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Erythema annulare centrifugum-type eruption in a patient undergoing cancer vaccine immunotherapy

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Abstract

Sipuleucel-T is a cellular immunotherapy approved for the treatment of metastatic castration-resistant prostate cancer. We report a patient developing an immune related adverse effect from sipuleucel-T drug-induced erythema annulare centrifugum-like eruption. A brief review of the mechanism and implications of this eruption are also included.

Keywords: immunotherapy, immune related adverse events, erythema annulare centrifugum, sipuleucel-T

Introduction

Within the last decade, the advancement in immunotherapies, particularly immune checkpoint inhibitors (ICIs), have improved the quality of life and survival of patients suffering from melanoma, among other malignancies. These agents modulate the immune system by inhibiting the body's innate negative feedback mechanisms facilitated by co-regulatory molecules such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death protein-1 and its ligand (PD-1/PD-L1). Another therapy based on immunotherapy used to treat prostate cancer is Sipuleucel-T. Sipuleucel-T, known as APC8015, is a cellular immunotherapy consisting of autologous antigen presenting cells (APCs) designed to stimulate lymphocytes and plasma cells against a protein present on prostate cancer tumor cells, prostatic acid phosphatase (PAP). The drug is produced by obtaining peripheral mononuclear cells from the

patient via leukapheresis and harvesting them with a recombinant fusion protein called PA2024, which is composed of PAP linked to granulocyte-macrophage colony stimulating factor [1]. The resultant product is then re-infused for three cycles over a period of six weeks.



Figure 1. Annular plaques with trailing scale on the upper arm and dorsal forearm.



Figure 2. Annular plaques with peripheral scale on the upper arm (closer view).

Despite the benefits, targeting the immune system is not without inflammatory toxicities, known as immune-related adverse events (irAEs). Skin manifestations, including rash and mucositis are the most common irAEs from ICIs, affecting anywhere from 30-40% of patients on PD-1/PD-L1 inhibitors and 45-70% of those on CTLA-4 inhibitors [2]. The long-term complications and toxicities of autologous cell and chimeric antigen receptor (CAR) T-cell immunotherapy are still under investigation. To the best of our knowledge, we report the first case of a patient treated with infusions of sipuleucel-T developing an infusion reaction consistent with erythema annulare centrifugum (EAC).

Case Synopsis

A 68-year-old man with a history of radical prostatectomy for prostate cancer, Gleason grade 9, presented to our clinic after worsening of a pruritic and burning rash two days after a second infusion;

the eruption started 2-3 weeks after first infusion of Sipuleucel-T for recurrent prostate cancer. For his prostate cancer, salvage radiation, androgen deprivation therapy with leuprolide and bicalutamide, and finally high dose oral ketoconazole and oral hydrocortisone were unsuccessful. At the onset, the eruption was composed of edematous annular plaques with peripheral scale on his forearms that progressively widened over several days. Empiric topical ketoconazole for presumptive tinea corporis was tried without improvement.

At our clinic, the lesions were still present and pruritic. A physical exam was notable for edematous annular plaques with trailing scale extending from the dorsal upper arms to dorsal hands (Figures 1, 2). A potassium hydroxide preparation was negative for hyphae. Two 4-mm punch biopsies of separate lesions demonstrated the same findings: patchy spongiotic dermatitis with rare eosinophils and superficial perivascular lymphocytic infiltrate with scattered neutrophils (**Figure 3**). Focal areas of parakeratosis were also noted. The histologic differential diagnosis, while nonspecific, included a drug eruption and erythema annulare centrifugum (EAC). Periodic acid-Schiff staining was noted to be negative. Clinically, the lesions were consistent with erythema annulare centrifugum but given the timing of the eruption and its worsening, a drug eruption/reaction to the Sipuleucel-T was also considered a possibility. Empiric triamcinolone ointment 0.1% was given to be used on the lesions; his oncologist decided to hold any further Sipuleucel-T infusions to see if they were related.

The patient was seen in follow up one month later with complete resolution of the rash and no further associated symptoms. Given that the eruption was only a grade 1 reaction to the Sipuleucel-T, it was not considered a definite reason to stop therapy. However, owing to a lack of treatment response against his prostate cancer, indicated by a rising prostate specific antigen (PSA) level, his chemotherapy was switched to abiraterone acetate.

