

Successful Clinical Remission of Perianal Extramammary Paget Disease with Intralesional IL-2 and Topical Imiquimod Treatment: A Case Report

Savonitto E^{1*}, Giacomantonio C¹, Helyer L¹

Abstract

Extramammary Paget disease is a rare intraepithelial adenocarcinoma that affects mainly in the perianal, genital and axillary regions. While wide local excision remains the gold-standard, not all patients are candidates for extensive surgical management due to metastases, poor baseline function, and patient preference. Herein, we present a case of successful clinical remission in a 63-year-old male with a perianal extramammary Paget disease.

Keywords: Apocrine Sweat Glands; Extramammary Paget Disease; Systematic Chemotherapy

Introduction

Extramammary Paget Disease (EMPD) is a rare intraepithelial adenocarcinoma that typically affects areas rich in apocrine sweat glands such as the genital, perianal and axillary areas. Just like mammary Paget disease, its typical presentation is a long-standing, well-demarcated, pruritic, eczematoid lesion. The diagnosis is confirmed with skin biopsy, histologically demonstrating the periodic acid-Schiff-positive Paget cells. Around 30 to 45% of patients have an underlying invasive carcinoma that correlates to the location of the skin lesion. Because of the risk of an underlying invasive carcinoma, physical exam should include examination of lymph nodes, genital and rectal exam, sigmoidoscopy and cystoscopy [1, 2, 3].

The gold standard treatment of noninvasive lesions remains wide-local excision. Systematic chemotherapy can be used when surgery is contraindicated or when patients opt for conservative management. Studies have shown up to an 83% success rate with the use of docetaxel.

Due to the significant morbidity associated with radical surgery and reconstruction, topical 5-FU, cryotherapy, radiotherapy or argon beam laser can be offered as alternative management options. Because of the rarity of this disease, limited data is available, and these medical options are more often seen as adjuncts to treatment. Topical imiquimod, an immune-response modifier, has been successfully used in a small number of EMPD cases when used as single-agent therapy, adjunct to other medical treatment or in combination with surgery, although evidence is limited to case reports and case series [4, 5, 6].

Intralesional IL-2 is currently being studied in the treatment of cutaneous squamous cell carcinoma and melanoma. IL-2 acts as a cornerstone in the immune response generated against malignant cells. Besides it being a T-cell agonist cytokine, it also promotes CD8⁺ T cell and NK cell cytolytic activity

Affiliation:

¹Department of Surgery, Faculty of Medicine, Dalhousie University, Halifax Regional Municipality, NS, Canada

*Corresponding Author

Savonitto E, Department of Surgery, Faculty of Medicine, Dalhousie University, Halifax Regional Municipality, NS, Canada.

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as well as differentiation of CD4+ T cells into T helper-1 and T helper-2. It additionally promotes the T regulatory cells, leading to induced cell death and thereby limiting inappropriate immune reactions [7]. It was previously used at Dalhousie University in a patient with extramammary Paget Disease of the groin with success [8]. Our current knowledge and experience with intralesional IL-2 was applied to a 63-year-old male who presented with perianal and anal canal extramammary Paget Disease that failed prior management with all forms of medical treatment. His positive response is described below.

Case Description

A 63-year-old healthy male presented to the Surgical Oncology clinic with a five-year history of a perianal rash in the absence of systemic symptoms. On physical exam, the lesion was extending radially from the anal verge at 6 o'clock on about 5-6cm into the anal canal up to the dentate line. Upon biopsy of the skin lesions, the histologic diagnosis of Paget Disease was confirmed. A PET scan demonstrated no evidence of disease outside this area. The patient was offered surgical management including an abdominal perineal resection (APR) and Mohs surgery. Considering the location of the lesion and surgical morbidity associated with these procedures, he opted for medical management. He was initially treated with Retin-A, Aldara, Uremol, Efudex and red light without benefit.

Considering the previous success with IL-2 injections for a patient with EMPD of the groin, the patient was offered an experimental trial of IL-2 injections. Potential flu-like side-effects were reviewed, and the patient was accepting of this.

From July 2019 to September 2019, the patient had 4 needles of 1.6 ml of 400,000 IU/0.1 ml of intralesional IL-2 every 2 weeks with as frequent follow-ups. To monitor the treatment effect, the patient had follow-up every two weeks with progress measured through photographs. After 4 cycles, the lesion appeared clearer and less raised but overall had minimal response. Surgery was again offered but the patient declined. In the context of limited response, a TOLL-receptor antagonist, topical Imiquimod (also known as Aldara) was added to the treatment regimen.

In October and November 2019, the patient was treated with 1.6 ml of 400,000 IU/0.1 mL of IL-2 monthly with the addition of Aldara 5 days/week. The patient continued to have follow-up every 2 weeks. With this regimen, he was found to have significant improvement that included a well-defined reduction in nodularity, but still not at the desired rate. The side-effects were minimal with a 24h post-injection flu-like symptoms.

Clinically, by the end of November 2019 there was a significant inflammatory response of the skin lesion with erythematous changes and softening of the epidermis, which

was promising. Since the clinical response was deemed subpar, the decision was made to increase the frequency and dose of the injections to 2.4 ml of 400,000 IU/0.1 ml either weekly or every 2 weeks as well as Aldara (as previous) and by December 18, 2019, there was a 50% reduction in the tumor size.

