Metastatic squamous cell carcinoma in a patient treated with adalimumab for hidradenitis suppurativa

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, debilitating, inflammatory skin condition characterized by recurrent painful nodules, cysts, and abscesses that can rupture and lead to the formation of sinus tracts and scarring. In 2015, the tumor necrosis factor-α (TNF-α) inhibitor, adalimumab, was approved for the treatment of moderate-to-severe HS.[1] TNF-α inhibitors may increase the risk of nonmelanoma skin cancers, particularly squamous cell carcinoma (SCC).[2] Patients with HS are 4.6 times more likely to go on to have nonmelanoma skin cancer than the general population.[3] Although the reasons for the increased risk in HS are not entirely understood, a known complication of scarring and chronic inflammation is a Marjolin ulcer (MU), a malignant degeneration (most commonly SCC) occurring in up to 3.2% of patients with HS.[4,5] Here we report a case of metastatic SCC, believed to be a MU, that developed in an HS patient being treated with adalimumab.

Abbreviations used:

HPV:	human papilloma virus
HS:	hidradenitis suppurativa
MU:	Marjolin ulcer
TNF-α:	tumor necrosis factor-α

CASE REPORT

A 48-year-old African-American man presented with a longstanding history of HS involving painful nodules and abscesses in the gluteal and perineal regions. Despite multiple courses of antibiotics and surgical excision of affected tissue in his left groin and thigh, the HS lesions were persistent and recurrent. He was started on adalimumab in November 2015. In November 2016, while still on adalimumab, the patient was given a clinical diag-

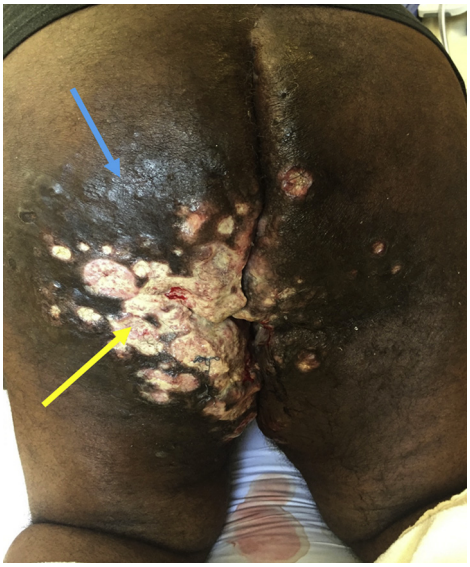

Fig 1. Hidradenitis suppurativa with squamous cell carcinoma transformation. Clinical image taken during most recent hospital admission (28 months after initiation of adalimumab). The blue arrow indicates chronic scarring, and the yellow arrow signifies indurated nodules and ulcerations consistent with SCC.

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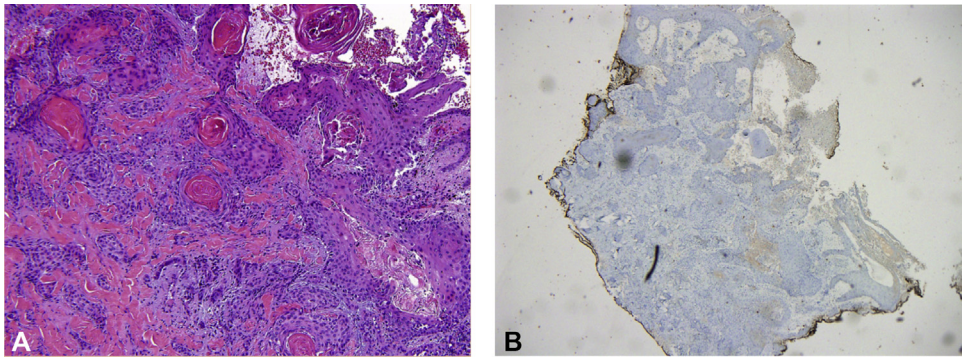

Fig 2. Gluteal ulceration biopsy results show SCC. Punch biopsy specimen taken at the same time as Fig 1. **A**, Invasive SCC, well-differentiated without perineural or lymphovascular invasion. **B**, HPV p16 negative. (**A**, Hematoxylin-eosin stain; **B**, p16 stain; original magnifications: **A**, ×40; **B**, ×10.)

nosis of pyoderma gangrenosum based on the development of new ulcerated nodules with a rolled violaceous border at the junction of the left inner thigh and buttocks, migrating along the scar from his previous surgery. Adalimumab was discontinued and prednisone and cyclosporine were begun.

