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Squamous Cell Carcinoma From Marjolin's Ulcer of the Foot in a Diabetic Patient: Case Study

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ABSTRACT

Squamous cell carcinoma (SCC) has been commonly reported by foot and ankle specialists. Marjolin's ulcer is a malignancy that involves a posttraumatic scar or ulceration that can develop into SCC from chronic neuropathic pedal wounds, venous stasis, or decubitus ulcerations. Most Marjolin's ulcers are found in the lower extremity, specifically the feet, and it is twice as common in females as males. Biopsy of the tumor is the reference standard to diagnose SCC, and wide excision of SCC is the most common treatment option. The present case study describes an 83-year-old diabetic wheelchair-bound female who presented to the wound care clinic with a right heel nonhealing pressure ulceration. After biopsy and surgical excision, the patient was found to have SCC. This case was followed up for 5 years in which the patient had successful excision of the tumor with no recurrence. The clinical significance of our case study is to assist in the diagnosis, management, and prognosis of patients with SCC. In addition, this study has shown that adequate excision of the tumor margins and depth is necessary to prevent potential recurrence and metastasis.

Squamous cell carcinoma (SCC) is the second most common form of cancer on the skin of the feet (1). The incidence of SCC presenting in the lower extremities has been ~1.5%; however, the risk of metastases and recurrence becomes high if not treated (2). SCC is defined as a malignant skin tumor of keratinocytes located in the epidermis, which can begin as small scaly bumps or plaques appearing inflamed and progress to hard, projecting callus-like lesions. The presentation of SCC in the feet can be caused by, but not limited to, the presence of a chronic ulceration, lichen planus, deep mycosis, and lichen simplex chronicus (3). The differential diagnosis for SCC includes keratoacanthoma, basal cell carcinoma, eccrine poroma, sweat gland carcinoma, amelanotic melanoma, pyogenic granuloma, reactive epidermal hyperplasia, an overlying site of infection, cutaneous Hodgkin disease, and mechanical trauma (4).

The term Marjolin's ulcer describes malignant degeneration in any chronic wound. Seventy-one percent of Marjolin's ulcers will develop into SCC, although basal cell carcinoma, melanoma, fibrosarcoma, liposarcoma, leiomyosarcoma, osteosarcoma, malignant schwannoma, and mesenchymal tumor have all been identified (5). Marjolin's ulcer is a malignancy that involves a posttraumatic scar or ulceration and can develop into SCC from chronic neuropathic wounds, venous stasis, sinus tracts, osteomyelitis, decubitus ulcerations, warts, burns, or other forms of traumatic injury to the skin (6). Approximately 60% of Marjolin's ulcers are found in the lower extremity, and it is twice as common in females as males (5). Malignant transformation of chronic wounds, regardless of the etiology, can result from the induction of neoplastic cells, radiation, or toxin-induced alterations of epidermal cells into the dermis (7). Currently, it is believed that Marjolin's ulcers develop by a slow healing process and chronic instability of scar tissue (8). When SCC occurs in a Marjolin's ulcer, it will be an aggressive malignancy; however, Marjolin's ulceration with SCC constitutes ~2% of all SCC cases (8).

The classic development of malignancy within Marjolin's ulcers includes nodule formation, induration, and ulceration at the site, which is indicative of the diagnosis. Additional clinical presentations include chronic ulceration present for >3 months, everted wound margins, excessive granulation tissue, purulence, an increase in size, bleeding on contact, crusting over, and pain (9). The reference standard for a definitive diagnosis of SCC is confirmation by biopsy, especially if it presents in chronic, nonhealing ulcerations (10). In the present report, we describe a case of Marjolin's ulceration that was treated and

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followed up for 5 years. In presenting this case, we sought to share the clinical significance of the entity and a strategy for diagnosis, management, and treatment of SCC developing from a Marjolin's ulcer of the foot.

Case Report

An 83-year-old female presented to the general surgery clinic in January 2011 with an ulceration on her right heel. Her medical history consisted of type 2 diabetes mellitus, cerebral vascular accident, residual left hemiparesis, polycythemia, benign hypertension, breast cancer in remission, lumpectomy, and oral chemotherapy for 5 years. Her surgical history consisted of vaginal hysterectomy, tonsillectomy and adenoidectomy, and bilateral cataract extraction with lens implants. The patient admitted to being a former smoker and denied a history of alcohol or substance use. The mechanism of injury was suspected to be neuropathic ulceration, because the right extremity was the primary weightbearing limb in this wheelchair-bound patient.

