Contralateral Humerus Avascular Necrosis Diagnosed Immediately After Radiotherapy in a Patient with Breast Cancer

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ABSTRACT

Radiotherapy (RT) is an important component of treatment for malignant tumors, and avascular necrosis (AVN), which is often associated with high morbidity and disability, frequently accompanies this type of therapy. It generally develops in the same extremity with the treated region and may continue long after the treatment is completed. Early identification of AVN has the potential to reduce morbidity and improve the patient's quality of life.

Herein, we present a case of contralateral humerus avascular necrosis diagnosed immediately after the first round of RT in a patient with breast cancer.

Keywords: Breast carcinoma, humerus avascular necrosis, radiotherapy, shoulder pain

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INTRODUCTION

Nowadays, radiotherapy (RT) is an integral part of the therapeutic program for cancer patients. One of the most severe, dose-dependent, and challenging long-term complications related to RT is osteonecrosis or avascular necrosis (AVN) (1, 2). It generally presents after radiation exposure in the same extremity as the irradiated area, and the humeral head is the second most common affected region (3).

Herein, we present a case of contralateral AVN of the humeral head that was diagnosed immediately after RT in a patient with breast cancer.

CASE REPORT

A 55-year old female was admitted to our clinic with pain and swelling of the right shoulder that had lasted for two weeks. The patient had no history of direct trauma. However, six months earlier, she had been diagnosed with mixed breast cancer (infiltrative intraductal carcinoma and invasive micropapillary carcinoma; modified Bloom-Richardson grade 3; T2N3MX) on the left side. The estrogen receptor (ER) and progesterone receptor (PR) markers were negative, but the fluorescence in situ hybridization (FISH) and HER-2/neu (C-ERB-B2) markers were positive. Her carcinoembryonic antigen (CEA) levels were 8.2 (0-4 ng/mL), and the cancer antigen (CA)15-3 results were within normal limits. Furthermore, her tumor mass had metastisized into the apex of the left lung. The patient then underwent a modified radical mastectomy and axillary dissection and was treated with postoperative chemotherapy. This included four rounds of 1000 mg cyclophosphamide and 100 mg doxorubicine and four rounds of 130 mg docetaxel and trastuzumab followed by 17 rounds of trastuzumab (450 mg, IV infusion). In addition, her conformal, CT-based RT had been

curative in nature. It included the left chest wall and axillary regions as well as the perypheral lymph nodes (200 cGy/25 fraction; a total of 50 Gy).

Eleven days after the her first round of RT and the fifth round of trastuzumab, the patient had begun to feel pain in her right shoulder that was more intense at night. Furthermore, the intensive pain increased with shoulder movement. Her physical examination at our facility revealed that her active and passive range of motion in all of the planes of her right shoulder were limited and painful, and her muscle strength in the upper extremities measured 4/5 on the Lovett scale. There was also swelling that measured 5x6 cm in diameter in the superolateral area of her right arm, and this was painful, tender, and sensitive upon palpation. Based on these findings, conventional radiography and magnetic resonance imaging (MRI) were performed on the patients' right shoulder. The radiography showed the deformation of the humeral head (Figure 1), and the MRI was consistent with AVN and detected bone marrow edema, fusiform fluid collection, effusion in the shoulder complex and bursae, two simple cysts, and a hematoma in the right humeral head (Figure 2). A bone scan revealed no metastases and showed no increase in the uptake at the right shoulder joint. Because of the continuing RT treatment, surgery was not considered. Hence, she was prescribed anti-inflammatory medications. In her follow-up appoinment, the patient's complaints had not resolved. Eleven months after the AVN diagnosis in her right shoulder, an MRI found progression of the AVN in the humeral head along with deformation, resorption, synovitis, and metastatic lymph nodes. Subsequently, when her chemotherapy and RT were completed, she underwent total shoulder arthroplasty. At the follow-up appointment, there was no improvement in her shoulder pain or other symptoms, and her deltoid muscle seemed atrophic. Additionally, she had leakage from the surgical incision that was consistent with a fistula. She also had an erythrocyte sedimentation rate (ESR) of 67 mm/h, a C-reactive protein (CRP) level of 16.9 mg/l (normal limit: 0-6), and a white blood cell count (WBC) of 7.93

K/mm^3. These findings led us to perform soft tissue debridement on the patient's right shoulder. A pathological evaluation of the debrided material showed active chronic inflammation, synovial hypertrophy, a foreign body reaction, granulation, and the presence of staphylococcus aureus. She was then prescribed the following antibiotics: peroral doxycycline 2x100 mg/per day, peroral sodium fusidate 2x500 mg/per day, peroral ciprofloxacin 2x750 mg per day, and sultamicillin tosylate 2x1 gr intramuscularly for 10 days. Additionally, fentanyl 25 µg/hr was also given via a transdermal patch. The patient is currently being followed up at our medical center.

DISCUSSION

AVN is defined as the cellular death of bone components due to the interruption of the blood supply. The bone structures then collapse, resulting in bone destruction, pain, and loss of joint function (3). However, in spite of technological improvements that have been made in diagnostic radiology, detection remains difficult because of the lack of early clinical symptoms associated with AVN (2).

AVN constitutes a very difficult diagnostic problem. Its slow progression in long-term cancer survivors means that symptoms often appear many years after RT; thus, patients do not associate them with this past treatment (1, 5). In our case, the AVN symptoms appeared immediately after the first round of RT, and to the best of our knowledge, this is the first case of its kind in the literature.

