Platelet-Rich Plasma Injection of Skin Graft in a Patient with Squamous Cell Carcinoma and Psoriasis on Prolonged Methotrexate Therapy: A Case Report

Florteresa G. Ollero, MD[1], Patricia Cleopatra Geluz Guieb, MD[2], Maria Cristina A. Puyat, MD[2], Maria Isabel Beatriz Puno-Gomez, MD[2], Erika Kim Chan, MD[2]

Abstract

Introduction: Psoriasis and some of its treatments such as methotrexate have been linked to the development of non-melanoma skin cancers including cutaneous squamous cell carcinoma (cSCC). Chronic plaque psoriasis, Koebnerization, and prolonged methotrexate therapy are some of the concerns that may impact wound healing and graft uptake when treating these patients.

Case Report: We report a case of a 64-year-old male with a 32-year history of moderate to severe psoriasis continuously self-medicating with methotrexate for 30 years who presented with a solitary indurated tumor with ulceration on the right anterior leg. Histopathology result revealed acantholytic cSCC. The patient concomitantly has generalized psoriatic plaques that complicated the selection of donor site for the skin graft, and raised concerns on wound healing and graft uptake. He underwent wide excision surgery with gastrocnemius (medial head) flap and split thickness skin graft. Platelet-rich plasma (PRP) injections were utilized post-operatively to increase graft survival and donor site regeneration.

Discussion: The main risk factors for the development of cSCC for this patient are the history of chronic plaque psoriasis and chronic methotrexate therapy. These two can also complicate the success of grafting and wound healing for this patient. PRP was utilized to for better graft survival, faster wound healing, and prevention of Koebnerization.

Keywords: *Platelet-rich plasma, squamous cell cancer, psoriasis, methotrexate*

INTRODUCTION

Psoriasis is a chronic disease characterized by skin inflammation and epidermal hyperplasia. It has multisystemic involvement, and is associated with increased risk of developing arthritis, cardiovascular morbidity, metabolic syndrome, psychosocial challenges (1), and less commonly, nonmelanoma skin cancer (NMSC) (2). Although systemic therapies have resulted in a significant reduction in disease burden for these patients, concerns regarding their association with malignancy persist (3). One of the most highly effective treatment for chronic plaque psoriasis is methotrexate, which has been found to have a 2.8-fold increased risk for NMSC (4). The most common NMSC in immunosuppressed patients is cutaneous squamous cell carcinoma (cSCC) (1). The prevalence of cSCC in patients with psoriasis is not known.

Standard treatment of cSCC is wide excision (5). In patients with active skin inflammation such as psoriasis, concerns on wound healing and successful graft uptake arise. Koebnerization may also occur in the donor site (6). Furthermore, there are uncertainties on the effects of methotrexate on wound healing and successful graft uptake (7).

We report a case of a 64-year-old male with chronic plaque psoriasis who developed cSCC. The patient underwent wide excision with flap and skin graft, and platelet-rich plasma was utilized to ensure good wound healing and successful graft uptake.

[1] *Resident, Department of Dermatology, Rizal Medical Center*
[2] *Consultant, Department of Dermatology, Rizal Medical Center*

CASE REPORT

A 64-year-old male with a 32-year history of chronic plaque psoriasis, on chronic methotrexate therapy with a cumulative dose of 4,000 mg, presented with a 10-month history of slow growing tumor on the right anterior leg. The lesion started as a yellow to brown, tender plaque, which was unresponsive to initial treatment with antibiotics. In the interim, there was a gradual increase in size, evolving into a brownish, ulcerated tumor. Notably, the patient had 40- pack year history of smoking, and no history of chronic UV exposure, though he underwent 30 sessions of narrowband UVB phototherapy 26 years prior. Progression prompted referral to our institution for further evaluation.

