Post-shingles granulomatous dermatosis related to anti-programmed cell death 1

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The most recent progress in the oncology field has led to a paradigm shift in the management of cancer with the tsunami of immune checkpoint inhibitors that are associated with a particular pattern of immunological adverse events. This is a case of a 54-year-old woman that demonstrated a granulomatous reaction in the same dermatomal distribution of a previously treated shingles infection during treatment with an anti-programmed death 1 agent (pembrolizumab) for a newly diagnosed stage IV Hodgkin lymphoma. The purpose of this case is to increase the awareness of oncologists dealing with a new pattern of side effects taking into account the patient’s background and recent exposures to latent viruses such as herpes zoster to prevent unnecessary diagnostic and therapeutic measures.

Keywords: Hodgkin lymphoma • immune checkpoint inhibitors • Immune granulomatosis • pembrolizumab • shingles

Recent advances in the drug-development field has led to a paradigm shift in the management of cancer with the emergence of immune checkpoint inhibitors (ICIs). These innovative agents include monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), and the programmed death-1 receptor (PD-1) and its ligand (PD-L1) and have earned their spot as the standard of care in numerous type of tumors [1–3]. They are associated with a particular pattern of tumor response and a constellation of unique immune-related adverse events (IrAEs) [4,5]. The most common sites affected by ICIs include the skin, colon, liver, lungs and endocrine organs, which are rarely life threatening, although there have been reports of other infrequent cardiac or neurological complications [6,7]. Usually, skin complications develop within weeks of checkpoint inhibitors initiation and have been reported in almost 34–45% of patients [2,8,9]. A broad spectrum of cutaneous IrAEs have been described including vesicular, maculo-papular, follicular, papular or exfoliative lesions [10,11] or lupus-like reactions [12]. These are self-limited and do not usually require dose reduction or drug interruptions. However, the appearance of new cutaneous lesions during ICIs treatment could also be related to other etiologies including viral infections or even secondary cutaneous localizations of the cancer itself, especially in the context of hematological malignancies. Prompt recognition and identification of these conditions is mandatory for the initiation of proper therapy. Herein, we report an interesting case of a Hodgkin lymphoma (HL) patient treated with an anti-PD1 agent (pembrolizumab) who developed a granulomatous reaction in the same dermatomal distribution of a previously treated shingles infection.

Case
A 54-year-old woman was referred to our hematology department in September 2016 for a newly diagnosed stage IV nodular sclerosis classical Hodgkin lymphoma. At diagnosis, the 18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) showed the presence of FDG-avid diffuse lymph nodes in the infra- and supra-
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diaphragmatic region with diffuse osteomedullary hypermetabolism. Physical examination was normal except for palpable lymph nodes in the axillary and supraclavicular region. Cervical lymph node biopsy confirmed the diagnosis of nodular sclerosis classical HL (CD30+, CD15+, MUM+). First-line therapy with four courses of escalated BEACOPP regimen (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone) failed to induce a complete response. Salvage therapy with DHAP regimen (cytarabine, cisplatin and dexamethasone) was then initiated. 1 month later, the patient developed shingles at the right C4–C5 dermatomes at the shoulder level, with a PCR confirming cutaneous herpes zoster infection. Herpes zoster infection resolved after valaciclovir with complete disappearance of the cutaneous lesions.

No response was observed after two cycles of DHAP therapy and the patient started an anti-programmed death 1 agent (anti PD-1) pembrolizumab at the dose of 200 mg with intravenous injections every 3 weeks. The patient achieved a partial response on CT scan and FDG-PET after four cycles of pembrolizumab. However, she started developing new cutaneous lesions in the previously treated shingles area of the right shoulder (nearly 6 months after the first episode of shingles). Clinical examination demonstrated nonpainful nonpruriginous maculo-papular erythematous lesions in the neck and right shoulder area without any spread to other body parts (Figure 1). Laboratory exams ruled out any signs of viral or bacterial infection while no new medications were recently introduced but unfortunately, a newer evaluation of herpes zoster was not performed due to the absence of similarity with the previous skin disorder after examination by a dermatology specialist. Interestingly, the FDG-PET showed increased standardized uptake values (SUV) uptake in the same cutaneous region but with disappearance of all target lesions related to the HL (Figure 2). Cutaneous biopsy showed reticular and granulomatous reaction (Figure 3). After thorough discussion in the multidisciplinary meeting, pembrolizumab was maintained and no specific therapy was initiated for the skin toxicity except for topical hydrants due to the absence of symptoms and the localized pattern of the skin lesions. The patient had a gradual resolution of the cutaneous lesions over the following few months, particularly after interruption of pembrolizumab. After a total of nine cycles, pembrolizumab was permanently stopped for a grade 3 pneumonitis that was treated with steroids. Thereafter, the patient remained in complete remission for her HL 16 months after starting pembrolizumab with no recurrence of cutaneous lesions. An informed consent was obtained from the patient.

