Radiation Esophagitis

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• The esophagus is frequently exposed to radiation during treatment of advanced stages of common cancers such as lung, breast, and esophagus. However, symptomatic radiation esophagitis requiring endoscopic and histologic evaluation occurs quite rarely, affecting less than 1% of patients receiving radiation treatment. Symptoms occur acutely, generally within the first 2 months. Patients typically present with nonspecific symptoms such as dysphagia and odynophagia. Endoscopic changes such as erythema and ulceration are also nonspecific and nondiagnostic. Biopsies from affected areas show variable inflammatory changes and radiation-related atypia of endothelial and stromal cells. Such atypia mimics cytomegalovirus cytopathic changes, which are ruled out through absence of immunostaining. Radiation esophagitis is thus clinically unsuspected and endoscopically and histologically quite different from the more common and familiar radiation proctitis for which angioectasia is the predominant finding.

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Although the esophagus is one of the most radiosensitive mediastinal structures,[1] symptomatic radiation esophagitis is a rare complication of radiation treatment for breast and thoracic cancers. Esophageal toxicity became apparent after the advent of megavoltage radiation therapy and was first described in humans in the mid 1950s.[2] In a randomized trial comparing combined radiation therapy with vinblastine and cisplatin to radiation therapy alone for small-cell lung cancer treatment, esophagitis occurred in only 1% of individuals in each treatment group.[3] The incidence of radiation esophagitis in patients with esophageal carcinoma is unclear. Patients who develop symptomatic radiation esophagitis after treatment of esophageal cancer frequently do not undergo esophageal biopsies as the disease is already clinically suspected or symptoms are attributed to the primary cancer. Though lung and breast cancers are common, it is not known why radiation esophagitis develops only in a few of the many patients receiving radiation treatment. Genetics may be a major factor in pathogenesis. Lopez Guerra et al[4] reported that single-nucleotide polymorphisms of transforming growth factor β-1 are associated with development of severe radiation esophagitis in patients with lung cancer. This cytokine likely plays a role in radiation-induced inflammation.[4]

CLINICAL FEATURES

An acute reaction develops within 3 weeks of radiation therapy.[5,6] Patients develop dysphagia and odynophagia, which may lead to weight loss.[2] Such symptoms occur with dosages exceeding 30 Gy.[7] Acute onset of pain is related to early esophageal mucositis.[8,9] Early onset of esophageal dysmotility may be due to radiation-induced damage of the Auerbach plexus.[6,10] Factors associated with increased severity of symptoms include twice-daily radiation treatment, higher nodal stage, increased age, and increased maximal point dose.[5]

Although radiation esophagitis is usually self-limited, complications, such as ulceration, perforation, and even tracheoesophageal fistula formation, can occur.[6,7,11] Such complications are especially likely to occur when adjuvant chemotherapy, such as doxorubicin, daunorubicin, bleomycin, cyclophosphamide, vincristine, or actinomycin, is used.[9,11] In a study of 10 patients receiving doxorubicin and radiation treatment for lung cancer, 4 patients required supportive hospitalization for symptomatic esophagitis.[12] Persistent ulceration may occur if high-dose radiation is used.[6]

Though the onset is typically acute, some studies[10] have shown complications to occur as late as 10 years after radiation treatment. Progressive dysphagia usually appears at least 2 months after radiotherapy.[1] The most common late complication is fibrosis leading to stricture formation.[2,6] Stricture formation occurs at a rate of less than 2% for dosages of less than 50 Gy and can increase up to 15% in dosages exceeding 60 Gy.[6] Strictures usually appear at least 3 months after treatment with a median onset time of 6 months.[6] Earlier age at time of radiation therapy has been associated with later onset of radiation esophagitis symptoms.[10]

ENDOSCOPIC FINDINGS

Endoscopic findings are variable and include erythema, erosion, mucosal sloughing, ulceration, and hemorrhage[13] (Figure 1). Strictures may be observed in patients with chronic symptoms. The incidence of ulceration and stricture formation increases in patients who have combined chemotherapy and radiation treatment.[1,13] A study by Mascarenhas et al[1] showed gastritis associated with