On initial examination, the wound measured 2.1 cm long, 2.0 cm wide, and 0.1 cm deep. It had a pink base, minimal slough, and was through to the subcutaneous tissue without exposed bone or muscle. No drainage, malodor, or signs of infection were present. The periphery of the wound was healthy. Conservative care included mupirocin (Bactroban) and Adaptic (Acelity, San Antonio, TX) and dry sterile dressing changes daily. The wound exhibited a gradual increase in size and depth until the spring of 2014. The patient refused to consent to a biopsy until May 21, 2014, when a central hypergranular tumor was visible. The soft tissue biopsy was obtained under sterile conditions using a 2-mm punch biopsy. Examination confirmed SCC in situ, with well-differentiated keratinizing features, grade 1, and a neutrophilic-inflamed hemorrhagic crust but could not rule out invasion (Fig. 1). The patient was then referred to the podiatry wound care clinic.

In August 2014, plain films and magnetic resonance imaging (MRI) studies were taken. The plain films of the heel noted osteopenia and heel ulceration, with no evidence of osteomyelitis (Fig. 2). MRI noted a dermal mass of the heel posteriorly corresponding to known SCC, with no evidence of osteomyelitis (Figs. 3 and 4).

In September 2014, the patient was medically cleared for wide excision of the SCC in the right heel. Intraoperatively, the ulcer measured 3.0 cm long, 3.0 cm wide, and 1.5 cm deep (Fig. 5). The SCC had not involved the Achilles tendon. From the surgeon's review of the current data, a recommended 1.0-cm margin was marked about the tumor (Fig. 6). A no. 15 scalpel was used to resect the tumor widely down to the periosteal tissue. The tumor was removed easily and sent for pathologic examination. The fatty tissue beneath the tumor was normal, with healthy borders (Fig. 7). The calcaneus was not exposed and because of the negative results for osteomyelitis on the radiographs and MRI studies, a bone biopsy was not considered. The surgical wound was cauterized using electrosurgery (Fig. 8). The pathologic results confirmed SCC with irregular epidermal hyperplasia, ulceration, and full-thickness atypia of keratinocytes with partial loss of polarity of maturation. The postoperative results were discussed with the pathologist, who confirmed that the SCC was invasive, well-differentiated, grade 1, and ulcerated and that it had been completely excised, with negative surgical margins (Fig. 9).

Wound vacuum-assisted closure (VAC) was applied to the right heel ulceration on postoperative day 1. The patient was referred to an oncologist who decided radiation was not indicated owing to the negative margins. The wound VAC was continued until postoperative day 45 when the patient returned to the operating room for debridement of the ulceration and application of Apligraf (Organogenesis, Canton, MA; Fig. 10). The wound VAC was reapplied postoperatively until the surgical site had healed. At the final follow-up examination in September 2015, complete wound closure had been achieved without complications (Fig. 11). In July 2016, 22 months following the wide excision of the SCC, the patient died of vascular complications; however, the right heel had no evidence of recurrence or reulceration.

