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Acute worsening of dermatomyositis after initiation of PARP inhibitor therapy in two women with advanced ovarian malignancy

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1. Introduction

Dermatomyositis (DM) is a rare autoimmune condition that most commonly presents with symmetric proximal muscle weakness and skin findings of Gottron's papules, heliotrope eruption, and pink-violaceous erythema of the upper torso, limbs, and neck (Dalakas and Hohlfeld, 2003). DM can have a significant impact on patient's quality of life and in severe cases lead to an inability to perform activities of daily living (Dalakas and Hohlfeld, 2003). Most cases are idiopathic, but 4–9% of cases have been associated with malignancy—especially ovarian, lung, breast, and colorectal cancers (Yang et al., 2015). The association between malignancy and dermatomyositis is still not well understood but the target antigens in affected tissue are also present in high levels in related tumors (Chen et al., 2014).

Case reports and series have described the acute worsening of paraneoplastic syndromes, especially DM, after the initiation of treatment for the underlying malignancy (Chen et al., 2014; Manson et al., 2019; Yoshino et al., 2013; Otsuka et al., 2017). The initiating factor in these cases is complicated by certain medications having been known to trigger or worsen DM (Chen et al., 2014). However, in these cases removal of the inciting agent led to improvement in disease severity and reintroduction again triggered a progression of the disease (Chen et al., 2014). In other cases, the worsening of DM severity appeared to be independent of chemotherapy administration after the initial period. The proposed mechanism was exposure of a large volume of antigen in the tumor cells leading to worsening autoimmunity, possibly in the manner similar to a "tumor lysis syndrome" (Manson et al., 2019; Yoshino et al., 2013; Otsuka et al., 2017).

In this series we present the cases of two women, both with ovarian malignancy status post-surgical management and adjuvant chemotherapy who developed acutely worsening dermatomyositis within a week of starting Olaparib.

2. Case 1

A 53-year-old with a history of stage IIIC high-grade serous ovarian cancer status post definitive surgical management and six cycles of carboplatin, paclitaxel, and bevacizumab was found to have no evidence of disease on imaging along with a normal Cancer Antigen (CA) 125 at her end of treatment follow-up scans. Tumor testing revealed a somatic BRCA mutation, germline negative. She was placed on Olaparib for maintenance therapy. She developed a violaceous rash on her hands, arms, and buttocks that she first noticed a week after initiating therapy. Prior to this she had noticed intermittent involvement of her hands that self-resolved. The rash progressively worsened to the point it involved a significant portion of her hands, face, extensor surfaces, and buttocks with pruritus impacting her sleep and quality of life. She contacted her care team approximately three weeks after initiating treatment and was told to discontinue taking Olaparib.

Over the next month she had minimal improvement in her cutaneous symptoms and developed slowly worsening proximal muscle weakness and ultimately dysphagia for which she was admitted for inpatient management. There she was found to have significant elevations in creatinine kinase (CK > 8000) and mildly elevated liver enzymes.

