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LETTER

Hidradenitis suppurativa—Pitfalls of long-term immunosuppressive treatment with tumor necrosis factor (TNF)-α inhibitors

Hidradenitis suppurativa (HS) is a chronic inflammatory disease characterized by inflamed lesions in forms of nodules, abscesses and sinus tracts with consecutive scarring in predominantly but not compulsory apocrine-gland bearing parts of the body such as axillary, inguinal or anogenital.[1,2] The exact pathogenesis remains unclear to date. Follicular hyperkeratosis results in follicle occlusion and eventually rupture with destructive inflammation; but also pathological signaling of TNF-α and IL-17 seem to be relevant.[1,3] Even if the primary (auto-)inflammatory process is not triggered by a bacterial infection, skin microbiome of HS patients is altered, promoting a bacterial biofilm maintaining inflammatory processes.[3] Depending on disease severity and comorbidities, different treatment approaches with either medical agents, for example, immunosuppressive therapy with biologics versus surgical approaches should be considered individually.[4,5] However, management of HS patients often remains challenging. An increased overall risk of cancer in patients with HS has been described repeatedly[6,7] and particularly the development of squamous cell carcinoma (SCC) secondary to chronic inflammation is a serious complication.[8,9] The tumors are typically localized gluteal, perianal and perineal, while displaying a high incidence of local recurrences despite wide surgical excisions.[9] Whether immunosuppressive treatment with biologics is associated with an increased risk of developing nonmelanoma skin cancer (NMSC) in patients with psoriasis or HS is still controversially discussed.[10,11] HS patients under TNF-α inhibitors and the occurrence of a SCC throughout have been described.[12,13] However, the underlying disease itself, that is, HS, in terms of pathogenesis and clinical course with longstanding inflammation increases the risk of developing a SCC.[14] To what extent the immunosuppressive therapy eventually affects the tumor genesis remains unclear.

Case 1: A 38-year-old male suffered from severe HS (Hurley stage III), showing recurrent absceding inflammation in both axillae, groins as well as anogenital. Over time, he received sequential wide local excisions and repeated systemic antibiotic treatment. Since June 2014, the patient was started on adalimumab in alternating dosage. In March 2020, the patient presented a severe worsening of his anogenital involvement with an extensive inflammation in form of widespread abscesses and fistulas accompanied by a decline of his general condition. Besides febrile temperatures, laboratory findings showed persistently elevated inflammatory markers and an anemia of chronic disease. MRI confirmed vast abscess formations perianal, transsphincteric, within the right ischio-anal fossa as well as urogenital with a fistula from the perineum into the scrotum (Figure 1). Clinical condition gradually declined further impending a septic course. Under antibiotic protection multiple abscess incisions and drainages were performed by our general surgical colleagues immediately. An intraoperative wound swab revealed growth of multiple anaerobic bacteria (*Finegoldia magna*, *Eggerthia catenaformis*, *Petponiphils lacrimalis*). To stabilize his clinical condition and prior to a planned

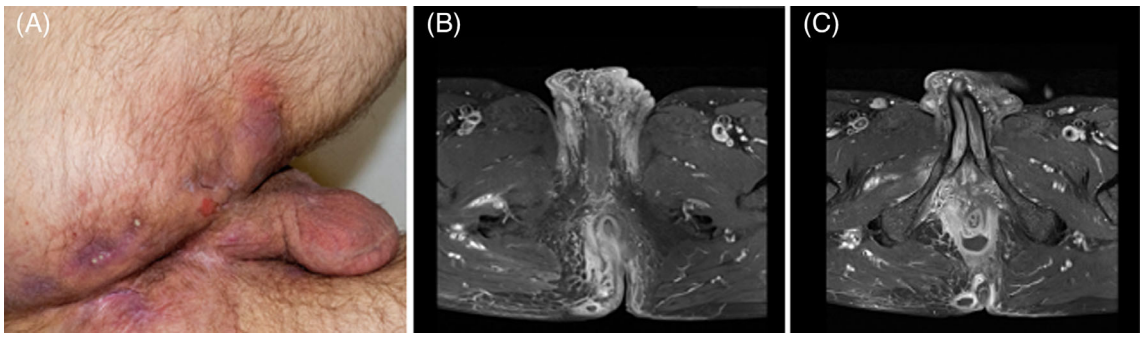

FIGURE 1 Case 1 showing advanced stage hidradenitis suppurativa with vast absceding inflammation. (A) preoperative clinical condition, (B) preoperative MRI with sphincter involvement, and (C) extensive abscess formation

