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CASE REPORT

A Case of Punctate Psoriasis Following Treatment with Cetuximab in a Patient with Metastatic Gastric Adenocarcinoma

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Background: In contemporary times, malignancies characterized by metastatic growth have been subjected to innovative therapeutic approaches involving immunological agents known as Programmed Death Receptor 1 (PD-1) inhibitors. Notwithstanding their remarkable immunotherapeutic effectiveness, these treatments can give rise to undesirable immune-related effects. Sintilimab, a PD-1 inhibitor sanctioned for marketing by the Chinese National Medical Products Administration in 2018, has been associated with 51 reported cases of adverse reactions on the market, excluding psoriasis, up to the present moment.

Case Description: Herein, we report the clinical characteristics of a patient with metastatic gastric adenocarcinoma who developed guttate psoriasis after receiving Sintilimab. The patient was an elderly male presenting with papules varying in size from that of rice grains to soybeans, accompanied by scattered erythematous lesions across his body. Notably, an atypical Auspitz's sign was observed, wherein certain lesions were covered with a minimal amount of scale, coupled with reported persistent itching. The progression of the disease manifested within a span of one week.

Conclusion: PD1 inhibitors have been associated with the recurrence, exacerbation, or new onset of psoriasis. Consequently, a personal or family history of psoriasis is an essential risk factor that needs to be considered before PD1 inhibitor medication, which helps with the early diagnosis of psoriasis. Early diagnosis of new-onset guttate psoriasis poses challenges. An early consultation with a dermatologist is recommended, and a conclusive diagnosis can be obtained through a histopathologic examination.

Keywords: adverse drug reactions, PD-1 inhibitors, psoriasis, sintilimab

Introduction

PD-1, a receptor known for its inhibitory effects, is predominantly expressed in T lymphocytes.[1] It binds to specific ligands on the surface of tumor cells (PD-L1/PD-L2) and promotes the immune escape of tumor cells. Currently, a frequently utilized immunotherapeutic strategy for managing metastatic malignancies involves targeting the PD-1 pathway to alleviate its suppression of the immune system.

Psoriasis is an immune-mediated chronic inflammatory disease whose pathogenesis is related to a variety of immune cells and cytokines. Among them, Th1 and Th17 lymphocytes play a critical role in the pathogenesis of psoriasis.[1] Studies in this field have demonstrated that PD-1 inhibitors alleviate the inhibitory effects of PD-1 on Th1/Th17 cells, resulting in the overexpression of IL-17 and triggering skin reactions such as psoriasis.[2] Through a search of the literature, we found that navulizumab[2] and pabolizumab[3] have been implicated in a number of foreign case reports of PD-1 inhibitor-associated psoriasis. In contrast, there were no case reports of psoriasis induced by China-made PD-1 inhibitors. Sintilimab is a PD-1 inhibitor approved for marketing by the Chinese National Medical Products Administration in 2018. Here, we report a case of Sintilimab-induced psoriasis as follows:

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Case Presentation

The patient was a 63-year-old male. There were multiple scattered guttate erythemas and papules distributed across his body, accompanied by persistent itching for a duration of one week. On April 16, 2020, the patient underwent a laparoscopic distal gastrectomy to treat "differentiated adenocarcinoma of the gastric antrum." Subsequent regular check-ups revealed multiple metastases in the cervical and mediastinal lymph nodes. The patient has been receiving 200 mg of the PD-1 inhibitor Sintilimab every three weeks for five cycles as of April 2021. The patient experienced sporadic erythemas and papules with multiple guttate lesions after completing the fifth cycle. Some of the lesions exhibited whitish scales and were accompanied by itching. There was no fever or joint pain. On August 4, 2021, when the patient sought consultation at the dermatology department, considering the possibility of guttate psoriasis, a skin biopsy was conducted for a comprehensive evaluation. The patient was in good physical health, had no prior personal history of psoriasis, and denied any family history of the condition. Clinical assessment: The patient's overall health was satisfactory, marked by the absence of fever. Dermatological evaluation: revealed erythematous lesions and papules on the trunk and limbs, accompanied by minor scales, varying in size from rice grains to soybeans (refer to Figure 1). The body surface area (BSA) involvement is 8%, the Psoriasis Area and Severity Index (PASI) is 6.5, and the Physician Global Assessment (PGA) is 2.3. Laboratory analysis: including blood routine, urine routine, biochemistry, and other parameters, demonstrated normal results. Histopathology of skin lesion: There was excessive keratinization, incomplete keratinization, and neutrophilic microabscesses within the stratum corneum; irregular hyperplasia of the epidermis, local spongiosis, thinning or absence of granular layer, neutrophilic pustules within the epidermis, dilated dermal papillary blood vessels, and infiltration of neutrophils and lymphocytes in the surrounding area (see Figure 2).