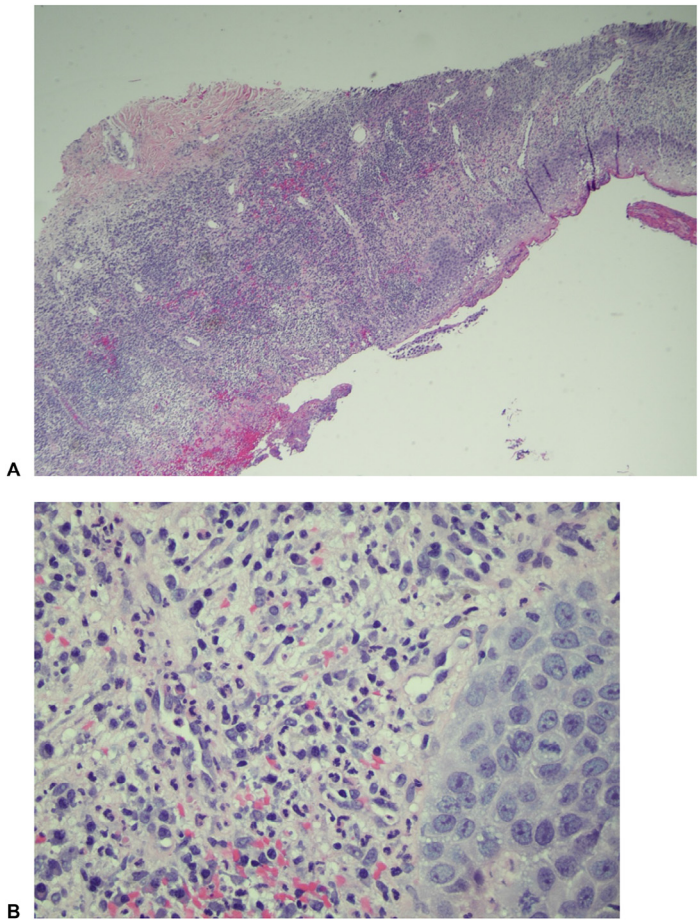

Fig. 1. *(A)* Skin biopsy showing epidermal ulceration (original magnification × 40; hematoxylin and eosin stain) composed of *(B)* acute and chronic inflammatory cells and organizing granulation tissue, with reactive degenerative changes (original magnification × 400; hematoxylin and eosin stain).

Discussion

SCC found in chronic wounds typically arises from poorly managed acute traumatic wounds, in addition to wounds that form because of vascular insufficiency, diabetic neuropathy, pressure, or hemoglobinopathy (7). SCC forming from a Marjolin's ulceration that initially developed from a pressure wound has typically been found to be more aggressive than other carcinomas developing in association with chronic wounds (6). Marjolin's ulcers have the ability to develop at any anatomic location; however, their incidence is greatest in the lower extremities, and 71% of Marjolin's ulcerations can progress to SCC (8).

Marjolin's ulcerations are associated with 2 common physical presentations. One presentation is typically a shallow, well-defined ulceration with a periphery consisting of nodular elevations, which is indicative of SCC located at the margins. The second presentation is more aggressive in growth, representing an exophytic tumor consisting of papillary granulations (6). SCC forming from a Marjolin's ulceration that is initially from a pressure wound has typically been found to be more aggressive than other carcinomas associated with

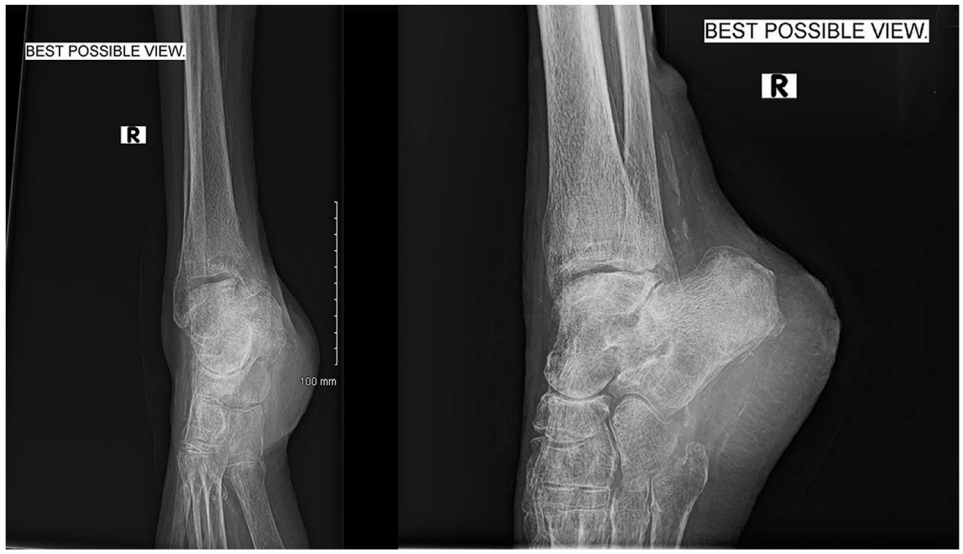

Fig. 2. Plain films of the right heel. Anteroposterior and lateral views of the right heel demonstrating severe diffuse osteopenia. A shallow heel ulceration is present. No evidence of osteomyelitis was seen. Vascular calcifications were noted.

chronic wounds (6). The metastatic rate is increased in associated pressure wounds or venous insufficiency ulcerations and ulcer-related SCC. Patients with depressed immune systems have an increased risk of susceptibility to malignant transformation (9).

