Postamputation diagnosis of squamous cell carcinoma in a patient with lymphedema

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ABSTRACT

Chronic lymphedema is fraught with morbidity, including tissue loss. We present the case of a woman with long-standing lymphedema suffering from nonhealing ulcerations despite multiple interventions, who underwent below-knee amputation. Surgical pathology yielded a diagnosis of invasive squamous cell carcinoma. We highlight the uncommon association between lymphedema and squamous cell carcinoma, and the importance of routine pathological testing with lower extremity amputations. (J Vasc Surg Cases Innov Tech 2023;9:1-4.)

Keywords: Squamous cell carcinoma; Chronic lymphedema; Amputation

Primary vascular disease accounts for the majority of nontraumatic lower extremity amputations.[1] In the diabetic population, an estimated 120,000 lower extremity amputations are performed annually in the United States. A subset of that population, approximately 1.3 in 1000, are major amputations, defined as amputations above the ankle, performed in the context of nonhealing ulcerations.[2] A neuroischemic etiology is prevalent in nonhealing ulcers,[3] whereas chronic lymphedema is an uncommon cause of ulceration necessitating amputation. Furthermore, squamous cell carcinoma (SCC) arising from chronic lymphedema is exceedingly rare, with fewer than 20 cases reported in the literature, and only 11 involving a lower extremity.[4] We present a case of SCC of the lower extremity, initially diagnosed as lymphedema, with definitive diagnosis after amputation performed for the nonhealing ulceration. Informed consent for publication was obtained from the patient.

CASE REPORT

A female in her 70s was referred to vascular surgery for bilateral lower extremity wounds present for more than 50 years. She had a previous medical history of lymphedema praecox and is a former smoker. The most significant wound involved full-thickness ulceration of the dorsal aspect of her ankle. Prior treatment attempts during the preceding 4 years at the referring practice included successful sclerotherapy of refluxing varicosities adjacent to the wound, with follow-up venous studies revealing reflux of the femoral and popliteal veins without residual varicosities of the lower leg. Additional prior workup included arterial studies with no arterial insufficiency. Her wounds persisted despite aggressive wound care and negative pressure therapy, as well as surgical debridement and skin grafting. No record of previously submitted surgical pathology samples, if any, was available. After these interventions failed, a below-knee amputation was recommended by her primary surgeon. She presented to our vascular surgery clinic for a second opinion. Unfortunately, given the extent of wounds and persistence despite extensive attempts at limb salvage, only major amputation was offered. She underwent an elective below-knee amputation in the standard fashion using a long posterior flap that was free from skin changes. Of note, significant edematous tissue was encountered intraoperatively; the tissue was otherwise unremarkable on gross examination. Following an uneventful postoperative course, she was discharged to an inpatient rehabilitation facility.

The specimen was sent, per our protocol, for gross pathology. After the patient's discharge from the hospital, the pathology report yielded evidence of SCC of the right ankle wound, with greater than 8 cm of tumor-free margin. She was referred to medical and surgical oncology, and an outpatient workup of her malignancy was initiated.

At 1 month postoperatively her incision was well-healed and the staples were removed. Oncologic workup included a positron emission tomography and bone scintigraphy scanning, which revealed a left lung mass, concerning for metastasis, as well as left inguinal lymphadenopathy, thought to be either metastatic or reactive in nature. Unfortunately, she returned to the clinic 2 months postoperatively with posterior knee swelling with associated permanent contracture of the knee joint. With concern for locoregional spread, the posterior knee mass was aspirated by interventional radiology, but found to be synovial and nonmalignant in nature. Nonetheless, the site of aspiration did not heal, and continued to produce seropurulent drainage

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Table. Literature review of lymphedema-related squamous cell carcinoma (SCC) of the lower extremity

Authors	Anatomy	Presentation	Etiology	Treatment
Epstein and Mendelsohn (1984)[22]	Foot	Proliferative lesion	Congenital lymphedema	Above-knee amputation
Ostrow et al (1987)[21]	Foot, groin	Ulcerative lesions	Congenital lymphatic dysplasia	Pedal amputation
Lister et al (1994)[18]	Lower leg	Ulcerative lesion	Trauma-related lymphedema	Local excision
	Lower leg	Proliferative lesion	Idiopathic	Local excision
Echenique-Elizondo and Florza (2002)[17]	Lower leg	Ulcerative lesion	Congenital lymphedema	Local excision
Furukawa et al (2002)[19]	Lower leg	Ulcerative lesion	Post-hysterectomy lymphedema	Local excision
Bilen et al (2003)[20]	Foot	Ulcerative lesion	Trauma-related lymphedema	Local excision
Gomes et al (2010)[16]	Leg, unspecified	Proliferative lesion	Trauma-related lymphedema	Local excision
Kumar et al (2013)[15]	Lower leg & foot	Ulcerative lesions	Filarial lymphedema	Above-knee amputation
Parthiban et al (2013)[23]	Lower leg	Ulcerative lesions	Congenital lymphedema	Not specified
Gulati et al (2022)[4]	Lower leg	Ulceroproliferative lesion	Filarial lymphedema	Local excision

over the following weeks. Given her significant discomfort, contracture, and nonhealing draining wound, a revision to an above-knee amputation was offered. After discussions with her family and with the palliative medicine service, inpatient hospice was eventually pursued.