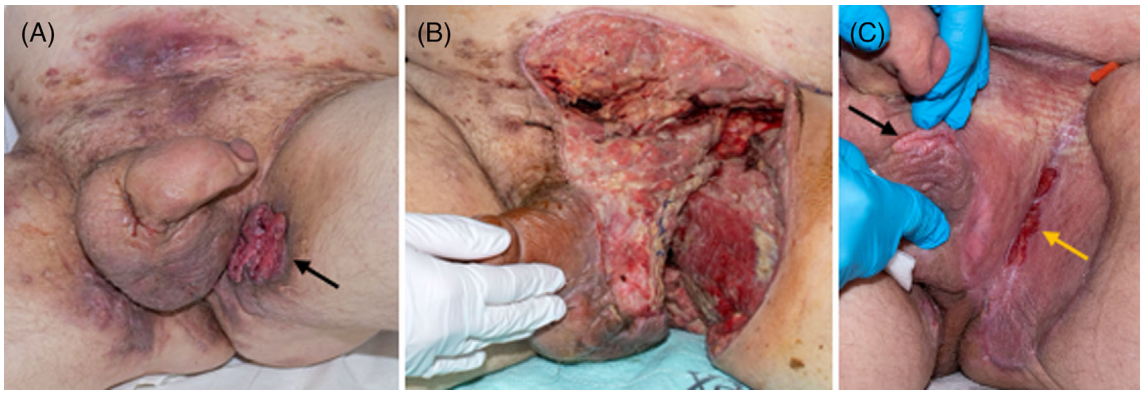

FIGURE 2 Clinical images of Case 2 showing (A) the initial squamous cell carcinoma (SCC) preoperatively (black arrow), (B) postoperative view after radical excision, (C) first local recurrence in march 2021 (black arrow) and wound healing disorder after the previous excision followed by a mesh graft (orange arrow)

wide surgical excision, the patient received a double-barreled sigmoid ostomy and antibiogram-compatible antibiotic therapy by our general surgical colleagues. Then, as a bridge-to-surgery and rescue treatment, antibiotic treatment was escalated to ertapenem 1 g/day intravenously according to the North American clinical management guidelines for hidradenitis suppurativa.[5] Subsequently, wide surgical excision of all affected areas in both groins, gluteal, scrotal, and perianal was performed. Eventually, the patient was discharged after several weeks into a rehabilitation clinic. Retrocession of the ostomy was performed 5 months later.

Case 2: Another male patient, 58 years old, presented with severe HS (Hurley stage III) in both axillae, groins, perianal, and gluteal. After nonresponse to systemic antibiotics, he was started on adalimumab 40 mg weekly in June 2018. Yet, he developed continuous exacerbations throughout. In October 2020, he experienced another flare in his left inguinal region and proximal thigh. Clinical distinction between inflammatory HS lesions and a secondary malignant process was difficult, thus skin biopsies were taken. After histopathology confirmed a SCC, treatment with adalimumab was immediately stopped. The case was presented in our interdisciplinary tumor board. In line with their recommendation, radical wide excision of the tumor mass and adjacent inflammatory HS lesions combined with extirpation of three previously wire marked inguinal lymph nodes was performed. Pathology reported a moderately differentiated SCC extending 7,7 cm horizontally and 3,2 cm vertically (G2, pT3, pN0 [0/9], L0, V0, Pn0, R0). Unfortunately, the patient developed two local recurrences throughout in March 2021 and June 2021, requiring again radical excisions as well as an ablatio of his left testis (Figure 2). The pathologic report respectively confirmed invasive SCCs. Further nodular or thoracoabdominal tumor manifestation was excluded by radiologic imaging. The case was again discussed in our tumor board and accordingly the patient received adjuvant radiotherapy due to repeated local recurrences of a multilocular invasive SCC. Up to November 2021, disease is controlled.

The presented cases highlight the pitfalls of long-term immunosuppressive treatment in severe and therapy-refractory HS. Even though biologics can be effective in certain patients, others fail to respond; yet, being still at risk for treatment-associated complications such as a higher risk of infections or secondary malignancies. Albeit HS is not initially caused by a bacterial infection, particularly the genital region is prone to superinfections with problematic bacteria, such as anaerobic species. This can eventually result in a life-threatening infection resembling a necrotizing fasciitis. The second case emphasizes the clinical difficulty to distinguish between inflammatory HS lesions and secondary malignancies such as NMSC. Considering the increased risk of SCC development in longstanding HS, biopsies of suspicious lesions should be taken to discover cancer early in the process. In addition, imaging is obligatory to evaluate the extent of invasion as well as possible metastases. Overall, the indication for systemic immunosuppressive therapy in HS patients requires an individual decision making depending on the presented clinical condition. In case of supposed nonresponse to immunosuppressive biologics, diagnosis and treatment strategy should be re-evaluated carefully, especially considering dosage escalations. Initial clinical symptoms of severe infections (Case 1) or tumor growth (Case 2) may be masked and complications difficult to perceive.

AUTHOR CONTRIBUTIONS

All the signing authors contributed to the clinical work (Kim Nikola Zeiner, Teresa Schreckenbach, Tatjana Gruber-Rouh, Frederik Roos, Johannes Frank, Roland Kaufmann, Markus Meissner, Eva Maria Valesky), data collection (Kim Nikola Zeiner, Markus Meissner, Eva Maria Valesky) and analysis of the data and drafting the manuscript (Kim Nikola Zeiner, Teresa Schreckenbach, Tatjana Gruber-Rouh, Frederik Roos, Johannes Frank, Roland Kaufmann, Markus Meissner, Eva Maria Valesky).

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Patients have given their written informed consent for the use of image and publication of their cases.

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