Besides RT, other common risk factors for AVN include trauma, corticosteroid administration, heavy alcohol intake, sickle cell disease, and other systemic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE),(5) but only RT was present in our patient. In their study, Assouline-Dayan et al. (3) determined that neoplastic

and marrow infiltrative disorders can also increase the risk of AVN and that chemotherapy may raise the risk for osteonecrosis in patients who receive RT. In our patient, the presence of neoplasms along with the chemotherapy might have precipitated the AVN.

In our case, the AVN developed contralateral to the head of the humerus. All of these factors can affect the RT areas, but we are not sure whether these factors can affect the more distant regions far from the RT region. However, these physiopathological explanations make the possibility of alterations in the more distant areas low. Nonetheless, we could not rule out the possibility that the RT might have triggered this pathology. Therefore, our patient's AVN could have been idiopathic, and it might have occurred coincidentally with the RT treatment.

The natural history of osteonecrosis varies and depends primarily on the size of the infarcted segment and the site of the occurrence. This condition is difficult to recognize because the initial symptoms are nonspecific, but pain is almost always the presenting symptom. In addition, range of motion is well preserved at the beginning of this disease, but it gradually deteriorates and can be limited by the accompanying pain (2,5). The initial symptoms of our patient were nonspecific. Interestingly, our patient's initial symptoms were severe and acute, and the physician also took the swelling of her shoulder into consideration when making the diagnosis. This palpable, painful, and very sensitive swelling required advanced imaging technics, repetitive evaluation, and follow-up.

The diagnosis of osteonecrosis is generally made by utilizing both the clinical and radiographic results, with the latter being used to establish the stage (6). Conventional radiographs are widely used in the evaluation of osteonecrosis because they provide excellent specificity; however, they often do not detect early lesions. Newer techniques, including MRI, selective angiography, and skeletal scintigraphy, are now being used to evaluate the presence of early disease and contralateral involvement afterwards. MRI is highly sensitive and can detect osteonecrosis before any abnormalities can be seen on radiography (2). Radiographic

staging and the size of the lesion are predictive of disease progression and can be used to determine the most appropriate intervention strategy (4). In our patient, we used clinical and radiographic evaluations along with MRI to establish a diagnosis.

Treatment of AVN depends on the chronicity and severity of the symptoms as well as the degree of clinical and radiographic progression (6). The general treatment strategies for humeral head AVN include nonoperative modalities for symptomatic early disease, with surgical intervention being reserved for more advanced disease or for those with recalcitrant pain (7). Several nonoperative treatment options have been described in the literature for osteonecrosis, including the use of pharmacological agents such as naftidrofuryl, statins, stanozolol, heparin, coumadin, enoxaparin, iloprost. and bisphosphonate. Other options that have been tried are pulsed electromagnetic fields, electrical stimulation with a current, extracorporeal shock wave therapy (ESWT), biological treatment modalities, and hyperbaric oxygen therapy (3). However, none of these options could be used on our patient because of the ongoing cancer treatment. Thus, the only available course of treatment was anti-inflammatory medications.

Surgical treatment options for early osteonecrosis include core decompression with small-diameter drilling, arthroscopic-assisted core decompression, and bone grafting while hemiarthroplasty or total shoulder arthroplasty are used in cases of more advanced disease.(6) Surgery involving core decompression or vascular flaps and arthroscopic debridement have also shown promise. In addition, arthroplasties have produced good results (4,8). Because of the RT treatment, surgery was not a viable option for our patient, and we noted in her follow-up appoinment that her complaints had not resolved. Moreover, delaying the operative treatment in our case precipitated her negative outcome by causing the progression of the AVN. Ultimately, she was forced to undergo total shoulder arthroplasty. Unfortunately, the

procedure was not successful, most likely because of the negative affects of her cancer treatment.

CONCLUSION

As seen in our patient, AVN can occur shortly after RT and can be found on the contralateral side of the malignant tumor. Because of this, we recommend that during RT, proper shielding of the vital structures and organs should take place, a multi-field technique should be employed, and all fields should undergo treatment every day to reduce the total radiation dosage (3). Although AVN seems to be a very rare side effect of RT, it must be kept in mind by clinicians since it may lead to severe functional impairment in patients who often have been cured of cancer. Furthermore, early diagnosis and proper treatment may prevent patients from long-term morbidities (1).

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Fig 1: The conventional radiography scan of the humerus showing the deformation of the humeral head.

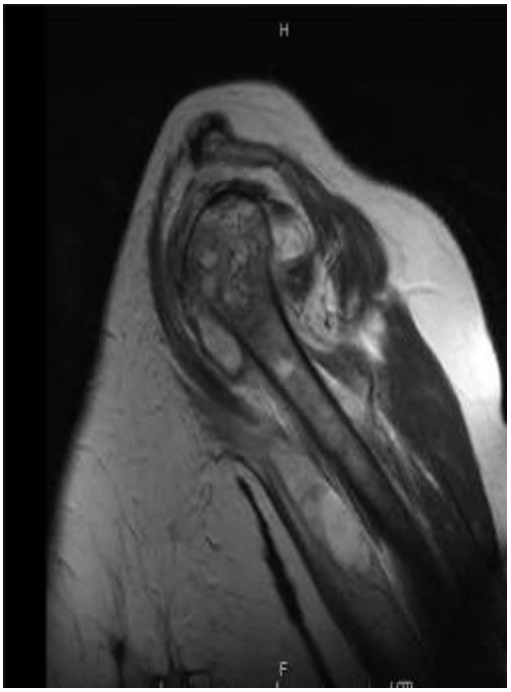

Fig 2: MRI scan of the shoulder showing AVN, bone marrow edema, fusiform fluid collection, effusion, cysts.