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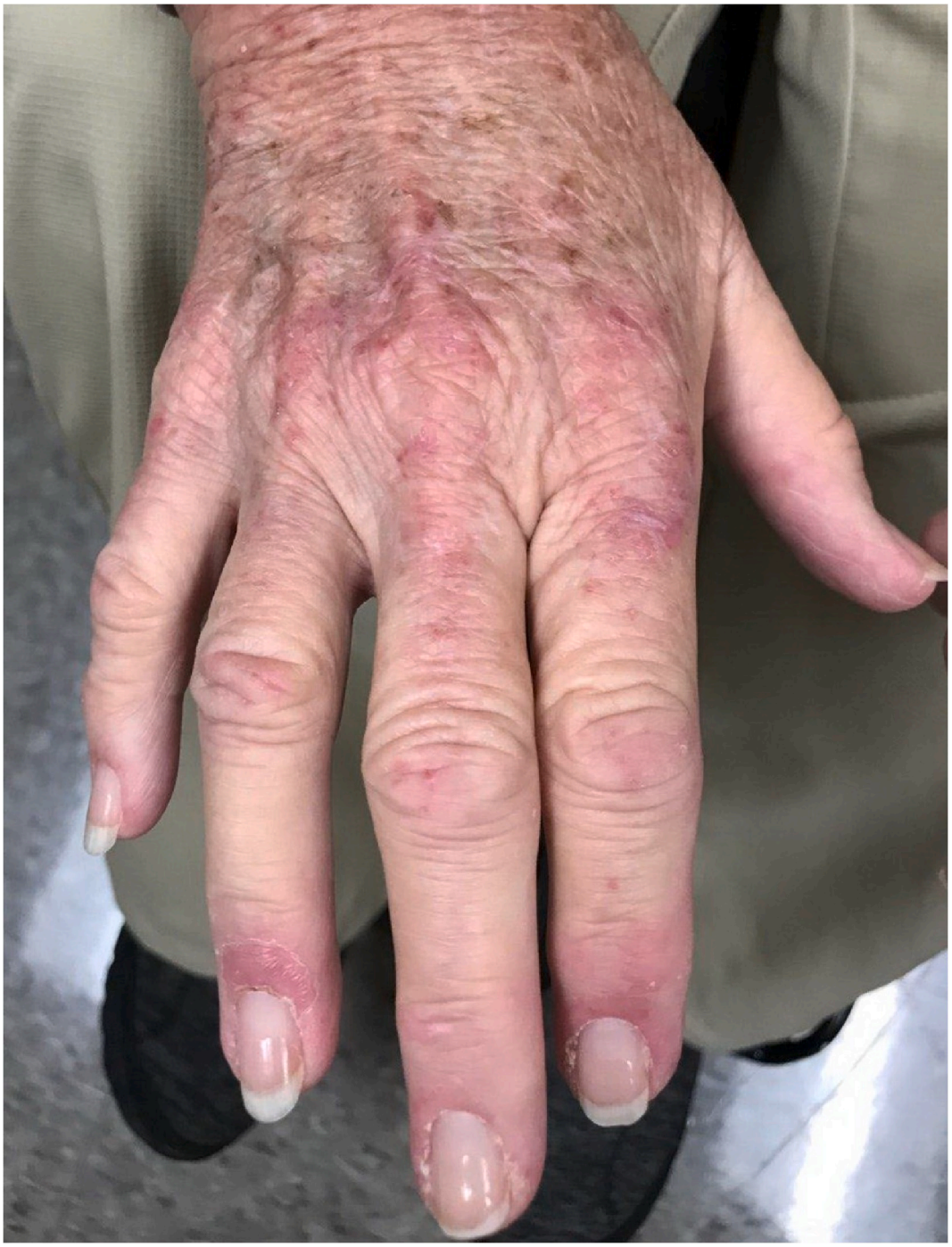

Image 1. Gottron's Sign on Hands.

Muscle and skin biopsies were consistent with myositis and interface dermatitis leading to a diagnosis of DM. The dysphagia had progressed to the point she had lost over 20 lb and required enteral feeding through nasogastric and ultimately percutaneous endoscopic gastrostomy (PEG) tube. She was initiated on Intravenous Immunoglobulin (IVIG) and solumedrol with significant improvement of her cutaneous and muscular symptoms over the subsequent four months. Ultimately, steroids were slowly tapered but she remained on low dose steroids. Once progression was confirmed (approximately 7 months after completion of primary therapy) she was started on platinum-based chemotherapy and completed 6 cycles with a partial response. She was then started on niraparib maintenance therapy, however after 2 cycles her CA-125 and imaging showed progression of disease. Although she initially responded well again to weekly paclitaxel/bevacizumab, she developed progression and ultimately enrolled on hospice and passed approximately 2.5 years after her primary debulking surgery.

3. Case 2

A 65-year-old with a history of stage IIIC high grade serous ovarian cancer status post-surgical management who presented after 6 cycles of carboplatin, paclitaxel, bevacizumab, and atezolizumab and 14 cycles of atezolizumb/bevacizumab/placebo maintenance therapy on clinical trial. Imaging showed recurrence on her right vaginal cuff and corresponding lymphadenopathy in the right external iliac chain. She then enrolled in a clinical trial and was randomized to Olaparib single agent.

