Squamous cell carcinoma arising in a chronic perineal wound in a patient with long-standing cutaneous Crohn's disease

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Key words: Crohn's disease; hidradenitis suppurativa; inflammatory bowel disease; medical dermatology; skin manifestations of internal diseases; squamous cell carcinoma.

INTRODUCTION

Cutaneous squamous cell carcinoma (SCC) is an invasive, malignant tumor with metastatic potential. This tumor can arise from various precursor lesions, including ulcers, actinic keratoses, and leukoplakia. A Marjolin ulcer is an aggressive malignancy of the skin, most commonly SCC, arising in chronic wounds or scars. Transformation from a chronic wound to SCC is rare and slow with an unknown pathogenesis, although proposed mechanisms include nonspecific or chronic antigenic stimulation.[1,2] Malignantly transformed wounds are challenging to differentiate from primary chronic ulcers, so having a high suspicion for SCC and diagnosis in a timely manner is key.[2] Clinically, it is important to monitor for changes in wound appearance and perform histologic evaluation early.[1] Chronic osteomyelitis is the clinical condition most frequently associated with Marjolin ulcers, with other common etiologies being trauma, burns, and diabetes.[2] Although cases of SCC developing in the setting of chronic hidradenitis suppurativa (HS) or Crohn's disease (CD) have been described in the literature,[3,4] SCC may be regarded as a rare complication of these diseases. We present a patient with chronic cutaneous CD that worsened focally on the gluteal cleft and perineum that then became refractory to multiple immunosuppressive therapies, including biologics and cyclosporine. After months of failed treatment, she was found to have SCC, and ultimately passed away approximately 18 months later.

Abbreviations used:

CD:	Crohn's disease
HS:	hidradenitis suppurativa
SCC:	squamous cell carcinoma
TNF:	tumor necrosis factor

CASE

A 55-year-old woman with CD and HS was referred to a dermatology clinic in July 2015 for evaluation of a peristomal rash. On examination, she was also found to have intergluteal cleft fissuring (Fig 1, *A* and *B*) with previous biopsies showing cutaneous CD (Fig 2, *A* and *B*). Azathioprine 50 mg once daily was added to her longstanding subcutaneous injection of adalimumab 80 mg every 2 weeks; then both drugs were replaced with cyclosporine 200 mg twice daily and dapsone 50 mg daily, but she continued to worsen. Despite improvement of the gluteal cleft ulcers, her HS and gastrointestinal CD worsened, so adalimumab therapy was restarted. In June 2016, the patient presented with worsening ulceration, severe perianal pain, bleeding, subjective fevers, and chills. On examination, her perineum appeared worse and a new, tender ulcer was noted with sanguinous drainage (Fig 1, *C* and *D*). There was concern for a perianal abscess, so the patient was admitted to the hospital. She also reported intermittent compliance with her immunomodulating medications in prior

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Funding sources: None.
Conflicts of interest: None declared.

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JAAD Case Reports 2018;4:346-8.
2352-5126

https://doi.org/10.1016/j.jdcr.2017.11.007

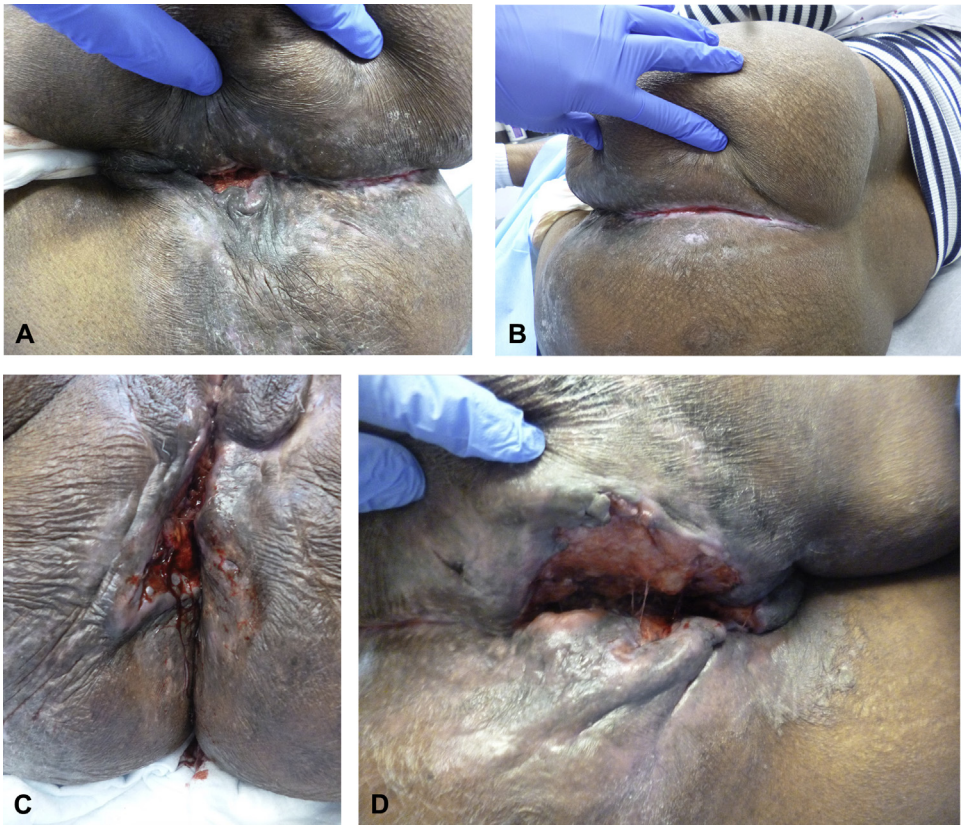

Fig 1. Clinical images of lesions of the gluteal cleft and perineum. **A** and **B**, Intergluteal cleft fissuring. **C** and **D**, Perineal ulceration.