Cutaneous examination revealed a solitary, well-defined, brownish tumor with an overlying ulceration, measuring 3x3 cm on the right anterior leg (Figure 1). His psoriasis was also in flare, presenting as multiple, well-defined erythematous plaques with white adherent scales all over the body, onychodystrophy, and palmoplantar keratoderma (Figure 2.). Incisional biopsy of the tumor revealed neoplastic squamous cells invading into the underlying dermis, mild to moderate nuclear pleomorphism, enlarged round to oval hyperchromatic to vesicular nuclei, prominent nucleoli, detached neoplastic keratinocytes, and occasional keratin pearls (Figure 3). The clinical and histopathologic findings were consistent with acantholytic squamous cell carcinoma, well-differentiated. The patient was then referred to General Surgery for wide excision with skin graft.

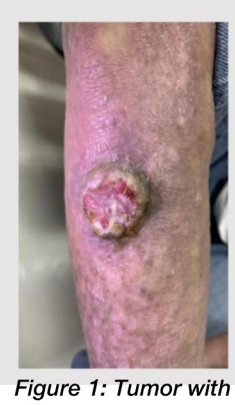

Figure 1: Tumor with ulceration on the right pretibial area

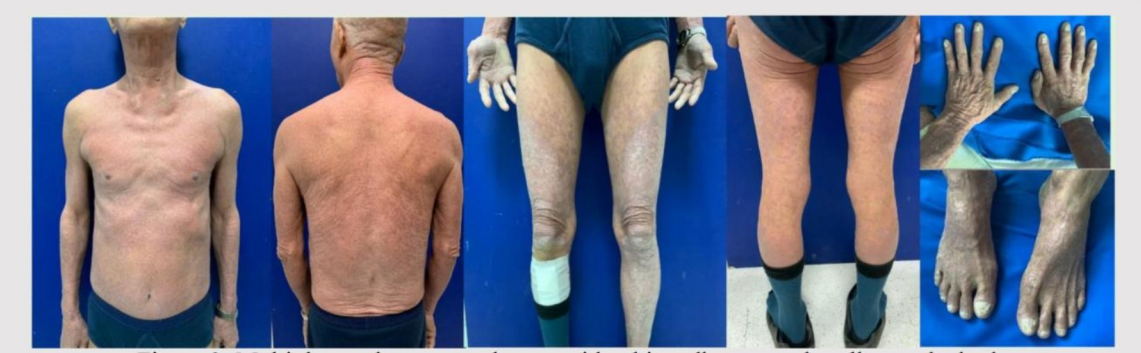

Figure 2: Multiple, erythematous plaques with white adherent scales all over the body

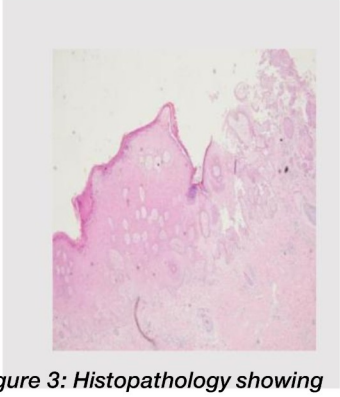

Figure 3: Histopathology showing acantholytic squamous cell carcinoma

Selection of the donor site for the skin graft was complicated by the patient's ongoing psoriasis flare. The right anterior thigh was selected as the donor site as it had less erythematous plaques compared with his trunk and upper extremities. Methotrexate 10 mg/week was continued, and clobetasol propionate 0.05% cream was applied on the area twice daily for 2 weeks prior to surgery to further decrease the inflammation. Wide excision with frozen section was done leaving a skin defect of 7 x 7 cm. Lazy S incision was done on the posterior part of the right leg, and a gastrocnemius (medial head) flap was created, which was applied on the wound bed. Split thickness of 0.6 cm graft was harvested from the right medial thigh, and was apposed to the wound bed (Figure 4).

