Sclerosing Epithelioid Fibrosarcoma of the Cecum

A Radiation-Associated Tumor in a Previously Unreported Site

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Data from the nuclear reactor explosion in Chernobyl and the atomic bomb detonations in Hiroshima and Nagasaki demonstrated an association between ionizing radiation and tumorigenesis. There is a significant association between external beam radiation and radiation-induced sarcoma. Sclerosing epithelioid fibrosarcoma is a rare form of malignant fibrosarcoma that is low grade and indolent with distinct immunohistopathologic characteristics that usually occurs in the soft tissues of the extremities. A 62-year-old man from Kiev who aided in the clean-up at Chernobyl presented with crampy abdominal pain, nausea, and vomiting. His workup revealed a cecal mass, and the final pathology from his laparotomy confirmed sclerosing epithelioid fibrosarcoma with metastasis to the liver. In addition to a review of the literature, we report the first case of sclerosing epithelioid fibrosarcoma arising from the large bowel. Exposure to ionizing radiation from Chernobyl could have played a role in the development of his tumor.

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The world’s worst nuclear power accident occurred April 25 to 26, 1986, at Chernobyl in the Ukraine. The subsequent release of more than a hundred different radioisotopes caused the evacuation of 135,000 people and has had severe environmental and medical effects on Western Russia. Most studies have focused on the incidence of solid tumors in the workers involved in the clean-up effort.

An association between ionizing radiation and cancer was made more than a century ago; the earliest reports of radiation-induced sarcoma were made more than 80 years ago. The introduction of external beam radiation in the treatment of cancer has led to a better understanding of the relationship between radiation and radiation-induced sarcomas. Additional data were collected in Japan after World War II on the subsequent development of solid tumors in atomic bomb survivors.

Sclerosing epithelioid fibrosarcoma (SEF) is a rare variant of fibrosarcoma first described by Meis-Kindblom in 1995. It is a low-grade neoplasm found in deep muscle tissue, bone, peristium, fascia, or neural tissue.

We describe a case of SEF of the cecum in a man who aided in the cleanup after the Chernobyl nuclear accident and provide a review of the literature to date. To our knowledge, this is the first report of SEF involving the gastrointestinal tract.

REPORT OF A CASE

A 62-year-old man with no medical or surgical history presented with several days of crampy abdominal pain, nausea, and vomiting. He denied melena, bright red blood per rectum, or weight loss. He had never undergone colonoscopy. He was a nuclear engineer in Kiev and aided in the cleanup of Chernobyl 19 years prior to presentation. He appeared well upon physical examination. His abdomen was slightly distended, with right lower quadrant tenderness to deep palpation. Laboratory values were within normal limits. His carcinoembryonic antigen (CEA) was 1.3. Chest x-ray was normal, but abdominal computerized tomography (CT) showed a 5 × 7-cm mass in the right lower quadrant. A gentle bowel preparation was administered, colonoscopy confirmed a cecal mass, and biopsy revealed only inflammatory tissue.

At laparotomy, purulent fluid was seen associated with an ileal interloop abscess. A cecal mass with perforation was identified, and a right hemicolectomy was performed. A 1-cm mass in the liver was sent for frozen section, which returned as a “sclerotic nodule, final diagnosis deferred to permanent section.” Pathologic examination revealed a 7.5 × 5.5 × 4.4-cm fungating, friable mass in the cecum that obstructed the appendiceal orifice. A draining sinus extended from the mucosa to the serosal surface. Large areas of necrosis extended to the mucosa and obliterated the muscularis propria (Figure 1). Small tumor nodules were noted in the mesenteric fat. Microscopic examination revealed a sclerotic neoplasm (Figure 2, A through C). The submucosa and muscularis propria were completely replaced by round cells with clear cytoplasm and pleomorphic nuclei. These “epithelioid” cells were arranged in single file, as well as in sheets, entrapped in a dense fibrous stroma. Other areas of tumor were composed of spindle-shaped cells arranged in fascicles. Large areas of necrosis were noted. Immunohistochemical staining was positive for vimentin (V9, Dako, Carpinteria, Calif) and Bcl-2 (124, 1:160, high pH steam AR, Dako). Focal smooth muscle actin (1A4, Dako) and CAM 5.2 (1:140, protein kinase AR, Becton Dickinson, San Jose, Calif) staining of tumor cells was also present. Stains for S100 (1:8, Dako), c-Kit (1:200, low pH steam AR, Dako), CD34 (QBEN10, 1:4, Dako), factor VIII (1:4000, protein kinase AR, Dako), myeloperoxidase (1:10,000, low pH steam AR, Dako), desmin (D33, 1:250, low pH steam AR, Dako), and HMB-45 (1:50; Dako) were negative. The overlying colonic mucosa was unremarkable. These histologic and immunohistochemical pat-
Figure 1. Cut surface of the cecum and pericolic fat showing a sclerotic tumor with necrosis extending from the mucosa to the pericolic fat. The muscularis propria is obliterated. Arrow points to mucosa.

