Metformin-induced Photocontact Dermatitis in a 67-year-old Male: A Case Report

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Abstract

Introduction: Photocontact dermatitis is a type IV delayed hypersensitivity response to an allergen that is activated by radiation energy. Its incidence is uncertain and only a small number of drugs causing such reaction have been studied. This is a case of a 67-year-old filipino male, diabetic, who presented with scaly, erythematous, and hyperpigmented plaques with areas of desquamation and erosions on sun-exposed areas of the skin after taking metformin.

Case: Four months prior to consult, the patient was diagnosed with type 2 diabetes mellitus and was started on metformin therapy. Days later, he started noticing scaly, erythematous and hyperpigmented plaques with areas of desquamation and erosions on sun-exposed areas, namely the upper and lower extremities, posterior neck, and forehead. There was notable sparing of areas that are usually covered with clothing such as the torso, inguina and both thighs. There were also no lesions on the scalp, palmar aspect of the hands and plantar surface of the feet. Skin biopsy was considered but was not done per patient's preference. After discontinuation of metformin and avoidance from sun exposure, the skin lesions gradually improved.

Conclusion: Metformin is rarely associated with adverse skin reactions. The diagnosis of photocontact dermatitis as a side effect of metformin needs to be considered as a differential diagnosis in patients who present with skin rashes, especially in sun-exposed areas. It is recommended that there should be a high-index of suspicion for adverse drug reactions in such patients. This would reduce medical errors and medical cost and would result to prompt initiation of appropriate treatment.

Keywords: metformin, photocontact dermatitis, type 2 diabetes

Introduction

Metformin is one of the most commonly used drugs in the field of medicine. It is an antihyperglycemic agent of the biguanide class. It decreases glucose levels primarily by decreasing hepatic glucose production and by increasing insulin action in muscle and fat.[1] Metformin has a long-standing evidence base for efficacy and safety, is inexpensive, and may reduce risk of cardiovascular events and death.[2] Thus, it is the mainstay in the initial treatment of type 2 diabetes mellitus (T2DM).

Like any other drug, metformin is not without side effects. Its common side effects, which occur in up to 20% of patients, include diarrhea, abdominal discomfort, nausea, metallic taste and anorexia.[1] Metformin allergy is rare. There is no current literature that convincingly implicate metformin as the direct cause of allergic reactions. Vasculitis and psoriasisiform drug erruptions have been reported, wherein the patients usually develop a rash within a few days of metformin administration and the skin lesions disappear after stopping the drug, however, no causal relationship was established.[3,4] We present a case of a patient who had metformin-associated photocontact dermatitis.

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Case Presensation

This is a case of a 67-year-old male who presented with pruritic erythematous, scaly and desquamating lesions in sun exposed areas of the skin, which were noted to erupt about four months prior to consult. There was no associated fever or other constitutional signs and symptoms. The patient had no history of skin trauma, nor had any exposure to potential skin irritants such as liniments and creams. He has no personal history of atopy however family history was not clearly established. The patient drives a motorcycle as his form of livelihood, which allows him to be directly exposed to sunlight almost daily.

The patient was diagnosed with T2DM four months prior to consult and was started on metformin 500mg tablet, taken

once daily orally for two months, then continued with poor compliance during the remaining months. Detailed history revealed that the patient had no other comorbidities, and had not taken any other drug or substance prior to the onset of the skin lesions. He sought consult and was given topical corticosteroids (mometasone) and an unrecalled oral antihistaminic agent, which afforded no improvement of lesions after one week of treatment.

On admission, vital signs were within normal limits. Scaly, erythematous and hyperpigmented plaques with areas of desquamation and erosions were noted on sun-exposed areas, namely the upper and lower extremities, posterior neck, and forehead. The torso, thighs, palms and soles, areas that are usually covered with clothing, are notably spared. There were also no lesions on the scalp, which was covered with hair. Complete blood count, renal and liver function tests and other routine blood tests were unremarkable. Fasting blood sugar was 110 mg/dL. The patient was started on antibiotics to address the secondary bacterial infection on the lesions, which turned positive for methicillin-sensitive *S. aureus* on culture. Referral to a dermatologist was done, who gave a diagnosis of metformin-induced photocontact dermatitis. A skin biopsy was considered however it was not done because of the patient's reluctance and no consent was given. Metformin was put on hold and was replaced with sitagliptin to maintain glucose control. Topical skin moisturizers were started. There were no systemic or topical steroids given. The patient was eventually discharged after five days and was followed-up as outpatient. He was advised to refrain from being directly exposed to sunlight.