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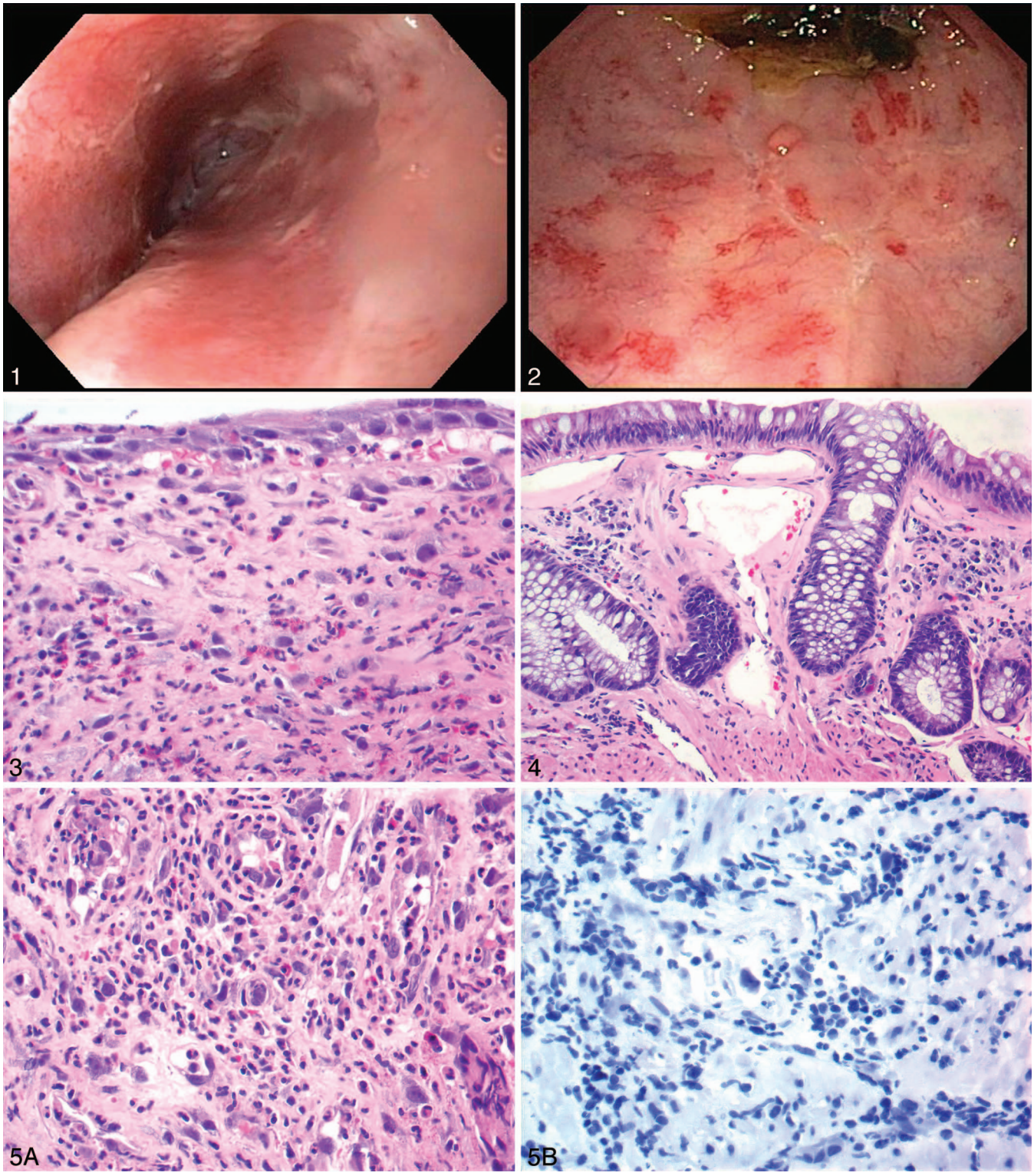

Figure 1. *Endoscopy reveals diffuse erythema with normal intervening mucosa in a patient with acute radiation esophagitis.*

Figure 2. *Endoscopy reveals mucosal edema and telangiectasias in a patient with radiation proctitis.*

Figure 3. *Bizarre stromal cells have hyperchromatic, pleomorphic, enlarged nuclei with a smudged appearance and increased cytoplasm (hematoxylin-eosin, original magnification ×400).*

Figure 4. *Hyalinization, angioectasia, and increased plasma cells are evident in a patient with radiation proctitis (hematoxylin-eosin, original magnification ×200).*