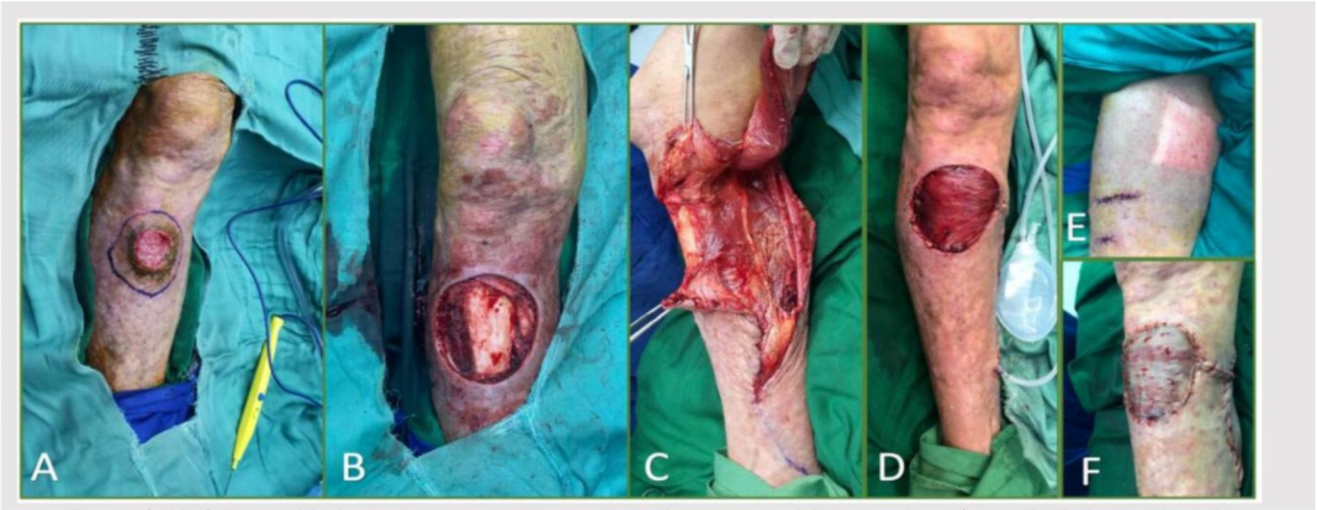

Figure 4: (A) 3.5 cm wide fungating tumor with marking of nearest excision margin at 1 cm. (B) 7x7 cm skin defect. (C & D) Gastrocnemius (medial head) flap. (E) 0.6 cm split thickness skin graft. (F) Skin graft apposed to the wound bed

On the 12th postoperative day, the recipient site showed partial separation of the edges of the incision site and yellow devitalized tissue were noted on the medial part of right leg (Figure 5) although there was no evidence of infection and graft failure. On the other hand, the donor site showed no evidence of extension or flare-up. To facilitate wound healing and increase graft survival, debridement of the yellow devitalized tissue was done, and platelet-rich plasma (PRP) was then injected intradermally on both the donor and recipient sites. He was monitored and treated with PRP every week. On his 33rd postoperative day and after his 4th PRP injection, the recipient site showed better graft survival, wound healing, and almost complete coaptation of the graft and surrounding normal skin. There was decrease in the size of previously dehisced wound with less edema and erythema. The donor site showed re-epithelialization (Figure 6).

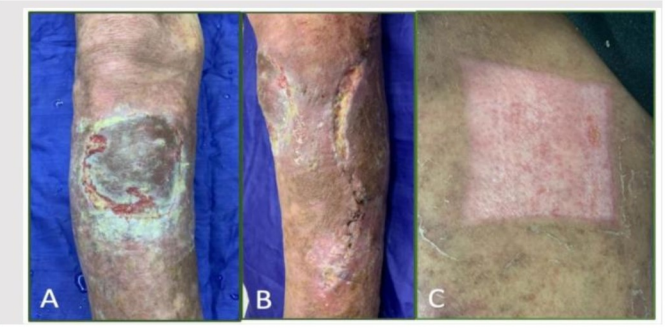

Figure 5. (A&B) Pre-PRP injection of recipient site (C) Pre-PRP injection of donor site

On follow-up, the patient had intermittent flares of psoriasis for which he was treated with methotrexate and topical steroids. The grafted site continued to heal which showed less hyperpigmentation and better texture (Figure 7). Additionally, the psoriasis lesions eventually showed improvement.