The present patient had SCC within a chronic pressure ulcer on her right heel. She also had a history of diabetes. For our patient, plain films were the initial diagnostic test; however, the findings were limited to the soft tissue surrounding bone. If SCC is suspected in association with a Marjolin's ulcer, the physician should have increased concerns for osteomyelitis, which would result in metastatic lesions of bone with diffuse demineralization and extensive destruction (3). MRI is considered a superior option for bones involved with SCC compared with computed tomography. On T1-weighted MRI studies, SCC and metastatic lesions will be hypointense. Our patient did not have a positive indication for osteomyelitis of her calcaneus on radiographic plain films or MRI; therefore, a biopsy of the calcaneus was not performed.

Staging and grading of SCC considers the size, lymph node involvement, and metastasis, in addition to the duration of the ulceration and risk of malignant transformation (9). A grading system has been implemented for SCC using a gradient determined by the percentage of differentiated cells within a biopsy sample of the tumor. Grade 1 consists of >75% of differentiated cells. Grade 2 consists of 25% to 75% of differentiated cells. Grade 3 consists of <25% of differentiated cells (9). After analysis of our patient's pathology results, it was confirmed that our patient had grade 1 SCC.

No definitive treatment exists for SCC. However, many treatment options can be used, with healing rates estimated at ~90% (2). Without a standard protocol regarding excision, lymph node dissection, or the use of radiotherapy or chemotherapy, a combination of procedures is sometimes necessary (8). A variety of treatment options can be performed, such as tumor curettage, followed by electrocauterization of the base, cryologic surgery, intralesional injection of interferon-alfa-2b, and amputation proximal to the lesion (2). However, wide excision

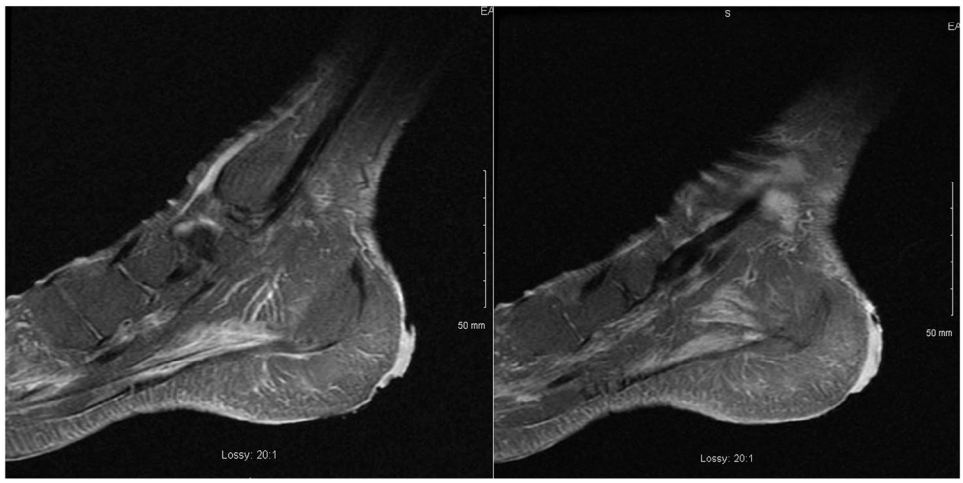

Fig. 3. Fat-suppression magnetic resonance imaging sagittal proton density. Increased density of the posterior heel indicates an ulcerated dermal mass, irregular skin thickening at posterior heel, with intradermal ulceration of biopsy-proven squamous cell carcinoma.