Discussion

The ICIs activate cytotoxic T lymphocytes in the cancer microenvironment but also in normal tissues which leads to the development of particular IrAEs, rarely encountered by cancer physicians in their daily practice [13]. Hence, there is an unmet need for a better identification and understanding of the physiopathology of ICIs and their toxicity in order to prevent harmful outcomes. Numerous recommendations and guidelines have been published in order to address this need for a better characterization of the newly emerging IrAEs [5,6]. In this case, we report the appearance of granulomatous, cutaneous lesions within the same region of a previously treated shingles infection while being treated with pembrolizumab for a stage 4 HL.

Cutaneous IrAEs are among the most common side effects in ICI-treated patients. Rash, vitiligo and pruritus are the most frequently reported skin AEs while other rare skin events have also been associated to ICIs including alopecia areata, stomatitis, autoimmune skin diseases, oral or nail mucosal changes, xerosis cutis and sarcoidosis [9,14]. Skin IrAEs occur early in the course of ICIs (weeks); however, some cases reported events even 1 year after treatment discontinuation [15]. Management depends largely on the severity and grading of the cutaneous signs and symptoms after thorough assessment and evaluation by dermatology experts. The treatment strategy is based on local treatments (antihistamines, topical emollients) in low grade IrAEs without discontinuation of ICIs; however, in grade 3 or 4 adverse events, treatment interruption is mandatory and intravenous steroids should be initiated [6]. In this intriguing case, cutaneous lesions are clinically and histologically compatible with the diagnosis of granuloma annulare (GA) in a localized manner even though some forms of disseminated disease have been previously reported [16,17]. The GA is a common and benign inflammatory dermatosis characterized by mucin deposition, collagen degradation and histiocytic infiltration. It is thought that tissue destruction and local inflammation to be related to the activation of macrophages by IFN γ-producing T-helper 1 (TH1) [18]. The exact cause of this rare entity is unknown and many factors have been associated with the occurrence of GA: trauma, sun exposure, but also infections and especially shingles [19]. In fact, some forms were characterized as isotopic responses secondary to shingles, a dermatologic term introduced to describe the occurrence of a skin disorder another at the same site of an older skin disease [20,21]. Rare cases are mostly iatrogenic and can be suspected after the introduction of some medications such as allopurinol or diclofenac [18,22]. Also, some cases have been described as paraneoplastic lesions associated with hematological
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Figure 1. Cutaneous toxicity after pembrolizumab. A maculo-papular erythematous lesions in the neck and right shoulder area (A) anterior view (B) posterior view.

malignancies including Hodgkin disease, diabetes and hyperlipidemia in particular [16,18,23,24]. Wu et al. reported the occurrence of three cases of GA secondary to anti-PD-1 and anti-PD-L1 agents (durvalumab, pembrolizumab and nivolumab) that responded well to topical or oral steroids but relapsed eventually upon the reintroduction of the ICI [22]. Optimal management of this entity is not clear but some forms were successfully treated with steroids, topical tacrolimus or immunosuppressive agents (methotrexate or adalimumab) [22,25–27].

In the initial evaluation of our patient, many hypotheses have been evoked including relapse of the neoplasia, immune related toxicity or infectious lesions. In the European Society for Medical Oncology guidelines on the management of skin IrAEs, the first step is to rule out other causes such as infections, skin reaction to another drug or systemic disease. Another important step is the rigorous physical examination and in most cases, a complete biological evaluation including blood cell count as well as kidney and liver functions in order to rule out dermatological emergencies such as sweet syndrome or toxic epidermal necrolysis [6]. The biopsy of these lesions is mandatory in order to obtain a pertinent diagnosis with optimal clinical management and care. It is crucial to shed light on the fact that the real role of anti-PD1 therapy in our case is difficult to affirm, but the sequence, as well as
Figure 2. FDG-PET showing increased standardized uptake values in the neck and right shoulder area without any spread to other body parts (see arrows).

The improvement after the interruption of injections, is highly suggestive of the inducing role of pembrolizumab. That said, we believe that the limitation in this case presentation is the evaluation of PD-1 and PD-L1 staining on macrophages and T cells which could have helped in establishing a potential link between anti-PD-1 therapy and the occurrence of GA.
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Figure 3. Histopathological findings. (A) A granulomatous inflammatory infiltrate in the papillary and reticular dermis with perivascular epithelioid granulomas admixed with lymphocytes and interstitial multinucleated giant cells (in frame; asterisk showing a Langerhans giant cell); (B) an epithelioid and giant cell granulomatous reaction in the papillary dermis; (C) a granulomatous infiltrate within arrector pili muscle (arrow).