Figure 5. *A, Radiation-related atypia creates mimicry to cytomegalovirus (CMV). B, However, CMV infection is ruled out by negative immunostaining (hematoxylin-eosin, original magnification ×400 [A]; original magnification ×400 [B]).*

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radiation esophagitis as well. Endoscopic findings do not always correlate with clinical findings. In a study by Hirota et al,[13] ulceration and erosion were found in patients who had only mild symptoms or no symptoms at all. Opportunistic infections such as candidiasis can complicate endoscopic findings in these patients. Patients are predisposed to opportunistic infections owing to a chemoradiation-induced immunocompromised state and radiation-induced sloughing of the protective squamous epithelial layer.[9,13]

Ulceration and stricture formation also occur in radiation proctitis.[11] However, the most common endoscopic findings are congested mucosa and telangiectasias that eventually coalesce[14] (Figure 2). Such specific endoscopic findings seen in radiation proctitis are lacking in radiation esophagitis. While radiation changes can be seen anywhere in the esophagitis, radiation proctitis changes are usually found in the distal rectum owing to close proximity to target areas of radiation.[11]

HISTOPATHOLOGIC FINDINGS

Acute effects primarily involve the basal cells of the squamous epithelium.[6] Within the first 48 hours, apoptotic bodies appear in the basal zone[15] and fewer mitotic figures are noted.[1,7] Within a few weeks, changes are noticed in the submucosal tissue as the epithelium regenerates.[16,17] Mucosal glands may show degeneration with a decreased number of acini or glands may be distended with secretions.[9] Submucosal endothelial swelling and capillary dilation produce erythema.[7] Within 1 month, active esophagitis with ulceration and erosion formation occurs.[15] Cytologic atypia affects both the epithelial and stromal cells.[15] These cells have irregular nuclear membranes and may have prominent nucleoli[15] or abnormal smudged nuclei with loss of nuclear detail[17] (Figure 3). However, the nuclear to cytoplasmic ratio of these cells is not increased.[15] Bizarre stromal cell changes can persist indefinitely.[15] Cytoplasmic vacuolization of the epithelial cells is noted,[1,17] and the cytoplasm displays a bubbly, degenerated appearance.[15] Other common findings include parakeratosis and mucosal atrophy.[1]

Cytologic analysis of esophageal brushings reveals cells with cytomegaly and pleomorphic, hyperchromatic nuclei with irregular chromatin patterns.[15,16] Inflammatory changes usually resolve within 3 to 4 weeks of the last fraction[7]; however, chronic changes can occur. Afterwards, the muscularis layer is affected as fibroblasts and inflammatory cells infiltrate the muscle wall.[6] Submucosal thickening, edema,[11,17] and mural fibrosis[15] can also occur, leading to stricture formation. Additional complications include total esophageal wall necrosis leading to perforation and mediastinitis.[16] Cellular homogenization may also be observed.[17] Such homogenization parallels the hyaline change seen in radiation proctitis[11,17] (Figure 4).

When the pathologic profile of radiation esophagitis was described by Seaman and Ackerman[17] in the 1950s, they proposed that most of the radiation injury was due to direct effect on the mucosal epithelium and submucosal structures rather than secondary effects due to vascular damage. This suggestion was supported by minimal vascular alterations seen in histologic sections.[17] Since then, reported vascular changes include obliterative vasculitis,[11] sclerosis, and intimal foam cell arteriopathy.[15]

In contrast to radiation proctitis, distinctive angioecstasia with intimal fibrosis and fibrinoid necrosis of blood vessels is not observed. Slow development of vascular changes seen in radiation proctitis results in a delayed clinical presentation.[11] Therefore, patients with radiation proctitis frequently have a chronic onset of symptoms.

Although not specific, when these radiation-induced changes are noted in an esophageal biopsy, the pathologist should consult the patients' electronic medical record or contact the clinician to verify prior radiation treatment if no history is provided. Chemotherapy is known to potentiate the effects of radiation[12]; however, the microscopic effects of chemotherapy and radiation therapy cannot be reliably distinguished individually. One difference between chemotherapy and radiotherapy would be more systemic cytologic changes with chemotherapy versus those limited to the field of radiation. When history of chemoradiotherapy is absent or unavailable, it is best to interpret these distinctive inflammatory changes in the esophagus as reminiscent of "therapy-related" esophagitis. This is provided an infectious etiology can be ruled out.