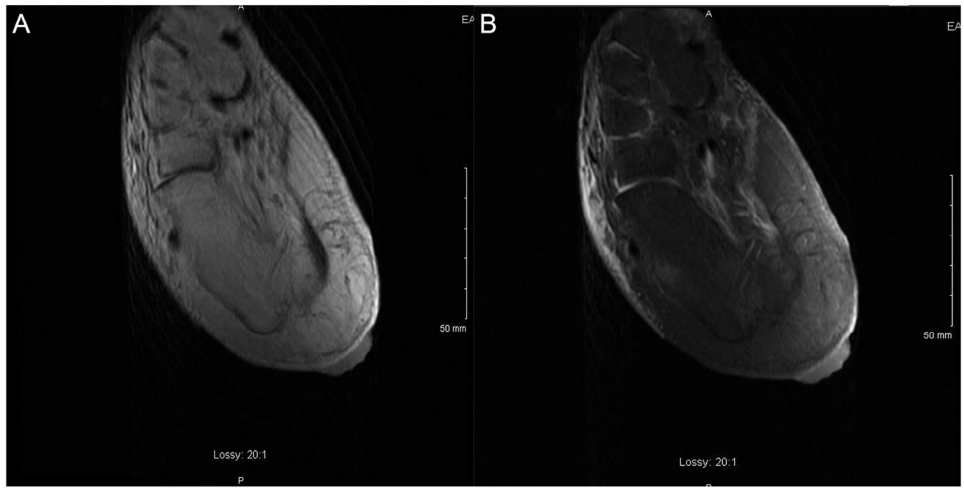

Fig. 4. Magnetic resonance imaging axial images: *(A)* axial proton density and *(B)* fat suppression axial proton density. Irregular skin thickening at the posterior, plantar surface of the heel is noted, which reflects the ulcerated dermal mass biopsy-proven squamous cell carcinoma.

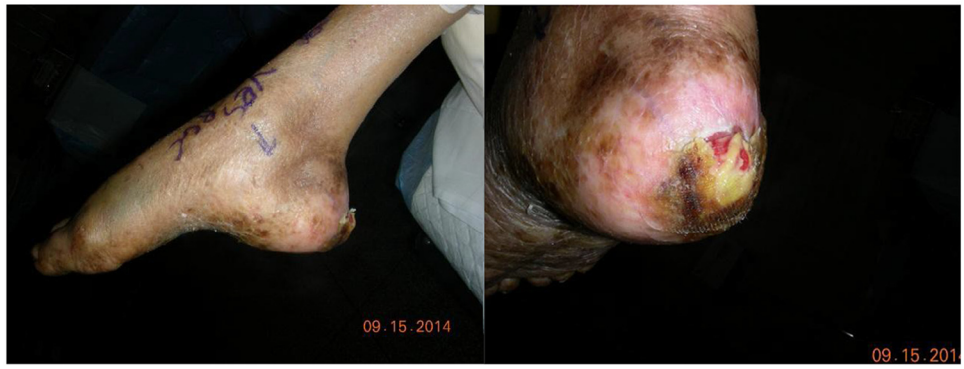

Fig. 5. Preoperative clinical images showing the right posterior plantar heel with the tumor centrally located within the site of the pressure ulceration. The ulcer measured 3.0 cm long, 3.0 cm wide, and 1.5 cm deep.

of SCC is the most commonly used treatment option. It involves an incision deep through the subcutaneous fat for superficial SCC with margins of ≥4 mm and 2 cm of normal-appearing tissue (10). It is important to cover a surgical site with a graft or flap or to perform primary closure in the early stages of malignancy to prevent recurrence of the malignancy (9). In present case, after surgical excision of the tumor, complete resection was confirmed by pathologic examination. After assisted granulation, Apligraf (Organogenesis) was applied in accordance with the reported data to prevent further formation of a possible recurrent malignancy.

Mirshams et al (11) reported a 37.5% rate of incomplete excisions related to difficulty with surgical closure, noting the importance of primarily closing the surgical site. The risk factors associated with incomplete excision of SCC included tumor location, such as areas of the upper lip, foot, forehead, cheek, nose, and ear (11). Ang et al (12) reported that tumors located near the genitals and lower limbs were associated with a high risk of incomplete excision. However, amputation is the most definitive option to treat SCC, especially in the case of infected bone or joint involvement (13). In addition, surgical intervention should be performed after an oncology consultation for preoperative and postoperative planning if radiation or chemotherapy will be necessary (14).