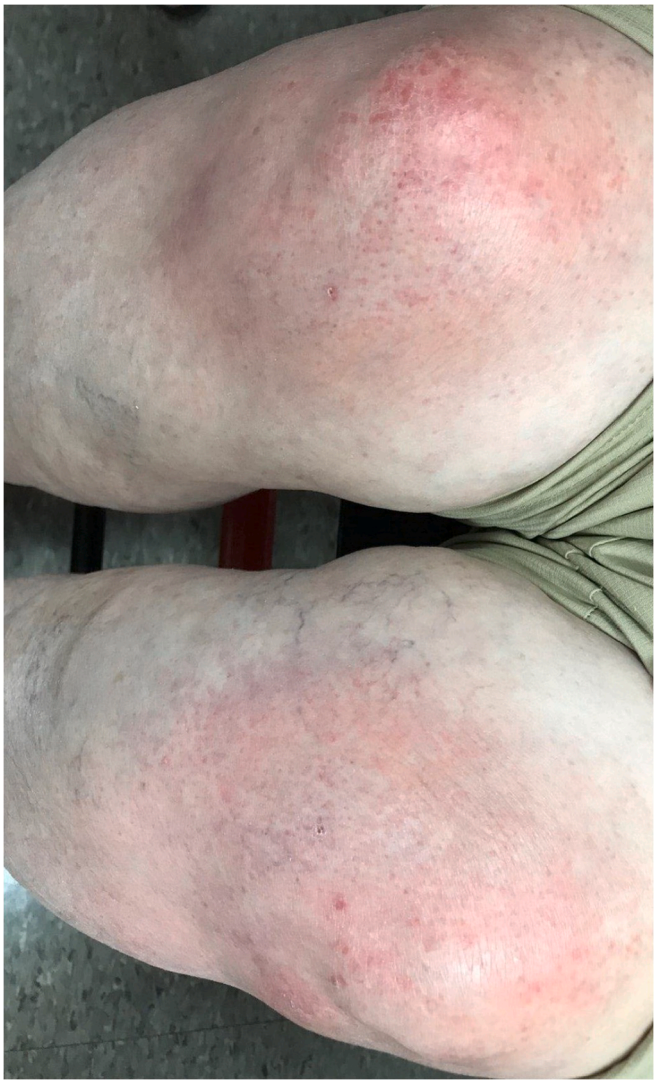

Image 2. Gottron's Sign on Knees.

Approximately one week after initiating Olaparib she had progressive worsening of a previously mild pruritic rash on her upper extremities that had been diagnosed on biopsy two months prior as chronic atopic dermatitis with superimposed lichen simplex chronicus. This quickly progressed to include the face, neck, and back despite topical steroids. Olaparib was held at this point given the temporal relationship to onset of symptoms. Over the following 3 weeks she had rapidly progressing proximal muscle weakness to the point she had difficulty getting up out of a chair, raising her arms, and ultimately dysphagia. Due to high suspicion for DM creatinine kinase (CK), C-Reactive Protein (CRP), and erythrocyte sedimentation rate (ESR) were drawn, and all found to be markedly elevated. Of note, paraneoplastic panel was negative. She was rapidly started on oral steroids (prednisone 1 mg/kg) and referred to Rheumatology. Exam findings were notable for alopecia, heliotrope eruption,[1] facial erythema, Gottron's papules + sign (Images 1 and 2), photo-distributed poikiloderma (shawl and V signs) (Image 3), periungual erythema, and proximal muscle weakness. A presumptive diagnosis of DM was made; she was continued on high dose prednisone and was recommended to start IVIG. She was referred for skin and muscle biopsies which confirmed the diagnosis.

[1] A distinctive erythematous or violaceous rash on the periorbital skin often accompanied by eyelid edema.

She quickly improved with steroids and was never initiated on IVIG given her rapid response to steroids. Steroids were tapered with a total duration of therapy of 92 days. At two-month follow-up both her cutaneous symptoms and muscle weakness had improved to her baseline prior to cycle 1 of Olaparib. Her dysphagia had essentially resolved as well. A discussion was held with the patient about the suspected indirect relationship between Olaparib and the worsening of her DM. She was amenable to resumption of Olaparib after holding it for 2 weeks. She was reinitiated with a dose reduction due to fatigue (200 mg bid). As of the time of writing she has tolerated nine additional cycles of dose reduced Olaparib with no recurrence of DM symptoms and remains without systemic steroids. Her ovarian cancer responded well to treatment with a partial response at 76.5% decrease in total tumor volume as of cycle 9. Interestingly, CA-125 initially increased from starting Olaparib, but as she her DM symptoms improved, her CA-125 also improved (from 64 prior to cycle 1, peaked at 164 after cycle 1, and normalized down to 18 as of cycle 9).