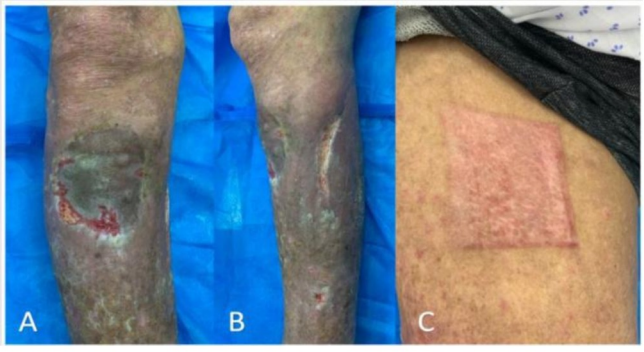

Figure 6. 33 days postoperative and after 4th PRP injection. (A&B) recipient site (C) Donor site

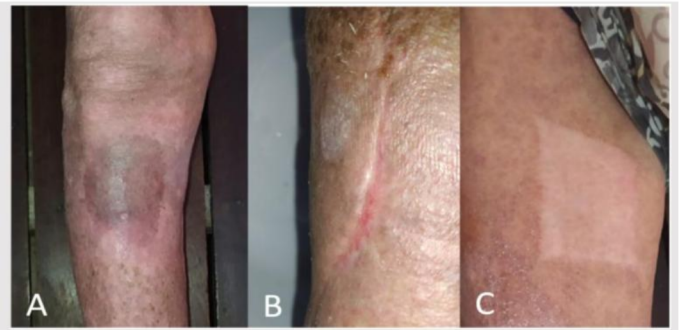

Figure 7. 104 days postoperative and 69th day from the 4th PRP injection. (A&B) recipient site (C) donor site (photos sent by the patient via teledermatology)

DISCUSSION

cSCC is the second most common skin cancer in immunocompetent individuals but the most common skin cancer in the immunosuppressed. Although the main environmental risk factor for cSCC is UV exposure, other risk factors include light skin complexion, exposure to arsenic or environmental carcinogens, immunosuppression, chronic use of photosensitizing drugs, long-term therapy with psoralen plus UVA radiation, HPV infection, and chronic inflammation of the skin (1).

For our patient, it appears that the main risk factors for the development of cSCC are the history of chronic plaque psoriasis and chronic methotrexate therapy. The link between psoriasis and the risk of NMSC is still unknown although one study by Wang et al. found out that patients with psoriasis had 1.72 times higher risk of developing NMSC (2). Aside from phototherapy, several therapeutic options for psoriasis, such as methotrexate, cyclosporine, and tumor necrosis factor-a inhibitors, have also been associated with increased malignancy risk (3). However, studies on methotrexate show conflicting findings. A study by Filippos et al. found that the use of methotrexate was linked to an elevated incidence of cSCC in patients with psoriasis. (8). Lang et al similarly found that both psoriasis and the use of methotrexate are associated with an increased risk of NMSC (4). However, a more recent study by Geller et al. showed that there was no increased risk for malignancy with low-dose methotrexate monotherapy of <30 mg/week orally, or 17.5–22.5 mg/week subcutaneously (3).

The primary therapeutic option for cSCC is wide excision (5). Skin graft transplantation is recommended for larger defects to improve cosmetic outcomes, as was the case for our patient. There is limited evidence on performing skin grafting in the background of chronic inflammatory diseases such as psoriasis. Due to the active psoriatic lesions on the donor site, there were several concerns regarding the success of skin grafting in active skin inflammation, including delay in wound healing, the possibility of Koebner phenomenon, and the risk of developing of psoriatic plaques on the graft. (6) Furthermore, there were uncertainties on the effects of methotrexate on wound healing and graft uptake (7).

