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Clinical manifestations and radiological features may contribute to the early diagnosis of radiation-induced sarcoma after breast cancer

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AIM: To describe the clinical manifestations and radiological features contributing to the early diagnosis of radiation-induced sarcoma (RIS) after radiotherapy for breast cancer.

MATERIALS AND METHODS: This retrospective analysis included four typical cases of RIS diagnosed at Affiliated Hospital of Academy of Military Medical Sciences between 1980 and 2013. Patient and imaging characteristics, treatment modalities, and outcomes were extracted from patients' medical records. Two pathologists reviewed all histological slides.

RESULTS: All four cases were misdiagnosed and treated for several months as cases of breast cancer relapse. CT using the bone-window setting and three-dimensional reconstructions clearly displayed bone tumours of RIS in three cases. Skin alterations were observed in all cases. At the time of RIS diagnosis, three patients were free of breast cancer. In one patient with bilateral breast cancer and lung metastasis, chemotherapy resulted in complete remission of the metastasis, but RIS progression. No RIS in this series responded to chemotherapy or endocrine therapy.

CONCLUSIONS: Abnormalities appearing in the radiation field long after RT should alert clinicians to the potential development of RIS. Careful physical examination and follow-up imaging studies are necessary. The presence of skin alterations, bone tumours at CT or radiography, and poor response to anti-cancer drugs may contribute to the early detection of RIS. Biopsy should be performed immediately when RIS is suspected.

Introduction

Multiple clinical trials have demonstrated that adjuvant radiotherapy (RT) plays an important role in the treatment of early-stage breast cancer in women, by decreasing the risk of local disease recurrence and increasing the rate of breast preservation.[1–3] However, a known complication of RT is the development of sarcoma within or at the edge of the radiation field, after a variable, but usually long, latency period.[4–6] Radiation-induced sarcoma (RIS), first reported in the early 1920s,[7] is a rare iatrogenic malignancy associated with poor outcomes. In 1948, Cahan et al.[8] defined the following criteria for the diagnosis of RIS: (1) history of RT; (2) asymptomatic latency period of several years (conventionally, >4 years); (3) occurrence of sarcoma within a previously irradiated field; and (4) histological confirmation of the sarcomatous nature of the post-irradiated lesion. Since that time, several studies have reported the incidence of RIS after breast cancer treatment, but most reported series have comprised limited numbers of patients.[5,9–21]

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The Cahan criteria have been modified by several groups, most of whom have recommended revision of the required interval between radiation exposure and sarcoma formation. Arlen et al.[22] reduced the minimum latency period from 5 to 3 years, and Gladdy et al.[23] recently suggested that a much shorter latency period of 6 months was sufficient to confirm the diagnosis of RIS. However, because of the very low incidence of RIS, this disease is often confused with local breast cancer recurrence in clinical practice. Given the major differences in the treatment and management of RIS and breast cancer relapse,[24] the early and accurate diagnosis of RIS is critical.

In the present study, the clinicopathological and imaging characteristics of four typical cases of RIS diagnosed according to the Cahan criteria[8] at Affiliated Hospital of Academy of Military Medical Sciences between 1980 and 2013 were retrospectively analysed. The clinical manifestations and radiological features contributing to the early diagnosis of this rare disease are described.

Materials and methods

Using the hospital's database, the records of 7600 patients with breast cancer who were treated between 1980 and 2013 were retrospectively reviewed. Ethical approval was obtained from the Ethics Committee and Review Board of the Affiliated Hospital of the Academy of Military Medical Sciences. Four patients diagnosed with RIS after RT for breast cancer were identified, according to the criteria established by Cahan et al.[8] The latency period was defined as the interval between the first radiation treatment and the histological diagnosis of RIS. Two of these cases have been reported previously in a Chinese-language article.[25]

Clinical data were retrieved from the patients' clinical charts, histopathology records, and electronic medical records. The following information was collected: patient age and sex, date of primary invasive breast cancer diagnosis, initial tumour stage, adjuvant therapy, radiation history, latency period, site of sarcoma development, sarcoma histopathology, and duration of follow-up. After reviewing the records, the clinical features, treatment, and outcomes of primary tumours and sarcomas were noted. The imaging features of these patients, including CT, radiography, and photographs, were also retrospectively reviewed.

Two experienced pathologists reviewed the patients' histological slides and pathology reports to collect data related to RIS. Paraffin wax-embedded tissues were stained with haematoxylin and eosin (H&E). Additional immunohistochemical studies were performed to reconfirm the diagnoses and histopathological classifications.

Results

Patient characteristics at the time of breast cancer diagnosis

Table 1 shows the characteristics of the primary breast cancers and their treatments in four women who developed RIS. The median age at the time of breast cancer diagnosis was 37 years (range 29–51 years). All patients underwent modified radical mastectomy and postoperative RT. The median dose to the treatment volume where sarcoma developed was 50 Gy (range 40–60 Gy). The RT modalities were cobalt-60 (patients 2 and 4) and radiography (patients 1 and 3). Three patients (patients 1, 3, and 4) received adjuvant chemotherapy, two (patients 2 and 4) were given adjuvant tamoxifen, and two patients (patients 3 and 4) also underwent electron irradiation.

Diagnosis and characteristics of RIS

The clinical, imaging, and histological characteristics of RIS are shown in Table 2. The median age at the time of RIS diagnosis was 41 years (range 47–58 years). The median latency period was 12 years (range 7–13 years). Three patients (patients 1, 2, and 4) were free of breast cancer at the time of RIS diagnosis. One patient (patient 3) had lung metastasis of bilateral breast cancer.

Intervals from the clinical manifestation of sarcoma to its diagnosis ranged from 4–37 months. All four cases were misdiagnosed and treated for several months as cases of breast cancer relapse. Three cases were misdiagnosed at other institutions, and one case was misdiagnosed at Affiliated Hospital of Academy of Military Medical Sciences.

In these patients, RIS most commonly manifested as a soft-tissue mass within the prior RT field (Table 2). The chest wall and supraclavicular area were involved in two cases each. Skin alterations, including red–purple discolouration, were observed in all four patients. Elevated skin (patient 1), bruising (patient 4), increased skin temperature (patients 3 and 4), and skin thinning (patient 3) were also observed.

Imaging data were not available for patient 1 due to the length of time elapsed since the examination. Three patients [patients 2 (Fig 1a), 3 (Fig 2c), and 4 (Fig 3c–d)] underwent CT examination, and two patients [patients 2 (Fig 1b) and 3 (Fig 2d)] also underwent radiography examination. Patient 4 underwent positron-emission tomography (PET)-CT at another institution. CT images obtained using the bone-window setting and three-dimensional reconstructions clearly displayed the structures and morphologies of bone tumours in all three patients (Figs 1a, 2c, 3c–d).

Histological analysis led to diagnoses of malignant fibrous histiocytoma (patient 1), chondrosarcoma (patient 2), pleomorphic soft-tissue sarcoma (patient 3), and osteosarcoma (patient 4). Histological micrographs from patient 3 showed the proliferation of atypical polygonal cells and presence of multinuclear giant cells with hyaline degeneration (Fig 2b). Micrographs from patient 4 showed the proliferation of short spindle-shaped cells with surrounding cartilage matrix (Fig 3b). Additional immunohistochemical studies for calretinin, cytokeratin (CK), vimentin, Ki-67 (index<5%), S-100, B-cell lymphoma 2 regulator protein (Bcl-2), CD34, WT-1 were performed to reconfirm the diagnoses and histopathological classifications (patient 4)