4. Discussion

Both patients developed acute worsening of DM within a week of initiating Olaparib. Interestingly, for both patients the characteristic rash occurred just a few weeks prior to their diagnosis of platinum sensitive recurrent high grade serous ovarian cancer. Neither had been formally diagnosed DM prior to treatment, but upon further discussion with the patients they reported stable rashes and symptoms of likely DM for weeks to months prior to starting therapy. There was quick improvement with systemic steroids and IVIG and no improvement with holding Olaparib initially alone. Additionally, both appear to have had good initial responses to PARP inhibitor therapy as evidenced by tumor markers and imaging. Rapid activation of symptoms may particularly occur in patients with a germline or somatic BRCA mutation. In this population, the objective response rate to Olaparib after 2-3 prior lines is 78.5% (Penson et al., 2020). Resumption of PARP inhibitor treatment did not result in a worsening of their DM, even when not taking systemic steroids or other DM specific treatment. These findings are suggestive of an indirect relationship between Olaparib and their acute DM presentation. We hypothesize that they both had preexisting dermatomyositis which was acutely exacerbated by a large volume of antigen cross reactivity similar to a "tumor lysis like syndrome" (Chen et al., 2014; Manson et al., 2019; Yoshino et al., 2013; Otsuka et al., 2017). A similar phenomenon has been described in patients with a wide range of cancers treated with PD-1 or PD-L1 immunotherapies as well as in cancers treated with traditional chemotherapeutic agents such as carboplatin/etoposide or 5-Fluorouracil. Certainly, the rash can easily be confused for drug toxicity. While light sensitivity can be seen with this class of drugs, occurrence of a rash in this distribution with accompanying proximal muscle weakness would be unusual.

This finding has not been previously described in the literature with PARP inhibitors but has been described with other chemotherapeutic agents, particularly with DM (Chen et al., 2014; Manson et al., 2019; Yoshino et al., 2013; Otsuka et al., 2017). It is unclear why DM is particularly prone to this phenomena, but ovarian cancer has one of the strongest associations with DM and providers should have a high suspicion when patients present with rash, fatigue, muscle weakness and myalgias, especially soon after initiating treatment in these patients (Yang et al., 2015). A thorough review should be undertaken to screen for DM so that it can be treated prior to initiation. Initial work up should include complete blood count with differential, comprehensive metabolic panel, thyroid stimulating hormone, CK, ESR, CRP, and myositis autoantibody panel, and myositis-associated autoantibody panel. Consultation with specialists should be performed depending on distribution of symptoms (Rheumatology, neurology, dermatology). If an acute exacerbation of DM does occur, consideration should be given to not stopping the PARP inhibitor while DM specific treatment is initiated. Providers should keep dermatomyositis in their differential diagnosis