DISCUSSION

Chronic lymphedema is a prevalent and morbid condition, affecting up to 5 million individuals in the United States.[5] Primary lymphedema, which is congenital in nature, is less common than the secondary phenotype, which most typically results after surgery, infection, malignancy, and/or radiation.[6] Chronic lymphedema can result in significant tissue loss in the absence of peripheral arterial occlusive disease. Unfortunately, owing to the relative paucity of lymphedema-related lower extremity wounds, the literature pertaining to clinical description, classification, and treatment is inconsistent and limited.[7] Ulceration in the context of lymphedema and concomitant SCC, as in this patient's case, is further complicated with even less available literature regarding its management.

Because lymphatic circulation is necessary for competent immune surveillance, maladaptive changes in the lymphatic system have been implicated in immunologic vulnerability and, in some cases, oncogenesis. Malignant transformation, such as Kaposi sarcoma and lymphangiosarcoma have been described as a result of lymphedema.[8] Chronic lymphedema is associated with a small number of other cutaneous malignancies, including SCC, basal cell carcinoma, melanoma, Merkel cell carcinoma,[9] extraosseous Ewing sarcoma,[10] and diffuse large B-cell lymphoma.[11] Lymphangiosarcoma resulting as a complication of long-standing lymphedema, also known as Stewart-Treves syndrome, is typically seen in the upper extremity after mastectomy and lymph node removal.[12]

Although there are reported instances of lymphedema and malignancies, cutaneous SCC as a result of lymphedema is exceedingly rare. In general, there are approximately 250,000 cases of cutaneous SCC in the United States annually, making it the second most common cancer. Of these cases, approximately 14% occur in the upper and lower limbs. The insults that cause this dysregulation of cell growth can be ultraviolet radiation, infection in the case of human papilloma virus, or, pertinent to our case, chronic wounds.[13] A subset of cutaneous SCCs, Marjolin's ulcers, refers to SCC that arises in the context of chronic inflammation and/or in the presence of scar tissue, often seen after a burn, surgery, or an inflammatory skin condition. Our patient, however, was diagnosed with lymphedema praecox, a congenital pathological etiology of lymphedema. Moreover, she had no history of burns or prior surgical interventions, other than an attempted skin grafting on the left lower extremity.

Chronic venous insufficiency has been associated independently with malignant transformation. In a prospective study,[14] 10.4% of patients with chronic venous ulcers that did not heal despite appropriate standard treatment for 3 months yielded malignancy on biopsy (56% SCC). In this light, concomitant chronic venous insufficiency and lymphedema, termed phlebolymphedema with a chronic, nonhealing ulceration should heighten suspicion for malignant transformation and lead to biopsy early in the clinical course for timely diagnosis and potentially result in limb salvage.

To date, 11 cases of SCC of a lower extremity affected by lymphedema have been reported (Table).[4,15-23] A congenital etiology of lymphedema was most common (36%), followed by post-traumatic (27%) and postfilarial (18%). The majority of these cases (64%) were treated with local excision with or without skin grafting of the defect.[4,16-20] Pedal amputation was required in a case of SCC in a patient with lymphedema and underlying epidermodysplasia verruciformis, with extensive involvement of the distal foot.[21] Above-the-knee amputation was required in a case of postfilarial lymphedema and SCC presenting with multiple ulcerations and wet gangrene who had been nonambulatory before presentation,[15] as well as in a case of nonhealing ulcers of the foot with long-standing lymphedema nonresponsive to multiple treatments.[22] One case[15] received postoperative locoregional radiation therapy owing to spread to the inguinal lymph nodes. Chemotherapy was not used in any of these cases, likely owing to the nonmetastatic nature of the remaining reported cases. Follow-up information is only reported in 5 of the 11 cases. One patient expired 4 days postoperatively from a pulmonary embolism. The remaining cases with follow-up data were alive without recurrence at 1 to 60 months.[4,16,19,20] Given the spectrum of treatments used in these cases, multiple factors need to be taken into account in determining appropriate therapy. Major amputation, as in our case and those described in the literature, should be considered based on ambulatory status, the number, severity, and nonhealing nature of wounds, and the patient's long-term goals.

This case also highlights the importance of histopathological sampling for lower extremity amputations. Although the majority of nonhealing ulcers of the lower extremity are secondary to common clinical entities including arterial or venous insufficiency, diabetic vascular complications, and pressure ulceration, malignancy should remain an important consideration given its morbidity and complexity in further management. Incidentally found SCC after lower extremity amputation has been reported previously—one in a case of chronic venous stasis[24] and another after hemipelvectomy for pelvic osteomyelitis.[25] Last, it is possible that gross samples of preamputation surgical debridement could have yielded the diagnosis of SCC at an earlier stage in this patient's clinical course, although it is unclear if it would have made a difference in her outcome. As such, it is important, for the nonhealing wound, that all tissue removed intraoperatively, whether during major amputation or local debridement, be sent for pathological analysis.

CONCLUSIONS

We report the case of a postoperative diagnosis of SCC after a below-knee amputation for primary lymphedema. Although nonhealing lower extremity wounds are common indications for lower extremity amputations, routine histopathological testing should be performed, because it may have important clinical implications, as it did in this case.

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