ANCILLARY STUDIES

Contrast studies reveal superficial ulcers as shallow barium collections.[10] In severe cases, edema and ulceration produce thickened folds with irregular contours[9,10] and granular-appearing mucosa.[8] In late cases, barium swallow reveals stricture formation.[6,9]

DIFFERENTIAL DIAGNOSIS

Cytomegalovirus (CMV) infection produces similar endoscopic and histologic changes. This disease may be clinically suspected in immunocompromised cancer patients receiving radiation or combined radiation and chemotherapy treatment. Endoscopically, CMV infection produces erythema, erosions, and well-defined ulcers with possible inflammatory exudates.[15] Histologically, CMV-infected endothelial and stromal cells also display enlarged nuclei and cytomegaly[15] (Figure 5, a). Granular cytoplasmic inclusions appear in vacuoles,[15] which may be confused with cytoplasmic vacuolation in cells affected by radiation.[17] However, unlike in radiation esophagitis, squamous cells are not affected by CMV.[15] Other characteristic CMV changes are nuclear inclusions that often are separated from the nuclear membrane by a halo and marginated chromatin.[15] In case of any diagnostic confusion, CMV can be ruled out by negative immunostaining (Figure 5, b).[15]

Radiation induces bizarre changes in the squamous epithelium that can be misinterpreted as squamous cell dysplasia or carcinoma. Like malignant cells, radiation-affected cells have enlarged pleomorphic nuclei, an irregular chromatin pattern, and abnormal mitoses.[16] However, radiation-affected cells display both nucleomegaly and cytomegaly, so the nuclear to cytoplasmic ratio is not increased. Other distinguishing characteristics of squamous dysplasia include disorganized, crowded cells with overlapping nuclei, loss of nuclear polarity, lack of surface maturation, and lack of inflammation.[15] In ambiguous cases, follow-up biopsies after resolution of the esophagitis are helpful.[15]

CURRENT TREATMENT

Radiation esophagitis is treated symptomatically. Pain is managed with topical analgesics such as liquid morphine sulfate. Combined solutions of equal parts viscous xylocaine, aluminum hydroxide–magnesium carbonate, and diphen-

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hydramine are used.[13] Since patients with esophagitis have decreased lower esophageal sphincter pressure,[9] reflux is treated with proton-pump inhibitors and dietary modifications. Sodium bicarbonate's alkalotic properties can treat reflux and prevent *Candida albicans* superinfection.[8] Strictures are managed with endoscopic dilation. Tube feedings or parenteral nutrition may be needed for patients with weight loss or failure to thrive.[8] Short breaks from radiation therapy have also been proposed[6,8] when patients are unable to swallow.[7] For patients with dysfunctional peristalsis, prokinetic drugs such as metoclopramide are used.[6] Treatments for diffuse esophageal spasm include nitrates, calcium-channel blockers, and anticholinergic agents.[6] Since mice experiments revealed elevated prostaglandin levels after whole-body irradiation, prophylactic treatment with nonsteroidal anti-inflammatory agents,[9] particularly indomethacin, has been proposed.[1,8] Such agents reduce prostaglandin-induced acute inflammation.

PROGNOSIS

Radiation esophagitis is usually self-limited. However, in the study of Greco et al,[12] of 10 patients receiving combined chemotherapy and radiation treatment for lung cancer, 4 patients had at least 1 recurrence. Recurrent esophagitis can occur after chemotherapy.[11] Radiation-induced carcinoma can develop in areas with chronic inflammation.[9] Case reports have implicated radiation therapy as a cause of esophageal carcinoma, with a latent interval ranging from 3 to 45 years.[11] In a study of more than 200 000 women who received radiation treatment for breast cancer during a 20-year period, the relative risk of esophageal squamous cell carcinoma increased 5-fold 10 years or more after treatment when compared to 5 years or less after treatment.[18] Such findings highlight the importance of close clinical follow-up for patients who develop radiation esophagitis.

CONCLUSIONS

In conclusion, radiation esophagitis is extremely rare and affects only 1% of patients undergoing mediastinal radiation for chest and thoracic cancers. Symptoms and endoscopic findings are nonspecific, so histologic analysis is needed for a definitive diagnosis. Unlike radiation proctitis, there is no distinctive angioectasia visualized endoscopically or histologically. Although frequently a self-limited disease, serious complications such as stricture, perforation, and fistula formation can occur. Additionally, radiation-induced squamous cell carcinoma of the esophagus can manifest decades after irradiation treatment.

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