Figure 2. A, Low-power view showing extension of the neoplasm from mucosa to serosa. Increased cellularity near the mucosa can be appreciated (short arrows). Less cellular, more sclerotic areas (long arrow) are present deeper in the bowel wall (hematoxylin-eosin, original magnification ×25). B, This medium-power view reveals a spindle cell component that was found in portions of the lesion (hematoxylin-eosin, original magnification ×100). C, High-power view of sclerosing epithelioid fibrosarcoma. Cords of infiltrating epithelioid cells in a dense fibrous stroma were noted in other regions of the tumor (hematoxylin-eosin, original magnification ×200).

The patient's postoperative course was uneventful. Thyroid ultrasound was unremarkable, and he is undergoing evaluation for an elevated prostate-specific antigen.

COMMENT

Most data on the medical effects of radioactive fallout from Chernobyl were collected from the 120,000 citizens of Belarus who served as liquidators. There has been a national cancer registry in Belarus since 1973. All malignant tumors are registered. They were mobilized to decontaminate the nuclear power plant and a 30-km zone around the facility. The isotope responsible for exposure early on was $^{131}$iodine (50–300 Ci/km$^2$), but more than 43,500 square miles were contaminated by other long-acting isotopes, such as cesium, strontium, and transurane.

On average, liquidators were exposed to 0.1 Gy of radiation.$^{5,6}$ By comparison, 80% of Hiroshima and Nagasaki survivors were exposed to <0.1 Gy.$^3$ Patients undergoing external beam radiation who develop radiation-induced sarcomas receive, on average, 10 to 50 Gy.$^2$

There is compelling evidence from the nuclear disasters at Chernobyl, Hiroshima, and Nagasaki that residents exposed to radioactive fallout are susceptible to gastrointestinal malignancies. Approximately 25% of cancers diagnosed in Chernobyl liquidators were of the digestive system, whereas 56% of cancers from Hiroshima and Nagasaki residents were of the digestive system.$^{3,6}$ The excess relative risk per 1 Gy for digestive malignancies is fairly high (relative risk, 1.21–2.41).$^{5,6}$ In contrast, the excess relative risk per 1 Sievert (Sv) for digestive system malignancies after Hiroshima and Nagasaki was 0.38 (1 Gy = 0.7 Sv).$^3$

Before the advent of nuclear power, other forms of ionizing radiation were associated with malignancy. The first cases were skin cancers in radiation workers in the 1900s.$^2$ Soon thereafter, sarcomas were reported in tuberculosis patients treated with radiation and in workers painting radium watch dials.$^2$ Radiation-induced sarcomas include...
osteosarcomas, angiosarcomas, fibrosarcomas, leiomyosarcomas, and spindle cell sarcomas found in bone, muscle, soft tissue, and nerves. The risk of radiation-induced sarcoma is 0.03% to 0.8%.2

In 1995, Meis-Kindblom3 described a neoplasm composed of epithelioid cells arranged in strands, nests, and sheets set in fibrotic and extensively hyalinized stroma. There have been 57 reported cases of SEF, confirming it as a distinct clinicopathologic entity.7 This rare tumor has been reported in bone, muscle tissue, fascia, and/or peristeam of the extremities, trunk, and head and neck.4 We were unable to find reports of this tumor in the gastrointestinal tract. The average age of patients is 45 years, with no sex predilection.4 Most reports describe the tumor as a low-grade, indolent malignancy, with a local recurrence rate of 48%, a metastatic rate of 60%, and a mortality rate of 35%.7 In 2001, Antonescu et al8 described a series of 16 cases, with a recurrence rate of 50%, a metastatic rate of 86%, and a mortality rate of 57%, suggesting that this neoplasm is more aggressive than originally reported. They later reported on bony invasion and necrosis, which had not been previously described.9

According to the literature to date, SEF has set a characteristic pathologic features. On gross examination, SEF averages 9 cm in diameter (range, 3.7–22 cm) and has a lobulated, firm texture with a tan, homogeneous appearance on cut section. Some cases have necrotic areas on gross examination.9 Sclerosing epithelioid fibrosarcoma is defined primarily by histologic criteria. Microscopically, the tumor is characterized by small, round epithelioid cells with sparse cytoplasm arranged in nests and cords, associated with a densely fibrotic, hyalinized stroma. There is minimal nuclear pleomorphism, and mitotic figures are rare. The chromatin pattern is usually fine, with a small nucleolus. The cytoplasm is clear, probably representing an artifact due to shrinkage during processing. The cellularity varies throughout the tumor, with some cases having patchy necrosis.