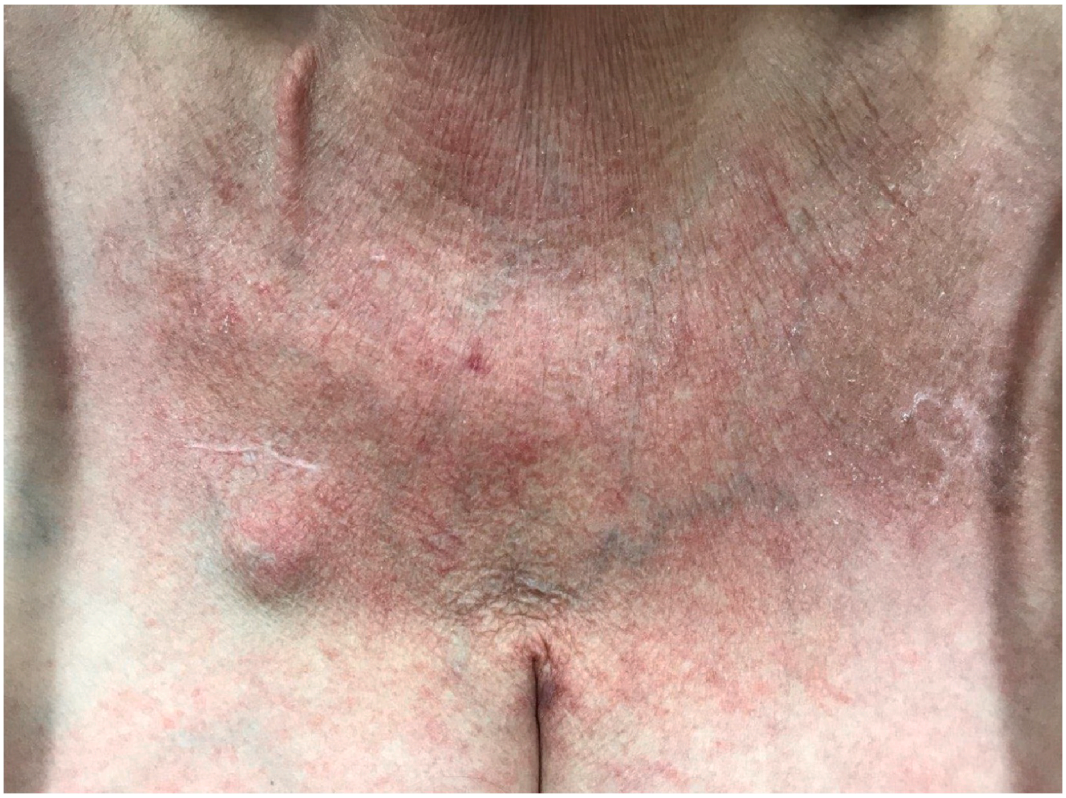

Image 3. Shawl Sign.

and avoid erroneously stopping potentially effective anti-cancer therapy as signs and symptoms of drug toxicity and emerging paraneoplastic syndromes such as dermatomyositis can overlap.

5. Consent

Both patients gave consent for this case series

Author contributions

SG and FB participated in developing the concept, study design, writing & editing of the manuscript along with literature review.

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.

References

Chen, F.W., Zhou, X., Egbert, B.M., Swetter, S.M., Sarin, K.Y., 2014. Dermatomyositis associated with capecitabine in the setting of malignancy. J. Am. Acad. Dermatol. 70 (2), e47–e48. https://doi.org/10.1016/j.jaad.2013.10.025.

Dalakas, M.C., Hohlfeld, R., 2003. Polymyositis and dermatomyositis. Lancet (London, England). 362 (9388), 971–982. https://doi.org/10.1016/S0140-6736(03)14368-1.

Manson, G., Maria, A.T.J., Poizeau, F., Danlos, F.-X., Kostine, M., Brosseau, S., Aspeslagh, S., Du Rusquec, P., Roger, M., Pallix-Guyot, M., Ruivard, M., Dousset, L., Grignou, L., Psimaras, D., Pluvy, J., Quéré, G., Grados, F., Duval, F., Bourdain, F., Maigne, G., Perrin, J., Godbert, B., Taifas, B.I., Forestier, A., Voisin, A.-L., Martin-Romano, P., Baldini, C., Marabelle, A., Massard, C., Honnorat, J., Lambotte, O., Michot, J.-M., 2019. Worsening and newly diagnosed paraneoplastic syndromes following anti-PD-1 or anti-PD-L1 immunotherapies, a descriptive study. J. Immunother. Cancer. 7 (1) https://doi.org/10.1186/s40425-019-0821-8.

Otsuka, Y., Watanabe, H., Kano, Y., Tatebe, N., Sunahori-Watanabe, K., Kawabata, T., Sada, K.-e., Wada, J., 2017. Occurrence of dermatomyositis immediately after mastectomy subsequent to severe chemotherapeutic drug eruption. Intern. Med. 56 (24), 3379–3383. https://doi.org/10.2169/internalmedicine.9194-17.

Penson, R.T., Valencia, R.V., Cibula, D., Colombo, N., Leath, C.A., Bidziński, M., Kim, J.-W., Nam, J.H., Madry, R., Hernández, C., Mora, P.A.R., Ryu, S.Y., Milenkova, T., Lowe, E.S., Barker, L., Scambia, G., 2020. Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): a randomized phase III trial. J. Clin. Oncol. 38 (11), 1164–1174. https://doi.org/10.1200/JCO.19.02745.

Yang, Z., Lin, F., Qin, B., Liang, Y., Zhong, R., 2015. Polymyositis/dermatomyositis and malignancy risk: a metaanalysis study. J. Rheumatol. 42 (2), 282–291. https://doi.org/10.3899/jrheum.140566.

Yoshino, Y., Akiyama, S., Ouchi, K., Oishi, T., Takahashi, H., Lee, J., Takahashi, S., Shimodaira, H., Kato, S., Ishioka, C., 2013. Acute exacerbation of paraneoplastic neurological syndrome after massive tumor lysis of neuroendocrine carcinoma by chemoradiotherapy. Int. Cancer Conf. J. 2 (4), 247–250. https://doi.org/10.1007/s13691-013-0100-3.