these tumors and only total gastrectomy may control the bleeding. This may also be necessary in patients with known metastases to the liver because of the severe effects of the disease and the relatively slow rate of growth.

Peptic ulcers can be identified both radiologically and endoscopically, but the cause of bleeding can be documented only by endoscopy. During an acute bleeding episode a clot may lodge in the ulcer crater and be completely missed on X-ray, yet readily found by endoscopy. It should be emphasized that the presence of a deformed duodenal bulb, common in our population, or even an ulcer crater, does not mean that the patient is bleeding from this site. Identification of the source of bleeding, therefore, may alter treatment decisions.

Esophageal and Gastric Varices
Varices, which can also be associated with exsanguinating hemorrhage, are most commonly caused in the general population by cirrhosis with intrahepatic block. In patients with cancer, varices only seldom account for bleeding, although it should be emphasized that these patients may have predisposing factors for cirrhosis, such as high alcohol intake or chronic active hepatitis. It has been previously reported that metastases from cancer rarely occur in a cirrhotic liver. However, in a review from our institution
utilizing matched controls, it was found that there is no difference in the incidence of hepatic metastases in the cirrhotic and non-cirrhotic liver. The presence of cirrhosis, therefore, does not protect the individual from the development of metastatic disease. In addition, cirrhosis, particularly of the macronodular type, occurs as a predisposing condition in about two-thirds of patients with hepatoma.

Another retrospective study at our institution demonstrated that patients

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with metastases to the liver, without underlying benign chronic liver disease, may develop significant portal hypertension with resultant esophageal varices and bleeding. These metastatic liver tumors have a relatively long life expectancy such as is seen with breast cancer.

With the development of varices, the portal or splenic vein may become obstructed by the tumor. Portal vein obstruction is frequently seen in patients with hepatocellular carcinoma and variceal bleeding. Obstruction of the splenic vein by tumor is a rare cause of portal hypertension. However, a tumor involving the body or tail of the pancreas or the large retroperitoneal lymph nodes, such as lymphoma, can produce this type of obstruction causing the blood from the spleen to flow through dilated variceal vasa brevia to anastomose with the branches of the gastroepiploic veins in the fundus of the stomach. Large varices in the stomach and esophagus may thus be produced and may be responsible for massive bleeding as the presenting complaint. Therefore, the combination of upper gastrointestinal bleeding and splenomegaly should suggest the possibility of occlusion of the splenic vein from benign or malignant pancreatic or peripancreatic disease.

Varices are generally better recognized by endoscopy, although radiology may reveal filling defects in the lower esophagus suggestive of varices. The grape-like bluish lesions seen on endoscopy are characteristic. In the acutely bleeding patient, a clot may adhere to the underlying mucosa and at times obscure the varix. Superior mesenteric arteriography in the venous phase will also identify varices and should be used when the bleeding is so massive that it prevents adequate endoscopic evaluation or when the extent of bleeding requires the intra-arterial infusion of vasoconstrictors.

**Esophagitis**

Peptic (reflux) esophagitis is an unusual cause of massive hemorrhage, but it not infrequently produces moderate bleeding. (Fig. 7.) The disorder is associated with an incompetent or absent cardioesophageal sphincter. Compromises of the integrity of the sphincter (prolonged use of naso-gastric intubation or surgical removal of the sphincter), increases the risk of peptic esophagitis and bleeding. Alkaline esophagitis from bile reflux following gastrectomy may also lead to bleeding.
Moniliasis (candidiasis) is a frequent complication in patients with cancer, particularly those with lymphoma and leukemia. In an autopsy series at our institution it was demonstrated that 13 percent of all patients with leukemia and lymphoma had histologically-proven Monilias infection of the gastrointestinal tract.\(^\text{24}\) In patients with solid tumors, the incidence was 1.5 percent. Monilias infection involved all segments of the gastrointestinal tract but was most common in the esophagus, and was generally associated with esophagitis with or without membrane formation. Gastrointestinal bleeding was the most frequent symptom although dysphagia, substernal pain and pain on swallowing were not uncommon. Bleeding is occasionally massive but is more often low-grade. Patients with lymphomas and leukemias receiving steroids, radiation or chemotherapy should be considered potential candidates for this infection. While monilial esophagitis is usually considered in patients with oropharyngeal thrush, it is not widely appreciated that it may also exist in the absence of oropharyngeal lesions.

Esophageal moniliasis may present radiologically as multiple filling defects or small ulcerations or it may simulate peptic esophagitis with narrowing at the distal end of the esophagus. (Fig. 8.) Hypomotility of the esophagus is a frequent finding on fluoroscopy or cineradiography. Endoscopy is critical for the diagnosis of esophageal moniliasis when the X-rays are negative or equivocal. With newer fiberoptic instruments, it has been possible to brush the involved area and obtain a smear for the cytologic diagnosis of pseudomycelia. In our experience, esophageal moniliasis is indistinguishable from esophagitis due to other etiologies, such as peptic esophagitis. The mucosa is hyperemic, frequently hemorrhagic and friable. Less commonly, discrete ulcers are seen. When a shaggy pseudomembrane is present that cannot be wiped free from the mucosa, the diagnosis is more certain. (Fig. 9.)