Immunohistologically, tumors stain consistently and strongly for vimentin with varying degrees of staining for epithelial membrane antigen (EMA), S100 protein, HMB-45, and cytokeratin (CAM 5.2). Nearly all reported cases have been positive for vimentin, with the exception of the Meis-Kindblom study, in which 1 of 14 cases was negative for vimentin.4,8–14 Cytoplasmic staining of CD99 has been noted.4,10,11,13 Focal EMA staining is noted in nearly half of reported cases (15/34), with rare noted positivity for CAM 5.2, AE1/AE3, S100, and neuron-specific enolase. All previously reported cases are negative for leukocyte common antigen, α-smooth muscle actin (2 cases with equivocal staining),4,8,15 desmin, HMB-45, and CD68.4,8–15 In our case, focal smooth muscle actin positivity was noted within tumor cells, an exception to the previously published literature.

Ultrastructurally, the tumor consists of spindle cells surrounded by tight bundles of collagen fibers. There is abundant, well-developed rough endoplasmic reticulum, which is distended with granular material. Cells are not surrounded by a basal membrane.4,7,8,14 Some reports have identified SEF with ultrastructural nerve sheath11 or myofibroblastic differentiation.4 These disparate ultrastructural findings call into question whether SEF represents a single entity or a heterogenous group of neoplasms with similar histologic features.

The histologic differential diagnosis of SEF includes a wide variety of benign and malignant tumors with significant sclerotic or epithelioid components. Immunohistolochemochemical analysis is an important adjunct to the diagnosis in cases of SEF, largely by revealing pertinent negatives in the immunohistochemical profile that allows the exclusion of epithelial tumors and other mesenchymal lesions. Differentiating between carcinomas and SEF can be exceptionally difficult, as up to half of reported SEFs have EMA or CAM 5.2 immunostaining.9,9 The single strands of epithelioid cells can mimic lobular or signet ring carcinomas in particular. Electron microscopy can easily differentiate these entities, and it should be used for a definitive diagnosis in difficult situations.

Benign fibrous entities to be considered include fibromatosis, fibrous histiocytoma, myositis ossificans, and nodular fascitis. Other variants of fibrosarcoma, such as myxofibrosarcoma, can be differentiated from SEF by the presence of myxoid zones, a whirling growth pattern, and curvilinear blood vessels in the latter tumor. Low-grade fibromyxoid sarcoma/hyalinizing spindle cell tumor contains poorly formed collagen rosettes, consisting of a hyalinized collagenous core cuffed by epithelioid fibroblasts, a feature not seen in SEF. Interestingly, areas suggestive of typical adult fibrosarcoma, with a herringbone pattern and prominent atypia, can be noted in SEF. Additionally, poorly differentiated areas in SEF can feature a hemangiopericytoma-like pattern, which can be confused with synovial sarcoma. Cytogenetic identification of t(X;18), found in synovial sarcoma, can differentiate these two entities. Gastrointestinal stromal tumors can be epithelioid but are rarely sclerotic. c-Kit immunohistochemical staining would differentiate the 2 lesions. Likewise, smooth muscle neoplasms, such as hyalinized leiomyoma or leiomyosarcoma, could superficially resemble SEF but would be characterized by diffuse smooth muscle actin and desmin positivity. Clear cell sarcoma may be difficult to differentiate due to positive S100 immunostaining in both entities; however, SEF is negative for HMB-45. Sclerosing lymphoma can be ruled out by negative leukocyte common antigen (CD45) immunostaining. In several of these entities, electron microscopy can be very helpful in differentiating these lesions, as SEF reveals purely fibroblastic origin as a rule, with only a single reported case having myofibroblastic differentiation.4

The treatment for this tumor is wide local excision. There is no evidence to support the use of adjuvant chemoradiation.7,12

We believe this to be the first reported case of the rare tumor SEF arising in the large bowel. The patient's exposure to ionizing radiation in the remote past likely played a role in tumorigenesis.

References


CAP ’08 ABSTRACT PROGRAM

Abstract and case study submissions for the upcoming CAP ’08 meeting will be accepted beginning on February 1, 2008 through March 28, 2008. Accepted submissions will be published in the September 2008 issue of the ARCHIVES.