Unfortunately, his December appointment was missed and by February 2020, after using Aldara as a single-agent therapy for 2 months, there was circumferential progression the lesion as it was more pronounced, inflamed and pruritic. Weekly injections of 2.4 ml was resumed for 3 weeks. A biopsy was performed in March 2020, confirming the persistence of Paget Disease, but also a new inflammatory response as expected.

In April 2020, the patient had intralesional injections of 1.6 mL or 2.4 mL IL-2 in the remaining diseased-looking skin every 2 weeks with ongoing Aldara treatment. A repeat PET scan performed in April 2020 again didn't show any evidence of a primary source. By May 2020, it was noted that the lesion demonstrated 80% resolution with subjectively healthy-looking previously occupied by Paget disease, By July 2020, >90% of the skin was clinically healthy. The patient had stopped Imiquimod cream in July due to pruritus. The patient continued to get intralesional injections every 2 weeks of either 1.6 mL or 2.4 mL of IL-2 400,000 units/0.1ml.

In September 2020, the patient seemed to have progression of a 1cm patch, with slightly raised and grey-ish tissue. Aldara was restarted, in addition to injections of 0.8 to 1.6 mL of Proleukin 500,000 units/0.1mL every 2 weeks. In October 2020, patient had excellent response with resolution of up to 95% of the initial lesion. Repeat biopsies in October 2020 showed residual Paget cells in the left lower perianal region, where disease was still clinically seen, but fibrotic and inflammatory changes in the normal appearing looking skin in the area previously occupied by Paget Disease. The persistently diseased-looking areas continued to be injected with 1.6 mL Proleukin 500,000 units/0.1ml every 2 weeks.

In December 2020, a rectal exam showed a suspicious white plaque in the anal canal consistent with Paget Disease. Intra-anal injections were initiated in addition to Aldara. Of note, the patient reported a burning sensation at the perianal area associated with the topical application of Aldara, which was felt to be a sign of good inflammatory response.

In February 2021, the perianal and anal canal lesion had completely clinically resolved. It was injected a final time, followed by examination under anesthesia and skin biopsies in June 2021.

A proctoscopy was performed, demonstrating a fairly prominent polyp of the lower 1/3 of anal canal suspicious for Paget Disease. The treated area demonstrated complete resolution. The final pathology of the anal polyp confirmed

a fibroepithelial polyp, and the anal canal biopsies confirmed lichen sclerosus. The perianal, anal and polyp biopsies came back negative for Paget Disease. Intralesional IL-2 and Aldara was then discontinued.

Unfortunately, our patient got lost in follow-up. In October 2021, patient noticed recurrence of the rough areas at the periphery of the original field of disease. Finally seen again in clinic in early April 2022 where four raised areas along the periphery of the left perianal region were found to be clinically convincingly positive for Paget Disease. Aldara was again restarted and 2 needles of 0.8 cc were injected. The patient was again seen 2 weeks later, where he was found to have a great response : this was thought to reflect some memory immunity in conjunction with the immune stabilization from the Aldara. He was again injected with 2 syringes.

In May 2022, the response was even more impressive where three of the four lesions had completely resolved. He was injected with 2 syringes and when seen again 3 weeks later in June 2022, all the lesions had completely responded : the paler sclerotic appearance lesion of most recently healed lesion was again injected with 2 lesions. The patient remains on Aldara.

He was brought back to clinic in June 2022 and there was no evidence of disease on physical exam. He was instructed to discontinue the Aldara for a month until reassess in clinic: no injection was done that day as the results were pleasing. Once again seen in clinic in July: the very impressive completely clinical response remains. Plan is to do close follow-ups with him every 3 months to clinically reassess the area in question and repeat imaging every year. If there is to be any evidence of recurrence, the lesion will be biopsied.



Figure 2: Complete response, biopsy proven, taken intraoperatively in July 2021. Patient in prone position.



Figure 3: Small area of recurrence observed in clinic in April 2022, retreated. Patient in prone position.



Figure 1: Original disease when seen in July 2019. Patient in prone position.



Figure 4: Complete clinical response in the retreated area as of June 2022. Patient in prone position.

Discussion

This paper reports a successful clinical and histological remission of perianal and anal extramammary Paget disease with intralesional IL-2 injections. Confounding factors include the concomitant use of topical Aldara: it is a well-known adjunct to treatment of EMPD and likely contributed to disease remission. However, considering that he had previously been treated with Aldara as a single-agent without success suggests that intralesional IL-2 injections played a role in disease remission. In addition to this, considering that there was clinical disease progression in the first 2 months of 2020 while using Aldara as a single-agent, this further suggests that intralesional IL-2 injections contributed to this patient's remission and that the combination of intralesional IL-2 with Aldara is the most beneficial. Unfortunately, due to the experimental nature of this treatment plan, the quantity of injected IL-2 was based on the surgeon's subjective measurement of disease improvement. Therefore, an objective protocol cannot be established from this case report. Finally, the long-term effect of this treatment is yet to be determined. This patient will need close follow-up and monitoring to determine possible recurrence as EMPD is well known for local recurrence, even after wide-local excision.

Overall, this case demonstrated a positive response with intralesional IL-2 in the management of EMPD. We are hopeful that this will be a potential treatment option for people who are not surgical candidates or who opt for conservative management.

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