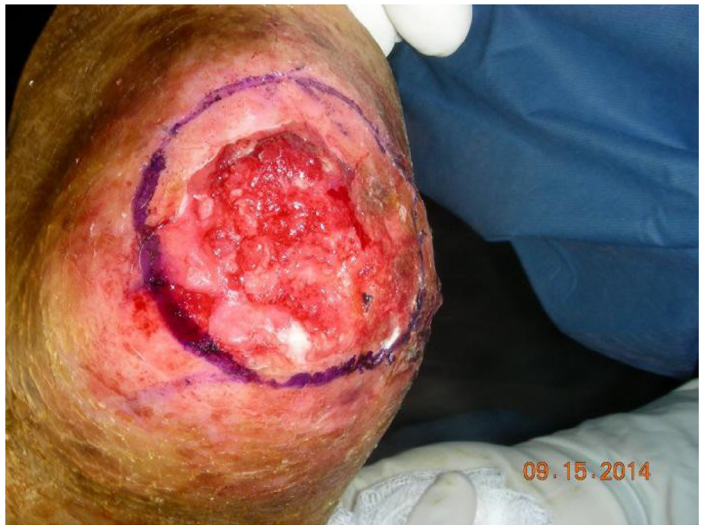

Fig. 6. Intraoperative image showing posterior plantar heel of squamous cell tumor with marked 1-cm margins for wide excision resection.

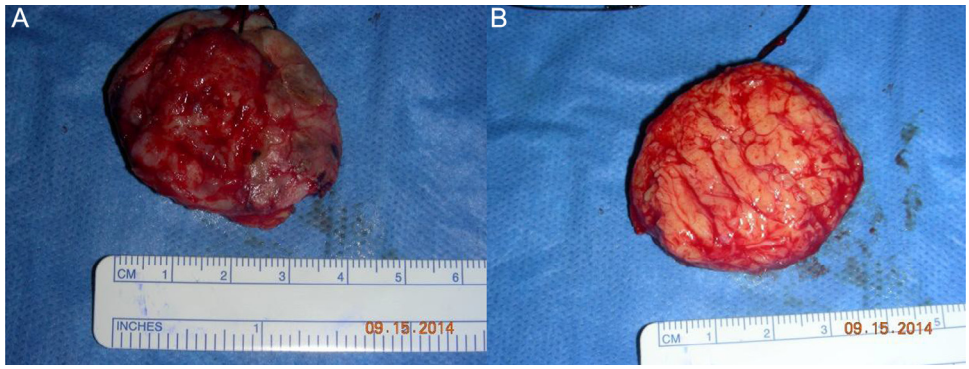

Fig. 7. Squamous cell tumor specimen. *(A)* Superficial aspect of squamous cell tumor. *(B)* Deep subcutaneous aspect of squamous cell tumor. The skin lesion with the squamous cell carcinoma measured 3.5 cm × 3.0 cm × 1.5 cm from the right posterior heel. Tumor was marked with 2-0 silk suture about the superior margin of the tumor.

Once SCC of the foot has been confirmed, the presence and potential for metastasis must be determined. SCC of the lower extremity has a rate of metastasis of ~30% (2). Most metastatic lesions originate from primary tumors stratified in the high-risk category when tumors are classified as grade 2 or 3. The characteristics of high-risk SCC on the extremities include a size >2 cm, indistinct borders, rapid growth, ulceration, poor differentiation, deep extension of tumor into subcutaneous fat, periwound, and perivascular or intravascular invasion (4). Recurrent SCC lesions have a greater rate of metastasis. Metastasis is typically seen in the brain, liver, lung, kidney, and distant lymph nodes (9). The use of cautery during excision could potentially prevent metastatic spread into the blood and lymphatic systems (9). In the present patient, intraoperative cautery was used at the surgical site to further reduce the risk of metastasis. Furthermore, our patient had a grade 1 tumor, which does not have a high risk of metastasis; therefore, our patient did not undergo radiation or chemotherapy. However, after excision of a grade 2 or 3 tumor, the oncologist and patient must decide whether and when to begin radiation and/or chemotherapy. The use of further imaging studies would be determined by the patient's symptoms after resection of the tumor. Our patient did not have signs or symptoms of metastasis or local recurrence; therefore, further imaging was not indicated.