Consequently, physicians prescribing anti-PD1 agents to their cancer patients should always keep high index of suspicion for the risk of infections, despite being minimal in comparison with chemotherapeutic agents. The overall risk of infectious complications in patients treated with ICIs was found to be of 7.3% [28]. In fact, PD-1 overexpression contributes to the development of an immunocompromised environment with high risk of microbial persistence and sepsis [29]; hence, the role of the ICI in countering the immune deficiency and aiding in the boosting of the microbial-specific immune response [30]. However, several forms of infectious complications have been reported during anti-PD1 administration including bacterial infections, varicella herpes zoster, pneumocystis pneumonia or pulmonary aspergillosis [28]. Of note, occasional cases of unmasked tuberculosis have also been reported [30]. The higher risk was noted among those who received steroids and/or other immunosuppressive agents for IrAEs [28,31]. In fact, the better understanding of the relationship between immune checkpoints and the immune environment have urged scientists to evaluate the role of ICIs in the management of several infectious diseases such as Hepatitis B infection, HIV and malaria [32]. Ruling out infectious causes, usually associated with cutaneous manifestations, is mandatory during the etiological evaluation skin IrAEs.

With the expanding indications of ICI in all solid and hematological malignancies, a better comprehension of the ICI-related skin toxicity is a must in order to tailor the management with utmost efficacy. Misdiagnosis of benign cutaneous conditions as relapsed disease in patients with history of shingles treated with ICI could lead to unnecessary diagnostic and therapeutic measures. The case described here indicates that the immune reactions generated by the anti-PD1 agent could occur in body territories previously sensitized by a viral infection such as zoster virus. Of note, anti-PD1 are not immunosuppressive agents, on the contrary they will boost the immune response against cancer cells and other infectious agents, viruses or bacteria or fungi [32]. This case suggests that the patient’s background history and recent exposures to a latent virus such as zoster are factors to keep in mind in the detection and management of immunologic side effects.

Conclusion

Checkpoint inhibitors-related dermatologic toxicities are frequent and physicians should not rush to the conclusion of disease relapse before a careful dermatological evaluation. Oncologists, dealing with both solid and hematological malignancies, should increase their awareness of immune-related side effects while prescribing the novel ICIs, with focus on the patient’s background history and recent exposures.
Future perspective
Recent advent of ICIs in the management of cancer have undoubtedly changed the outcomes for thousands of cancer patients, but ultimately lead to the emergence of a wide array of rare adverse events [33]. The diagnosis and management of these IrAEs is challenging, especially to physicians and oncologists who are mostly overcome by the daily care and needs of their cancer patients. Therefore, it becomes mandatory to improve the management of these patients by the multidisciplinary interaction between all the different medical specialties. Special courses, formations, fellowships and workshops for internists, endocrinologists, gastroenterologists and all other medical specialists must be organized in order to increase the awareness and optimize the management of toxicities related to ICIs. With the increasing indications for ICIs in all types of cancer as well as the combinations between ICIs or with chemotherapy, the incidence of IrAEs will continue to rise [34–36]. Consequently, many cancer centers have already adapted various strategies to confront these needs including mobile applications, weekly multidisciplinary meetings on ICI toxicity and collaborative work between various medical centres in order to ensure the permanent availability of specialized physicians from the different medical fields for urgent consultations. In this new era in the fight against cancer, scientists and physicians are urged to collaborate and invest their efforts for a better understanding and recognition of IrAEs.

Executive summary
- A 54-year old woman with stage IV Hodgkin lymphoma was treated with pembrolizumab after failure of conventional chemotherapy.
- After demonstrating partial response upon completion of four cycles of pembrolizumab, she developed new cutaneous lesions in a previously treated shingles area at the shoulder level.
- Cutaneous biopsy showed reticular and granulomatous reaction (Figure 3). No specific therapy was initiated for the skin toxicity except for topical hydrants with gradual disappearance over few months, particularly after pembrolizumab interruption.
- Cutaneous toxicities secondary to immune checkpoint inhibitors are frequent and cutaneous biopsy is often needed to obtain a pertinent diagnosis with optimal clinical management.
- This is the first case of post-shingles granulomatous dermatosis compatible with the diagnosis of granuloma annulare after pembrolizumab administration.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct
The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Informed consent disclosure
The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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Immunotherapy (2019) 11(7)
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