Esophagitis from herpes virus infection has been reported in immunosuppressed patients with cancer. It develops in patients who have had chest radiation, nasogastric intubation, corticosteroids or chemotherapeutic agents. It is characterized by dysphagia, retrosternal pain and hemorrhagic erosions of the esophagus. The esophagitis frequently resolves as the patient responds to antitumor therapy. At esophagoscopy, the mucosa may reveal numerous small erosions with surrounding erythema. These often have a white base or are covered with a white exudate, similar in appearance to esophagitis from Monilia, peptic disease or radiation. Diagnosis is made by biopsy, identifying the characteristic inclusion bodies.\(^\text{25}\)

**MISCELLANEOUS CAUSES OF UPPER GI BLEEDING**

Patients with cancer may, of course, develop upper gastrointestinal bleeding from the same causes as patients without cancer. For instance, a longitudinal tear of the cardio-esophageal junction (Mallory-Weiss disease) with massive hemorrhage may occur following retching and vomiting. Diagnosis can usually be made accurately by endoscopy.

The columnar-lined esophagus (Barrett’s esophagus) may result in the development of a localized area of esophagitis with an ulcer in the mid-esophagus having all the clinical characteristics of a peptic ulcer. This may bleed suddenly and massively without previous symptoms, although dysphagia is common. It is diagnosed by endoscopy and biopsy, which show columnar-lined epithelium of the gastric type. This condition is usually accompanied by a hiatus hernia. There appears to be an increased risk for the development of a later adenocarcinoma in patients with Barrett’s esophagus.

Benign intramural tumors such as leiomyomas, lipomas and fibromas may remain silent until the sudden onset of hemorrhage. Ischemic necrosis due to involvement of the vascular supply by tumor may lead to the formation of a very deep ulcer at the center of the intraluminal projection. Adenomas of the upper gastrointestinal tract, as well as the hematomas of the Peutz-Jeghers’s type are associated with oozing of blood but rarely
with massive hemorrhage.

Multiple congenital hemorrhagic telangiectasia (Rendu-Osler-Weber disease) frequently involves the stomach and less commonly the lower esophagus and duodenum and resembles the cutaneous form when examined endoscopically. Extensive chronic hemorrhage is characteristic of the disorder and these patients require repeated multiple transfusions.

Rupture of an aortic aneurysm into the third portion of the duodenum may occur when the aneurysm enlarges to a diameter of five cm. or more. Usually by the time the aneurysm reaches this size, calcium has been deposited in the wall of the aorta. The condition usually occurs in older patients with arteriosclerosis, which may also be associated with ischemia to the bowel wall, subsequent ulceration and bleeding. However, it is more likely to occur in the small intestine or colon rather than in the upper gastrointestinal tract.

**BLEEDING SECONDARY TO THE TREATMENT OF CANCER**

As discussed, salicylates, steroids and cytotoxic agents tend to predispose to gastric mucosal bleeding. Specific cytotoxic agents may have a direct effect on the gastrointestinal mucosa. Antifolic compounds such as methotrexate, and the fluorinated pyrimidines, such as 5-fluorouracil, may cause many ulcerations throughout the gastrointestinal tract and in rare instances have been associated with gastrointestinal hemorrhage. Decreased mitotic counts in epithelial cells of small bowel mucosa have been noted with the use of methotrexate. Interference with epithelial cell proliferation in the colon with marked cellular changes has followed the use of fluorinated pyrimidines. Acute gastritis with bleeding has occurred with the infusion of high concentrations of antimetabolites into regional arteries, such as the gastroduodenal artery. 

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Fig. 6 Endoscopic view of a benign gastric ulcer with surrounding erythema and a smooth non-nodular margin.

Fig. 7 Endoscopic view of reflux esophagitis just above the cardioesophageal junction demonstrating marked inflammation and some exudate.
Because of its radiosensitivity, abdominal radiation of over 5000 rads may cause considerable damage to the gastrointestinal tract. Although the small intestine and colon appear to be more sensitive than the stomach, indolent gastric ulcerations have been produced resulting in considerable bleeding. Pathology examination of the gastrointestinal tract following intensive radiation therapy initially reveals a granular, friable mucosa with superficial ulcerations, submucosal edema and hyperemia, which usually reach a maximum by the fourth week after initiation of radiation therapy. Because of the relatively rapid rate of epithelial cell regeneration, superficial ulceration usually heals within a few weeks after cessation of radiotherapy. Following heavy radiation, the mucosal injury is more extensive and ulceration may extend into the submucosa. Endarteritis, with reduction of luminal vessels from hyaline thickening of intima and media, and subsequent thrombosis is frequently seen and may result in ischemic changes and further ulceration.

CONCLUSION

Since most patients with upper gastrointestinal bleeding and cancer are not hemorrhaging from their tumors, it is clear that an aggressive diagnostic approach is essential to identify the source of bleeding. Early endoscopy should therefore be performed after stabilization of the patient and lavage of the stomach with iced saline. If massive bleeding prevents visualization, diagnostic angiography may be necessary.

Bleeding from varices or from a single gastric or duodenal ulcer may be demonstrated in this manner, but gastric mucosal bleeding is more difficult to identify. Endoscopy is the preferred diagnostic method for gastric erosions—the most frequent cause of upper gastrointestinal hemorrhage—since barium X-ray studies cannot visualize these superficial lesions. In our series, endoscopy was able to diag-
nose the source of bleeding in 90 percent of patients.

Although it has not been conclusively demonstrated that the mortality rate from upper gastrointestinal hemorrhage is altered by early, more accurate endoscopic diagnosis, it is evident that treatment decisions can be made clearly and rapidly and transfusion requirements lessened. In addition, various centers have been looking into newer methods for the successful treatment of bleeding from gastric mucosal lesions and from peptic ulcers using endoscopic electrocoagulation, lasers, infrared heat probes, tissue adhesives and pharmacologic agents such as prostaglandins, Cimetidine and growth hormone. However, the successful use of any of these modalities depends upon rapid and accurate diagnosis.\(^{27,28}\)

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