Patients with SCC developing in diabetic ulcerations have had a 5-year survival rate of 40% to 69% (9). If the patient had undergone wide excision, the 5-year survival rate was 60% and was 69% for patients who had undergone amputations proximal to the lesion (9).

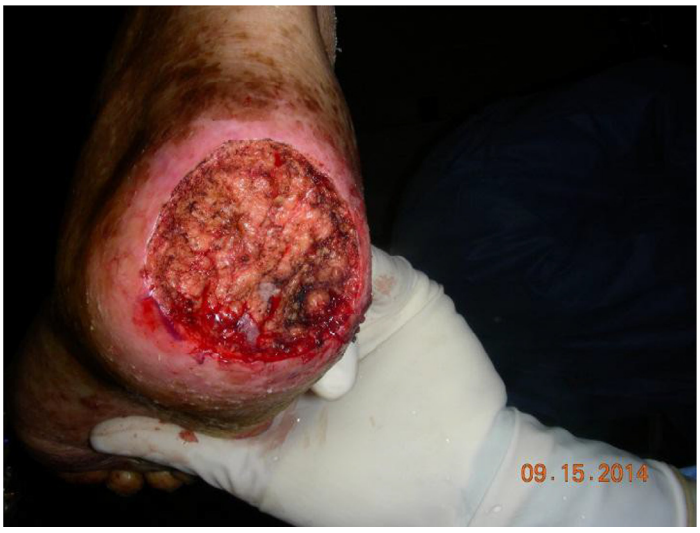

Fig. 8. Intraoperative image of right heel ulceration after resection. The site was cauterized using electrosurgery intraoperatively to assist in the prevention of metastasis.

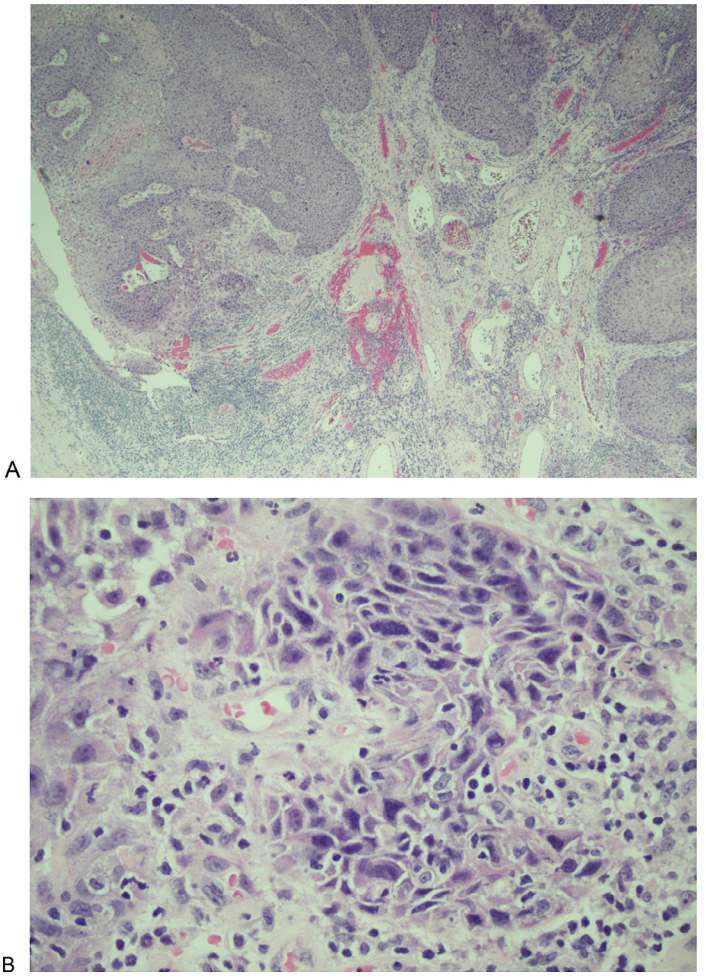

Fig. 9. *(A)* Well-differentiated, invasive squamous cell carcinoma showing ulceration (original magnification × 40; hematoxylin and eosin stain). *(B)* Nest of mild to moderate atypical cells showing abundant eosinophilic cytoplasm and large nuclei with vesicular chromatin (original magnification × 400; hematoxylin and eosin stain).