Diagnosis

The patient was diagnosed with guttate psoriasis vulgaris. Subsequently, the PD-1 inhibitor Sintilimab was replaced with a combination of Irinotecan and capecitabine. The prescribed treatment regimen included an intravenous infusion of 80 mg of compound glycyrrhizin once daily for one week, along with the application of epidermic mometasone furoate cream combined with mucopolysaccharide polysulfate cream twice daily for two weeks. Remarkably, the majority of the rash vanished, and the itching subsided within this two-week period. Subsequent follow-ups confirmed the complete disappearance of the rash.

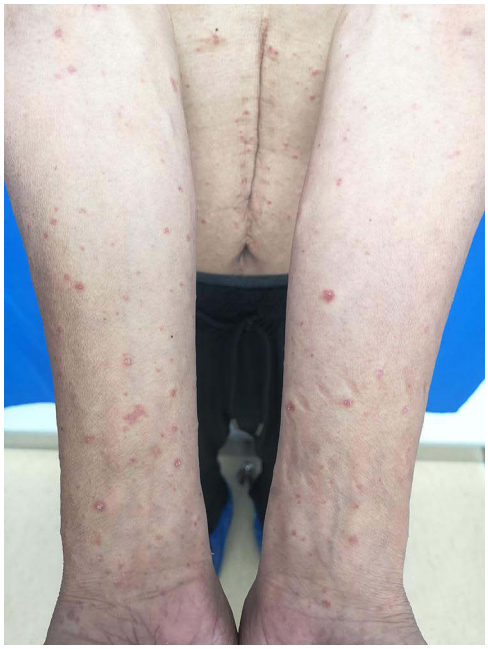

Figure 1 Scales, erythema, and papules on the trunk and limbs that range in size from rice grains to soybeans.

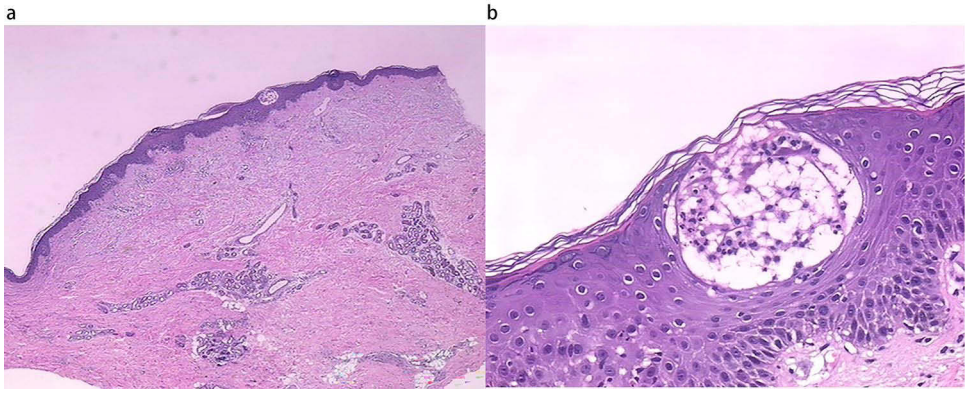

Figure 2 (**a**) (X low magnification) (**b**) (X high magnification). Pathology examination: Excessive keratinization, incomplete keratinization, and neutrophilic microabscesses within the stratum corneum; irregular hyperplasia of the epidermis, local spongiosis, thinning or absence of granular layer, neutrophilic pustules within the epidermis, dilated dermal papillary blood vessels, and infiltration of neutrophils and lymphocytes in the surrounding area.

Discussion

Exhibiting lesions characterized by dispersed erythematous macules and papules, varying in size from that of rice grains to soybeans, distributed across his entire body. Notably, an atypical Auspitz's sign was observed, where certain lesions were covered with a minimal amount of scale, accompanied by reported persistent itching. The disease had progressed over the course of one week. The patient had no prior personal history of psoriasis, nor was there any family history of the condition. The histological examination displayed characteristic features indicative of psoriasis. Consequently, a diagnosis of punctate psoriasis vulgaris was established, with the PD-1 inhibitor Sintilimab identified as the causative factor. The Naranjo score was 5. Early clarification of such diagnoses can be achieved through timely histopathological examination of skin lesions, especially in patients suspected of having early-stage psoriasis.

