

Delayed Cellulitis Associated With Conservative Therapy for Breast Cancer

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Background and Objectives: Delayed breast cellulitis is an infrequently reported entity after conservation therapy for breast cancer. We describe our experience with this entity at Naval Medical Center, San Diego.

Methods: Eight patients who presented with delayed cellulitis after wide local excision/axillary dissection and breast radiotherapy (RT) are presented. Their clinical characteristics and therapy are described and possible causative factors are analyzed.

Results: The latency of breast cellulitis is variable after breast conservation therapy, although most cases in our experience and in the literature occur within a year post-RT. These infections are frequently refractory to a single course of antibiotics (n = 4 cases in our experience). Some patients suffer multiple episodes separated by months.

Conclusions: Breast cancer patients are at risk for delayed cellulitis after conservative surgery and RT. The mechanism of such events probably involves lymph stasis, however, therapy is no different from the more frequently occurring cases of cellulitis presenting perioperatively.

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INTRODUCTION

Delayed cellulitis is an infrequent complication of surgery and radiation therapy (RT) for breast cancer. Recently, several authors [1-3] have documented the frequency of this entity in patients receiving breast conservation therapy (BCT). This article describes the experience at the Naval Medical Center, San Diego, and provides insight into causes and treatment.

MATERIALS AND METHODS

The records of the Breast Health Center and the Radiation Oncology Clinic at Naval Medical Center, San Diego, were screened for patients who presented for definitive therapy of breast cancer between 1 January 1991 and 31 July 1996. A total of 230 patients were identified during this period; 16 charts (7%) were unavailable for evaluation or lost to follow-up. Specific note was made of patients treated with lumpectomy, axillary lymph node

dissection (ALND), and irradiation for early stage breast cancer, which resulted in the exclusion of 33 patients who did not receive this therapy. The remaining 181 patients were evaluated for the development of delayed cellulitis.

Eleven cases of breast cellulitis were diagnosed on follow-up visits. Specifically excluded were three perioperative cases, defined as those arising within 1 month of the completion of surgery. No patients presented with isolated upper extremity cellulitis. The remaining eight

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TABLE I. Study and Patient Data

Total patient charts	230
Excluded	49
Charts unavailable	14
Lost to follow-up	2
No RT	33
Total cases reviewed	181
Total cases of cellulitis	11
Perioperative	3
Delayed, after BCT	8

patients constitute the subject of this report. Details of their presentation and therapy are listed in Tables I and II.

All patients had undergone wide local excision of their lesions with ALND. Perioperative antibiotics, consisting of a single preoperative dose of a first-generation cephalosporin and rarely a second postoperative dose, were routinely used. Surgical wounds were closed with subcutaneous and subcuticular absorbable suture, without obliteration of the dead space of the surgical site. Axillary drains were used and discontinued when drainage was less than 30 cc/day.

Approximately 1 month postoperatively (median 37 days; range 19–220 days), patients began RT to the involved breast using tangential portals. This interval was longer in two of the three patients who received chemotherapy prior to RT (patients 54 and 154). The supraclavicular fossa was treated in two patients with involved axillary lymph nodes and posterior axillary boost portals were used in a single case. Doses of irradiation are listed in Table II, but ranged from 46 to 50.4 Gy (median 50 Gy), with a subsequent electron boost to the excision site.

Three patients received chemotherapy, although none was on chemotherapy at the time of the development of cellulitis. Five patients were on tamoxifen when cellulitis developed.

Patients were followed in the Breast Tumor Clinic every 3–4 months for the first 2 years, every 6 months for years 3–5, and annually thereafter.

RESULTS

Table II contains data regarding the eight patients described. At the time of ALND a median of 25 nodes was removed (range 8–35). In most cases, initial presentation consisted of pain, erythema, and axillary swelling, with the exception of one case presenting with fever and axillary pain. The diagnosis of cellulitis was made on the clinical findings of erythema, tenderness, edema, and warmth in the involved breast. Routine blood cultures and laboratory evaluations were not obtained for those patients treated as outpatients.

Three patients underwent ultrasonography to rule out an underlying breast abscess as the source of cellulitis. In all three patients (54, 72, and 176) the ultrasound showed

no evidence of underlying abscess. Two patients underwent biopsy of the area of cellulitis to include skin and underlying breast tissue. Both biopsies were negative for carcinoma. Three patients had blood cultures obtained and all were negative for growth of any organisms.