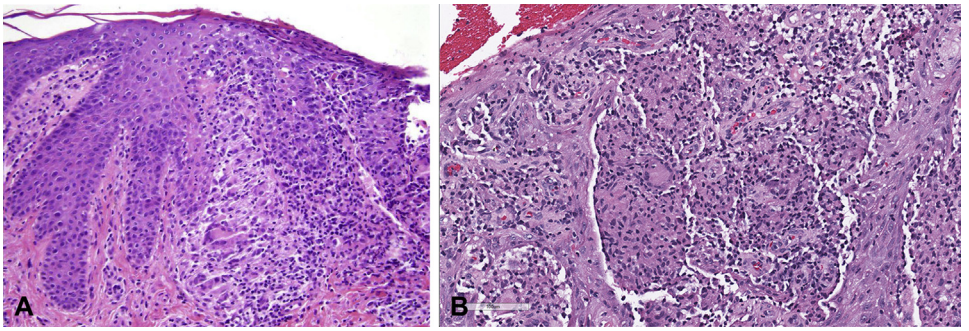

Fig 2. Histologic examination of tissue from patient with cutaneous Crohn's disease (CD). **A**, Original peristomal biopsy taken in 2006 showing cutaneous CD. **B**, Biopsy of skin showing irregular benign epidermal hyperplasia that embraces collections of epithelioid histiocytes and multinucleated giant cells. Cultures and special stains were negative for bacterial, mycobacterial, and fungal pathogens. These alterations are consistent with cutaneous CD.

months. A computed tomography scan revealed a residual fistulous tract but no abscess. Despite improved medication compliance after discharge, her ulcers worsened over the next 2 months. In September, an initial biopsy showed findings of reactive epidermal hyperplasia at the ulcer edge; however, repeat punch biopsy results were consistent with SCC (Fig 3). The patient was immediately referred to gynecology-oncology, but in the meantime, she was readmitted for worsened pain and drainage of the perineal lesion. During this admission, she underwent wound debridement and primary chemoradiation with radio-sensitizing cisplatin. Six months later, she was readmitted for pancytopenia and hypotension. At that time, biopsies of enlarged regional lymph nodes showed

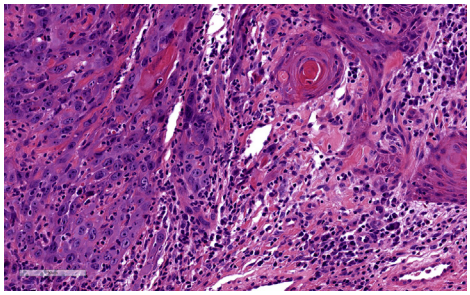

Fig 3. Biopsy of skin shows malignant cells infiltrating the dermis in cords and nests. Focal keratinization and keratin pearl formation are evidence of invasive squamous cell carcinoma.

invasive SCC. She was started on a first cycle of carboplatin and paclitaxel. After a family meeting discussion, the patient elected for a do not resuscitate/do not intubate status and was discharged with home hospice. Unfortunately, she succumbed to her disease 2 months later in May 2017.

DISCUSSION

As observed in this case, a CD patient in whom SCC develops is likely to receive delayed care because of a low clinical suspicion for malignancy. Clinicians should be wary of malignancy when caring for immunosuppressed patients with chronic nonhealing ulcers in whom infection has been excluded. Biopsy should be considered sooner rather than later. The pathogenesis of SCC in this case is not well understood but could be related to poor wound healing, constant cell turnover in areas of inflammation and trauma, or chronic immunosuppression.[5] Another mechanism could be decreased immunologic reactivity to tumor cells in scar tissue; also, a lack of vasculature for defense against metastases could permit tumors growing to a critical size.[6] There have also been case reports on the development of SCC in patients on long-term tumor necrosis factor (TNF)-inhibitor therapy for rheumatoid arthritis, psoriasis, and ankylosing spondylitis.[7,8] Such cases raise the question of whether nonmelanoma skin cancer surveillance in patients on TNF-inhibitors should be further investigated, and whether there is a need for identifying patients at high risk for malignancy.[9] Because cure of SCC is possible through a combination of both surgical and oncologic methods, early diagnosis and intervention is crucial.[10] Chronic wounds in patients with CD are common, so suspicion for malignancy is low, and subsequent patient outcomes are poor given delayed surgical management.[5] Ulcers or wounds that do not heal normally within 2-3 weeks despite adequate treatment are particularly worrisome and warrant consideration for biopsy.[6] Clinicians need to be aware of any change or worsening in clinical symptoms of existing perineal disease, such as refractory pain, discharge, or bleeding that is resistant to medical treatment.[11] In the event of biopsy-proven SCC, first-line treatment is local excision with consideration for lymph node evaluation in locally advanced disease. As seen here, adjuvant chemoradiation is an option in more advanced cases. The most important prognostic indicator is lymph node metastases. Close follow-up is imperative as risk for local recurrence is high.[1] In summary, vigilance for SCC in patients with a history of longstanding cutaneous CD is encouraged through identification of risk factors and maintaining a lower threshold for biopsy.[1]

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