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Case report

Rapidly progressing vulvar soft tissue infection as a result of severe hypogammaglobulinemia following CAR T-cell therapy

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1. Introduction

Vulvar ulcers present as deep defects into the epidermis and may present with pain, pruritus, or even necrosis. Women may report systemic symptoms suggestive of systemic illness or have co-existing medical conditions such as inflammatory bowel disease or immunosuppressive disorders that can increase their risk of developing ulcers. In wheelchair or bedbound individuals, pressure ulcers might be more common. Alternatively, clinical history may suggest the presence of an infectious ulcer. Depending on the etiology, treatment might include pain management, wound care, antibiotic or antiviral therapy, steroids or laser therapy. When the lesion appears atypical or is not responding to treatment, malignancy should be excluded via biopsy or excision. In patients who require vulvar excision, postoperative complications remain a major cause of morbidity. These complications include wound separation, hematoma, postoperative infection, or hospital readmission for surgical site infection (Mullen et al., 2019). Risk of postoperative infection may be as high as 47% following surgery for malignant disease and 29% for benign disease (Mullen et al., 2019). Women who undergo a large excision or reconstruction, use tobacco, or are immunosuppressed are at increased risk for postoperative complications.

The immune system is a key factor in wound repair, which is a regulated process involving hemostasis, inflammation, proliferation, and tissue remodeling. An intact immune microenvironment is important in protecting the wound from overwhelming bacterial load and colonization, particularly through neutrophil extracellular traps (Larouche et al., 2018). In patients receiving chimeric antigen receptor (CAR) T-cell therapy, cytopenia and hypogammaglobulinemia following CAR T-cell therapy can occur, increasing a patient's risk for wound infection. In fact, the incidence of hypogammaglobulinemia is approximately 15% in patients with diffuse large B-cell lymphoma and occurs as early as 9 weeks after infusion (Stewart and Henden, 2021; Doan and Pulsipher, 2018). In this case report, we describe a patient with a history of chimeric antigen receptor (CAR) T-cell therapy who initially presented with vulvar ulcers and subsequently developed abscesses requiring multiple debridements and vulvar reconstruction.

2. Case

A 68-year-old woman with a history of marginal zone lymphoma was seen for a vulvar lesion. She had previously undergone chemotherapy and bendamustine with rituximab for cytoreduction prior to successful CAR-T cell infusion 2 years prior to presentation and was considered to be in complete remission.

On initial evaluation, exam revealed a $3 \times 4 \times 0.5$ cm ulcerated right labial lesion, which was unable to be biopsied secondary to extreme patient discomfort (Fig. 1a). She was taken to the operating room for an excisional procedure, which required resection to the underlying fascia given the full thickness ulceration. An intraoperative frozen section showed benign findings. Final pathology demonstrated reactive squamous mucosa with ulceration, granulation tissue and abscess formation. Gram stain, Grocott methenamine silver stain (GMS) and Periodic acid–Schiff (PAS) stain were negative for microorganisms. All specimens were negative for dysplasia or malignancy.

The patient presented on postoperative day 7 with fevers and exam consistent with superficial cellulitis. She was discharged home with oral antibiotics. An outpatient wound check on postoperative day 11 showed worsening erythema extending to the right buttock. White blood cell count was 6,000/mm^3 and serum lactate normal. Imaging revealed extensive soft tissue stranding extending to the inferior gluteal and