Therapy is described in Table II. Six of the eight cases responded to outpatient oral antibiotics with complete resolution of the cellulitis. Four of the six cases responded adequately to a single course of oral antibiotics and required no further treatment. Two cases required one to two additional courses of oral antibiotics for resolution. Two of the eight cases required hospital admission for intravenous antibiotics. These patients were noted to have severe symptoms with fever and leukocytosis, and blood cultures were obtained; these were negative. These patients had white cell counts of 15,500 and 21,200, respectively, on admission. In addition, one patient had an admission temperature of 103°F. One case was treated with 24 hr of intravenous antibiotics prior to discharge on oral therapy and subsequently resolved; another case was admitted for intravenous therapy for a refractory episode after a course of oral antibiotics and subsequently resolved.

At no time did evaluation of delayed breast cellulitis in these patients lead to a diagnosis of an in-breast tumor recurrence.

DISCUSSION

Delayed cellulitis occurring after BCT has a low frequency of occurrence. Initial treatment for mild cases consists of oral antibiotics to cover normal skin flora. Six of our eight cases responded to such management. For persistent cases or patients who present with fever and leukocytosis, hospital admission for a course of intravenous antibiotics is warranted. Consideration should be given to performing an ultrasound to rule out an underlying abscess. Cases refractory to antibiotics should undergo a biopsy to exclude the possibility of inflammatory carcinoma.

Historically, most episodes of cellulitis occur perioperatively after surgical procedures, although a few were noted at a significant interval after breast conservation without demonstrable trauma or other identifiable insult to the breast. In our experience, 8 of 181 patients (4.4%) developed delayed cellulitis after surgery and RT for early stage breast cancer in a 66-month period. This crude frequency corresponds with a per year incidence of approximately 0.8% in our population.

Few other reports have discussed breast cellulitis after BCT. Rescigno and associates [1] described 21 episodes of breast cellulitis in 11 patients. Three patients presented with elevated white counts and four with elevated temperatures. Of seven patients with blood cultures obtained, only one was positive for a streptococcus species and of two leading edge breast aspirates, both were negative for

TABLE II. Therapy Data

Patient no.	Age (years)	(+) Nodes	Stage	Adjuvant	RT dose (Gy) ^a	Post-RT latency (months)	Therapy
54	63	13/24	T1N1	CMF/TAM ^b	50 + 16	4	Dicloxacillin
72	52	4/20	T1N1	CMF/TAM	50 + 10	4	Dicloxacillin plus subsequent intravenous treatment as inpatient ^c
74	62	0/35	T1N0		50 + 10	2	Azithromycin
106	69	0/26	T1N0		50 + 16	4	Azithromycin (×2) Clindamycin
138	68	0/29	T2N0	TAM	50.4 + 10	4	Dicloxacillin Azithromycin
144	61	0/8	T1N0		46 + 14	16	Amoxicillin + clavulanate
154	52	0/31	T2N0	CMF/TAM	50 + 10	13	Amoxicillin + clavulanate
176	66	0/19	T1N0	TAM	46 + 14	7	Intravenous treatment as inpatient ^c plus subsequent cephadrine as outpatient

^aDoses include tangential dose + scar boost dose.

^bCMF = cytoxan, methotrexate, 5-fluorouracil chemotherapy; TAM = tamoxifen.

^cData on inpatient antibiotic regimens not available.

TABLE III. Literature Results

Ref.	Patients			Median latency (months)	>1 course antibiotics	No. of cases		
	Total	With cellulitis	Cases of cellulitis			Delayed acute	Chronic recurrent	Chronic persistent
Rescigno et al. [1]	NS ^a	11	21	4.3	NS	5	2	4
Loprinzi et al. [3]	NS	1	1	2	—	1	—	—
Staren et al. [2]	184	10	10	NS	2	5	—	5
Present study	181	8	8	4	4	8	—	—

^aNS = data not stated.

growth on culture. Three distinct clinical scenarios were discussed: acute cellulitis which resolved after appropriate therapy; chronic recurrent cellulitis which responded to therapy but manifested as multiple recrudescences in two patients; and chronic persistent cellulitis wherein symptoms stabilized after therapy, without complete resolution and with subsequent negative cultures.