In March 2017, the patient was admitted for palpitations and worsening HS (Fig 1). Bilateral pulmonary emboli were diagnosed, and he was found to have bilateral nodular airspace opacities on chest radiograph concerning for infection versus malignancy. Workup found leukocytosis and hypercalcemia. Bronchoscopy with bronchial brushing and bronchoalveolar lavage, bacterial culture, and fungal and acid-fast bacilli smears were all negative. Left upper lobe lung biopsy result was negative for malignancy. Despite antibiotics, repeat computed tomography scans showed increasing opacities of the lungs along with necrotic pelvic lymph nodes.

A wound culture of a gluteal ulceration showed growth of pseudomonas. Biopsy of the left buttock found invasive SCC, negative for human papilloma virus (Fig 2). Biopsies of a left inguinal mass and iliac ala found invasive SCC involving fibrous tissue and metastatic SCC in the bone, respectively. A positron emission tomography scan, performed to stage the malignancy, showed multiple areas of positive lymph nodes in the pelvis and lungs. It remains unclear if the pulmonary nodules represent metastatic disease or inflammatory changes from recent pulmonary emboli, as the lung biopsy found normal lung tissue. The SCC stage was determined to be T2, N3, M1. The patient received radiation therapy to the left iliac bone but later opted for hospice because of decline in performance status.

DISCUSSION

HS is a relatively common, chronic, painful skin disease. HS patients may rarely get SCC, which has a poor prognosis with a 50% 2-year survival rate.[6] The diagnosis of HS relies solely on clinical features and may be delayed an average of 7 years from the onset of disease.[7] The frequently delayed diagnosis of HS often results in progression to chronic wounds, which could be a contributory factor in the development of SCC. Although chronic inflammation from HS likely plays a role in the development of SCCs, other risk factors can contribute to de novo SCC development. When SCC arises in HS, it is difficult to determine whether it is de novo, related to the pathogenic features of HS, or if it is part of an MU. The mean time of symptomatic history of HS before SCC diagnosis is 25 years.[8] Although HS is more common in women, SCC transformation occurs more commonly in men.[6] Body location is another important risk factor, as malignant transformation occurs almost exclusively in extra-axillary sites, particularly the gluteal region.[8] Additionally, human papilloma virus (HPV) may play a role in the development of de novo SCC in HS, correlating with higher risk sites of involvement.[8] Smoking is another risk factor for the development of SCC.[8]

Immunosuppression may also play a role in the transition of HS to SCC. To the best of our knowledge, there is only 1 report of an HS patient who had SCC while being treated with a TNF-α inhibitor (in this case, infliximab).[9] The 2 phase III trials of adalimumab for HS found similar rates of adverse events in treatment and control groups.[10] However, the relatively small sample size and brief follow-up period limit the ability of these clinical trials to detect rare events, such as the development of malignancies. It is controversial as to whether TNF-α inhibitor treatment promotes the development of skin cancer, as temporality does not necessarily imply causality. It is possible that our patient might have had SCC before and independent of adalimumab use, because his disease was longstanding and

severe, and we do not have a baseline biopsy. It is also feasible that the SCC was misdiagnosed as pyoderma gangrenosum in November 2016. Yet the combination of immunosuppressive effects from TNF-α inhibitor use and independent risk factors (including disease duration, gender, site, HPV status, and smoking) associated with HS could have played synergistic roles in the development of this patient's SCC. Although adalimumab is clearly of clinical benefit in the treatment of HS, the ability of this therapy to prevent complications such as SCC should be weighed against the possible risk of lowering the threshold for the development of SCC. We suggest that by better recognizing HS patients who are at higher risk for the development of SCC, management can be improved leading to increased surveillance and lower threshold to biopsy with the goal of earlier detection of the rare complication of SCC.

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