The potential for poor wound healing may be explained by the pathophysiology of psoriasis with inappropriate activation of cutaneous cellular immunity inducing hyperplasia of keratinocytes with rapid and incomplete differentiation (6). However, Young et al. revealed no significant differences in the healing of traumatic wounds between psoriasis patients and non-psoriasis patients (6). In addition, in vitro and experimental studies suggest that methotrexate adversely affects wound healing. There was one report of graft failure possibly due to methotrexate therapy (7). In contrast, another study showed that low-dose methotrexate is safe and does not affect the incidence of postoperative wound complication (9).

Although current evidence is limited, platelet-rich plasma (PRP) injection has been shown to increase graft take. Several studies have been done PRP for diabetic foot ulcers, venous leg ulcers and burns (10). However, data regarding the use of PRP as an adjunct treatment for skin graft in the context of cSCC and psoriasis is lacking. PRP is an autologous blood-derived biomaterial that has 2- to 6- fold concentration of platelets, multiple growth factors (PFGF, EGR) and anti-inflammatory components. It promotes wound closure, stable adhesion of skin graft and increase oxygen diffusion. In addition, they may play a significant role in inhibiting infection (10). These could contribute to better

graft survival and faster healing of the wound. After several sessions of PRP in our patient, we noted graft take, contraction of the previously dehisced wound, faster regeneration of the donor site, and prevention of Koebnerization.

After treatment for cSCC, the National Comprehensive Cancer Network (NCCN) advises regular follow up, sun-protective measures, and frequent self-examination of the skin. Patients with a history of cSCC have a higher risk of developing new cSCC. Regular follow up every 3-12 months for 2 years is essential for early detection of new lesions (11). Our patient is regularly monitored and had no recurrent or new cSCC after 4 months post-operation.

CONCLUSION

Several studies have linked psoriasis and methotrexate to the development of cSCC. As such, it is important to conduct regular full body examination of the skin on psoriasis patients with a risk for developing cSCC. Surgical management is the treatment of choice for cSCC. Due to limited evidence, there are no guidelines for the treatment of psoriasis patients with concomitant cSCC despite concerns of poor wound healing and poor graft uptake. Though further studies are needed to strengthen the evidence, PRP injection appears to be a promising adjunct treatment to improve wound healing and graft survival in these patients.

REFERENCES

1. Kang S. Fitzpatrick's Dermatology, Ninth Edition. 9th Editio. Vol. 148. McGraw-Hill Education / Medical; 2019. 148–162 p.
2. Wang X, Liu Q, Wu L, Nie Z, Mei Z. Risk of non-melanoma skin cancer in patients with psoriasis: An updated evidence from systematic review with meta-analysis. J Cancer. 2020;11(5):1047–55.
3. Geller S, Xu H, Lebwohl M, Nardone B, Lacouture ME, Kheterpal M. Malignancy risk and recurrence with psoriasis and its treatments: A concise update. American Journal of Clinical Dermatology. 2017;19(3):363–75.
4. Biscaldi L. Methotrexate therapy in psoriasis increases nonmelanoma skin cancer risk [Internet]. Dermatology Advisor. 2021 [cited 2021 Oct2]. Available from: https://www.dermatologyadvisor.com/home/meetings/aad-2021/psoriasis-treatment-associated-with-elevated-skin-cancer-risk/
5. Zhang G, Bu W, Wang S, Li X, Wang S, Li F, et al. Autologous full-thickness skin graft for treating squamous carcinoma in a patient with psoriasis. Medicine (Baltimore). 2020 Sep 25;99(39):e22252.
6. Scupham L, Ingle A. Split thickness skin graft in active psoriasis in patient with clear cell