Staren and colleagues [2] reported a crude frequency of 5% for breast cellulitis occurring more than 3 months postoperatively. In their entire cohort of patients, they could determine no clinicopathologic difference between the 10 patients developing cellulitis and the 174 who did not. They reported a mean white blood cell count of 8,000 and a mean temperature of 37.5°C in these patients and both blood cultures and leading edge aspirates were negative for growth. From their data, persistent disease refractory to antibiotic and anti-inflammatory therapy for more than 4 months required biopsy to ensure recurrent cancer was not the cause; one of the five such patients with persistent disease was found to have recurrent carcinoma.

Loprinzi and associates [3], in a discussion of breast changes which mimic inflammatory breast cancer, described a case of delayed breast cellulitis subsequent to BCT. Other cases in their discussion were clearly peri-

operative events, and as such may have been due to more acute trauma than the delayed case. Table III summarizes the previous reports in the literature and the present report.

The concept that lymphedema contributes to cellulitis is well documented, and breast lymphedema, clinical or subclinical, is likely a factor in the cases presented here [1–3]. Patients who have undergone axillary dissection and RT as BCT typically experience altered lymphatic flow. A low volume insufficiency, or mechanical insufficiency, develops within the lymphatic system secondary to a significant decrease in the lymph transport capacity. This decrease in transport capacity is caused by trauma to the lymph vessels and/or nodes either as a direct result of the surgery or RT, or due to subsequent tissue fibrosis. In general, primary lymphedema is classified as a congenital disorder of the lymphatic system, while secondary lymphedema is a condition arising from an external influence (e.g., axillary surgery or RT).

Although patients may not present in follow-up with significant edema, they should be considered to be in a stage of subclinical lymphedema. This stage develops as a result of lymphatic sclerosis, which in turn causes the decreased flow discussed above. Stasis of lymph in the breast predisposes the patient to infection because it

serves as a medium for bacterial growth in the interstitial spaces [2]. It is the role of the lymphatic drainage system to clear bacteria from the breast parenchyma, but with altered lymphatic flow and stasis bacterial overgrowth occurs more frequently. Clearly, this risk may continue for years after surgery [1,4].

Infectious processes can also cause decreased lymphatic flow. With the development of infection, there is an increased permeability of capillary membranes due to inflammatory mediators. This increased permeability leads to increased interstitial fluid—edema—and increased load on the lymphatic system [5]. Thus, a cycle is created which contributes to the perpetuation of lymphedema and continued risk of infection.

With the knowledge that lymphedema, clinical or subclinical, increases the patient's risk of infection, all patients undergoing BCT should be educated on proper maintenance of skin care as well as precautions for lymphedema, both of the upper extremity and the breast [1,5]. For the patient with clinical lymphedema, measures should be taken as soon as possible after presentation to manage lymph accumulation so that fibrotic skin changes and risk of infection may be minimized. The patient also must be able to recognize signs and symptoms of cellulitis so that immediate treatment may be sought. By properly educating the patient, the clinical role of lymphedema management appropriately shifts from secondary treatment to primary prevention.

Lymphedema management may range from invasive to non-invasive techniques [6–8]. Non-surgical techniques are more widely accepted for cases of secondary lymphedema, while surgical options may be closely examined for primary cases [8]. Among the conservative, or non-operative, methods of management available to patients are manual techniques to enhance venous and lymphatic drainage; compression therapy; proper skin care; and exercise [6–11]. Implementation of these four practices in an attempt to restore a balance between lymphatic protein load and lymph transport capacity is known as complex decongestive physiotherapy [11]. With proper education and clinical management, the risk of infection may be significantly reduced in patients undergoing BCT.

Few of the patients in our series had robust clinical

breast edema at the time of cellulitis presentation. These cases provide a clear reminder, however, that subclinical processes may still put the post-BCT breast at risk for cellulitis some time after the last fraction of RT. Continued close follow-up of such patients is of paramount importance.

CONCLUSIONS

Our findings in regard to the development of delayed cellulitis following conservative therapy for breast cancer are in agreement with the few other reports in the literature. All of our patients responded to antibiotics, although a prolonged course of oral antibiotics was required for two patients and a course of intravenous antibiotics was required for another two. In our evaluation and as noted in other reports, blood cultures and laboratory evaluations were of little help. Initial therapy for the cellulitis as well as possible mechanisms for its development have been discussed. In particular, prevention of delayed cellulitis using complex decongestive physiotherapy has been advocated.

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