Sintilimab, a PD-1 inhibitor approved for marketing by the Chinese National Medical Products Administration in 2018, has demonstrated its efficacy as an immunotherapy for various malignant tumors. Nevertheless, it is important to note that immune-associated adverse effects may also manifest as a result of its administration. From the time Sintilimab was listed until June 2022, a total of 51 adverse reactions were reported. Of those, 10 cases or 15.15%, were cutaneous adverse reactions, including 6 cases of rash, 1 case of toxic epidermal necrolysis, 1 case of Stevens-Johnson syndrome, 1 case of purpura, and 1 case of vitiligo. No cases of psoriasis had yet been reported.[4]

PDL1 is expressed in the cytoplasm and plasma membrane of a range of malignant tumor cells, while PD-1 molecules are primarily expressed in activated T cells. PD-1 binds to PDL1, their ligand, and transmits negative costimulatory signals to thwart lymphocyte activation and proliferation. This process weakens lymphocytes, rendering them ineffective and leading to apoptosis. Additionally, it exerts peripheral immune-suppressive effects, inhibiting normal immune responses in tumor cells.[5] On the other hand, T cells (especially Th1 and Th17) play an important role in the pathogenesis of psoriasis, and PD-1 inhibitors can strongly affect the Th1/Th17 pathway, leading to the overexpression of IL-17, resulting in the typical inflammatory cascade response,[6–8] thus inducing the development or exacerbation of psoriasis, particularly in individuals with a personal or pertinent family history of the disease.

An instance of a psoriasis-like rash brought on by the PD-1 inhibitor pembrolizumab used to treat squamous cell lung carcinoma was reported by Chen et al in China. After the onset, the dosage of pembrolizumab was reduced to 100 mg, administered every 4 weeks. Topical calcipotriol ointment and hydrocortisone butyrate cream were used in combination, along with narrow-band medium-wave ultraviolet radiation (NB-UVB) twice weekly. Within a span of two weeks, most of the erythema and scales had diminished, and the intensity of itching was notably reduced. Subsequently, by the end of the third month, the symptoms had significantly subsided.[9] Dimitra et al reported 5 cases of psoriasis induced by anti-PD -1/PD-L1 therapy. Among them, 2 cases had a personal history of psoriasis, 2 cases had a family history of psoriasis, and 1 case had no personal or family history of psoriasis. All 5 cases exhibited manifestations of psoriasis vulgaris; among them, 1 case had concurrent psoriatic arthritis, 2 cases experienced improvement after discontinuing PD-1 inhibitors, and 2 cases continued PD-1 inhibitor therapy for persistent psoriasis while receiving topical corticosteroids and NB-UVB

treatment. In cases where psoriasis vulgaris and psoriatic arthritis coexist, the prescribed treatment regimen typically includes oral methotrexate administered at a weekly dose of 10 mg, along with daily prednisolone tablets at a dose of 20 mg. Additionally, the application of topical corticosteroids forms an integral part of the therapeutic approach.[10] Cutroneo et al reported that psoriasis or psoriasiform dermatitis induced by PD-1 inhibitors nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, and cemiplimab accounted for 2.9% to 4.9% of adverse skin reactions in the European pharmacovigilance system; 70.8% of the reported patients had a history of psoriasis, and nearly half were being treated with topical corticosteroids or corticosteroids combined with vitamin D therapy, 7.7% with phototherapy, and 3.2% with systemic treatment. Of the systemic treatments, 18 patients received systemic steroids, 2 cases received acitretin, 1 case each received cyclosporine, methotrexate, and efalizumab, 2 cases received etanercept, and 3 cases received apremilast.[11] Coleman et al reported 12 cases of psoriasis induced by anti-PD-1/PD-L1 therapy, with an average latent period of 5.7 months. The majority of the cases were chronic plaque-type psoriasis or scalp-type psoriasis, with 2 cases of inverse psoriasis, 2 cases of palmoplantar pustulosis, and 1 case of psoriatic arthritis.[12]

Conclusions

In conclusion, PD1 inhibitors may cause the recurrence, exacerbation, or new onset of psoriasis. A personal or family history of psoriasis is an important risk factor that needs to be considered prior to PD1 inhibitor therapy, for the early diagnosis of psoriasis. Early diagnosis of guttate psoriasis is complex. A prompt dermatologist visit is advised, and a histopathologic investigation can provide a conclusive diagnosis. Oncologists face the crucial decision of continuing PD1 inhibitor therapy, balancing its efficacy in treating advanced metastatic disease. Mild cases of psoriasis can often be managed with topical steroids and NB-UVB phototherapy. In contrast, severe cases necessitate systemic therapy, with treatment options including drugs such as methotrexate, etanercept, apremilast, acitretin, among others. This prevents quality-of-life issues from developing, as well as issues with therapeutic management and patient prognosis.

Abbreviations

PD-1, Programmed Death Receptor 1.

Data Sharing Statement

The data and materials used to support the findings of this study are available upon request.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of Yuncheng Central Hospital, Shanxi Medical University. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Informed Consent for Publication

The participant provided written informed consent for the case details and images to be published.

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Disclosure

The authors declare that they have no conflicts of interest regarding this work.

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