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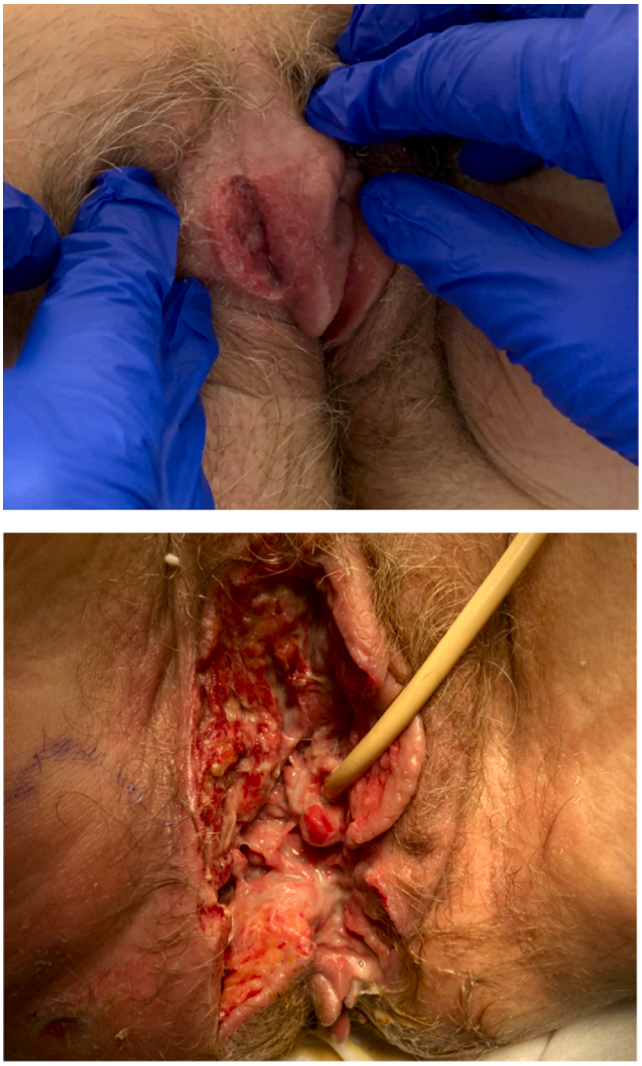

Fig. 1. Progression of vulvar ulcer (1a) to surrounding soft tissue necrosis (1b).

medial thigh consistent with cellulitis. She was admitted to the hospital and started on intravenous vancomycin and meropenem. On hospital day 4, the patient became acutely febrile (40 °C), hypotensive and altered. She was taken emergently to the operating room. The wound was debrided and the fascia noted to be intact without evidence of obvious purulence or necrosis (Fig. 1b). She continued wound care but had persistent fevers despite antibiotics and repeated surgical debridement. Due to her lymphoma history, hematology/oncology was consulted. Immunoglobulin levels were obtained and demonstrated severe hypogammaglobulinemia (Table 1). Replacement intravenous immunoglobulin (IVIG) 5 g/kg was administered daily for 3 days. At this time, multiple blood cultures were negative. Bacterial, fungal and AFB wound cultures were also negative except for a single fungal culture growing candida albicans. While it was not clear if this was a true pathogen or colonizer, caspofungin was added to the antimicrobial regimen.

After the administration of IVIG, the patient subsequently improved. After serial debridement, a vacuum-assisted wound closure device was placed, and she underwent wound reconstruction with a profunda artery perforator (PAP) flap on postoperative day 37. The remainder of her course was uncomplicated, and she was ultimately discharged to a skilled nursing facility on hospital day 41 without antibiotics. In follow up 12 months later, she continues to do well with a healed flap and no residual sequalae (Fig. 2).

Table 1
Immunoglobulin levels before and after IVIG infusion.

Immunoglobulin	4/28/2021	5/3/2021	Reference (mg/dL)
IgG (mg/dL)	118	1290	726–1521
IgA (mg/dL)	<8	<8	87–426
IgM (mg/dL)	28	42	44–277