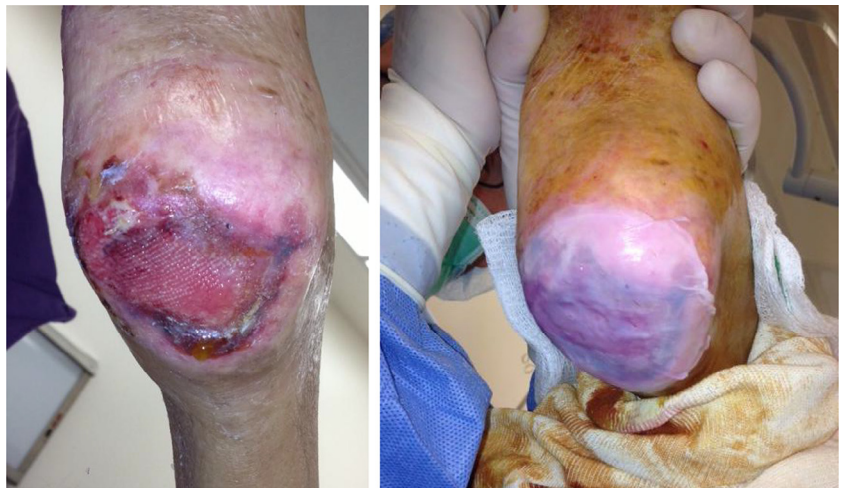

Fig. 10. Intraoperative application of Apligraf to the right heel ulceration. This was performed to assist in delayed primary closure in an effort to prevent recurrence.

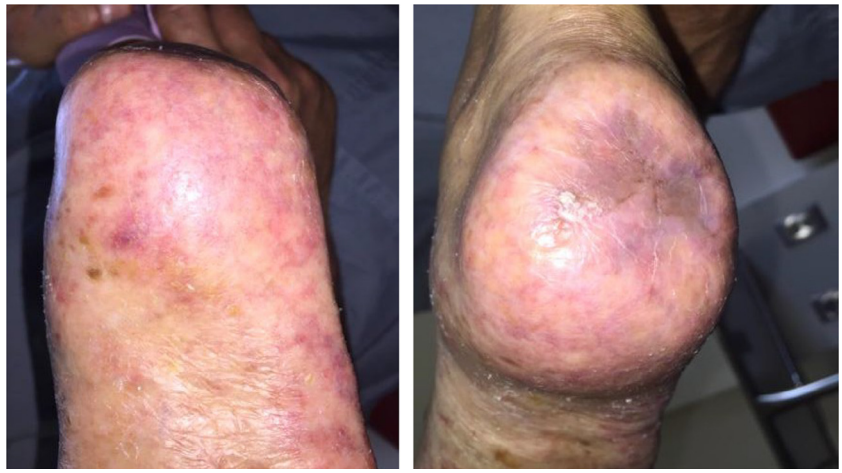

Fig. 11. View ~1 year postoperatively. The surgical site had healed with no open lesions or signs of recurrence at the site of resection.

Patients who develop 1 SCC lesion have a 40% risk of developing additional SCC within the next 2 years (4). A tumor size >2 cm doubles the risk of recurrence and triples the metastatic rate compared with smaller lesions (4). Grade 1 SCC lesions typically do not recur after appropriate treatment, which was demonstrated in our patient. Numerous case reports have demonstrated the development of SCC; however, studies focusing on the lower extremity, especially pedal manifestations of SCC, are rare. We reported the present case study to assist in the diagnosis, management, and prognosis of a patient with a diagnosis of SCC from a diabetic ulceration. Timely primary or secondary closure to prevent malignant transformation is necessary. Although the development of SCC in a diabetic foot is uncommon, its presence should be determined by early biopsy, surgical wide excision, and consultations with a multidisciplinary team to assist in the treatment and reduce the risk of recurrence.

In conclusion, adequate excision of the tumor margins and tumor depth is necessary to prevent potential recurrence and metastasis.

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