Case Discussion

Cancer therapies have transitioned over the past decade from targeting certain components of the

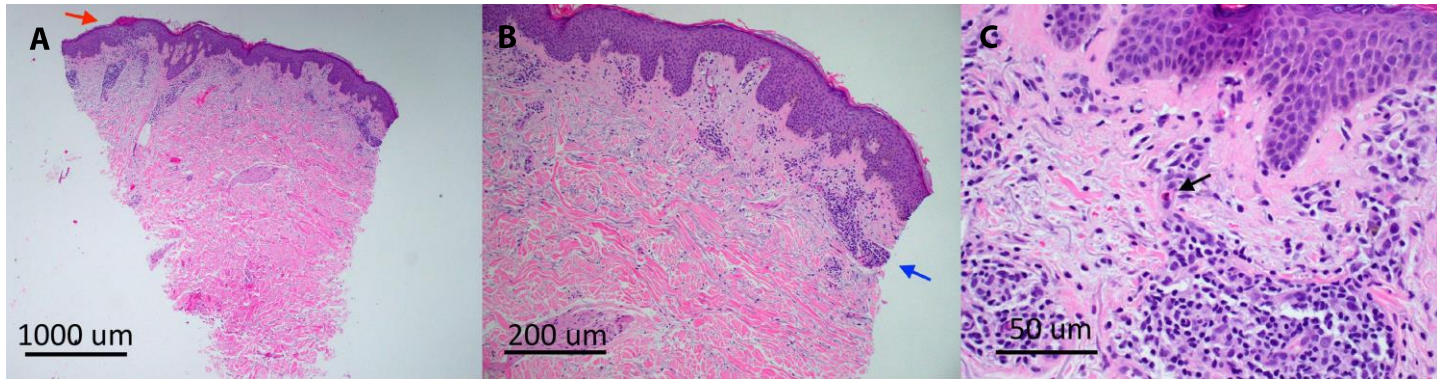


Figure 3. **A)** Mild epidermal spongiosis (red arrow) with superficial dermal infiltrate, 20 \times . **B)** The infiltrate is predominantly arranged in a loose perivascular pattern (blue arrow, 20 \times) with rare eosinophils. **C),** black arrow, 20 \times). H&E.

immune system to utilizing the body's own immune cells. This idea of isolating a patient's own mononuclear cells and lymphocytes, expanding them *ex vivo* in specialized facilities, and re-infusing them back into a patient is known as adoptive cell therapy (ACT). The process utilizes fusing the autologous T-lymphocytes to a highly specific chimeric antigen receptor (CAR) coupled with costimulatory domains, such as CD28 or 4-1BB, to enhance T-cell proliferation and cytokine production *in vivo* against tumor associated antigens on the surface of targeted cells [3]. APC8015 was given FDA approval in 2010 for the treatment of metastatic castration-resistant prostate cancer after demonstrating survival benefit in three phase III clinical trials (D9901, D9902A, IMPACT trial), [4-6]. Adverse events reported in the D9901/D9902A trials included chills, pyrexia, headache, asthenia, dyspnea, vomiting, and tremor. These effects were relatively mild to moderate (grade 2 or less) and subsided within 2 days of the infusion [4]. Chills, pyrexia, fatigue, nausea, and headache were all reported within one day of infusion in the IMPACT trial [6]. Severe (grade 3) side effects among patients treated with sipuleucel-T included chills, fatigue, back pain, hypertension, hypokalemia, and muscular weakness [6]. No cutaneous eruption was reported in any of these randomized clinical trials. A MEDLINE search for sipuleucel-T and rash/cutaneous eruptions failed to yield any results.

The etiology and significance of the EAC-like eruption is unclear. The pathogenesis of EAC is

unknown but believed to be a delayed type hypersensitivity reaction. Supporting this hypothesis is the finding that cultured lymphocytes from a woman with progesterone induced EAC demonstrated an increase in interferon-gamma release upon *in vitro* exposure to progesterone [7]. Alternative hypotheses surrounding the pathogenesis may include cytokine storm mediated via cytotoxic T-lymphocytes, cross reactivity of autologous immune cells to keratinocyte surface antigens, or a hypersensitivity reaction to unbound proteins in the infusion medium. Sipuleucel-T has been shown to induce antigen-specific CD4+, CD8+, and memory T-cells that concentrate at the prostate tumor interface [8]. The immunotherapy has also correlated with an initial IgM response followed by isotype switching to IgG producing memory plasma cells [8]. Given the presence of robust humoral and cellular immune responses, it is conceivable that antigenic mimicry and a failure of the immune system's protective self-tolerance pathway may play a role in the underlying pathogenesis of this cutaneous eruption. Preliminary studies demonstrated that the development of vitiligo following treatment with pembrolizumab and nivolumab, both PD-1 inhibitors, was associated with improved survival in metastatic melanoma patients [9, 10]. Whether a cutaneous eruption in association with Sipuleucel-T correlates with a favorable treatment response in patients with prostate cancer has yet to be determined.

Conclusion

In conclusion, this is the first case, to our knowledge, of an EAC-like eruption reported in a patient treated with an autologous dendritic immunotherapy agent.

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Future studies will need to investigate whether these adoptive cell therapies have similar irAE profiles as current immune checkpoint inhibitors used to treat metastatic melanoma.