3. Discussion

CAR T-cell therapy harnesses genetically modified T-cells to enhance anti-tumor immunity (Larouche et al., 2018). These engineered receptors are grafted on to immune effector cells and transferred back to the patient. These cells proliferate within the patient and enhance tumor immunogenicity via cross priming. Reported adverse events following CAR T-cell therapy include cytokine release syndrome, neurotoxicity, immunosuppression, infection, and dermatologic toxicities (Mullen et al., 2019; Stewart and Henden, 2021). The description of dermatologic toxicities following CAR T-cell infusion are limited. Rubin et al. reports 5 patients with dermatologic eruptions, dermatologic malignancy, and soft tissue infection possibly associated with CAR T-cell infusion based on pathologic features. Two patients receiving CAR T-cell therapy developed maculopapular rashes within two weeks of treatment with biopsies showing predominantly lymphocyte infiltration suggestive of an “eruption of lymphocyte recovery.” Another patient presented with skin necrosis due to a staphylococcus infection one day after therapy due to the immunocompromised state. Two other patients presented 5–7 months following therapy with cutaneous papules and pseudovesicles with lymphocytic features (Rubin et al., 2016). Hu et al describes a patient with refractory B-cell lymphoma who received CAR T-cell therapy and developed an acute dermatologic reaction following therapy. The patient became febrile 2 days post-infusion and presented with a maculopapular rash and tense bullae on his extremities. Fluid from the lesions was collected, and flow cytometery confirmed the presence of CAR T-cells and elevated cytokine levels (Hu et al., 2020).

Long-term follow-up of patients who received CAR T-cell therapy suggests that immune recovery is variable and may be prolonged in some patients. The time to B-cell recovery can range from 2 to 59 months, and up to 79% of patients require IVIG infusions after treatment. Particularly at IgG levels < 400 mg/dl, IVIG replacement in the setting of acute infection can be beneficial in correcting ongoing, severe infection (Doan and Pulsipher, 2018). These findings suggest that even a

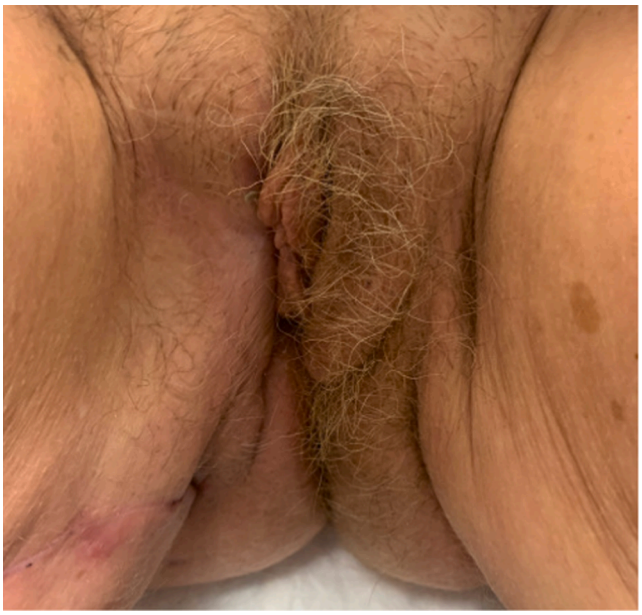

Fig. 2. Healed vulvar wound.

remote history of CAR T-cell therapy may be associated with long-term altered immunity. Sustained immune dysregulation remains an important predictor of soft tissue infection (Larouche et al., 2018).

In the presented patient, the persistent hypogammaglobulinemia indicates that CAR T-cell treatment may have had long-term immune-related effects contributing to her postoperative wound complications. In patients with a history of CAR T-cell therapy, considerations of delayed dermatologic and immunosuppressive adverse events are important aspects to consider. As the use of CAR- T cell therapy is more widely adopted, in addition to being explored as a treatment for ovarian cancer in early phase clinical trials, the knowledge gained from this case report may have increasing importance. Recognition of these unique toxicities is key to timely management. Healthcare providers caring for these patients should consider immune dysregulation in the setting of a rapidly progressing soft tissue infection unresponsive to appropriate medical and surgical management to develop an effective treatment plan. Engagement of a multidisciplinary team, including hematology/oncology, is vital to the treatment of these patients.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author Contribution

All authors contributed substantially to writing, reviewing, and editing the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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