Subsequently, the patient was followed-up on a regular basis. There was gradual improvement of the lesions following discontinuation of metformin over the course of two weeks (Figures 1-4). Metformin was never resumed and there was almost complete resolution of the lesions with no apparent recurrence. The patient however was lost to follow-up after the second week of continuous improvement.

Discussion

Photocontact dermatitis or photoallergy, is a type IV delayed hypersensitivity response. It occurs when a compound or photoallergen absorbs radiation energy and becomes activated and subsequently conjugates with a carrier protein forming a complete allergen. Once the complete allergen is formed, the mechanism of photoallergy is similar to that of contact dermatitis. The antigen is taken up and processed by langerhans cells, which then migrate to regional lymph nodes to present the antigen to T lymphocytes. Cutaneous lesions develop when the activated T lymphocytes circulate to the exposed site to initiate the inflammatory response.[5]

In the general population, the incidence of photocontact dermatitis is unknown. The available incidence data are

Figure 1. Scaly, erythematous and hyperpigmented plaques with areas of desquamation and erosions on sun-exposed areas, namely the upper and lower extremities, posterior neck, and forehead.

Figure 2. Sparing of non-exposed areas.

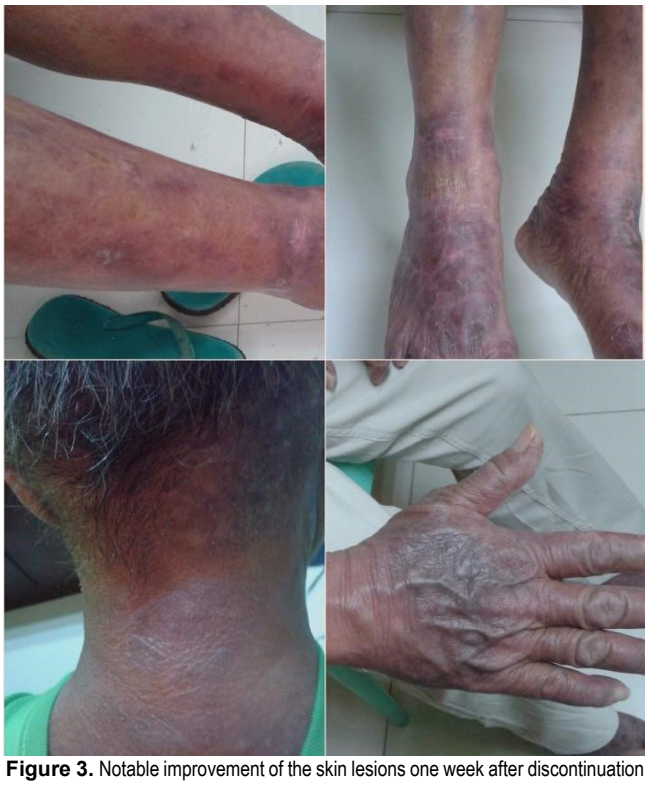

Figure 3. Notable improvement of the skin lesions one week after discontinuation of metformin

Figure 3. Significant improvement two weeks after withdrawal of metformin.

based on positive photo-patch test results in groups of patients with presumed photosensitivity. It appears that from these data, the incidence of photocontact dermatitis is 10-20%.[6] Only a small number of systemic drugs causing photoallergy have been well studied. Listed in Table I are systemic drugs that are considered as photoallergens.[5,7]

In sensitized individuals, exposure to the photoallergen and sunlight results in the development of a pruritic, eczematous eruption within 24-48 hours in sun-exposed areas of the skin. In our case, the patient was exposed to metformin for the very first time, upon which, gradual sensitization to the drug may have been initiated, which in turn explains the gradual onset of symptoms. The distribution of eruption in photocontact dermatitis is predominantly confined to sun-exposed areas, although the morphology is clinically indistinguishable from that of allergic contact dermatitis.[5] Indeed, the patient's lesions were located on the forehead, upper and lower extremities with sparing of the scalp, torso, palms and soles and inguinal area. Phototests and photopatch tests are an integral part of the evaluation of photosensitivity when history and physical examination alone are insufficient to determine the responsible agent.[5] Unfortunately, this was not done in our patient because of its unavailability in the local setting. There are no specific histologic findings for photocontact dermatitis, thus skin biopsy has no definite role in the diagnosis except for ruling out other skin conditions.

Notably, metformin is not one of the identified systemic agents causing photocontact dermatitis. In literature, photoallergy is not a typical side effect of this medication. Although there are no case reports of metformin causing photoallergy, there are reported cases of leukoclastic vasculitis and psoriasisisiform dermatosis associated with metformin.[4] In the former, a 59-year-old woman presented with purpuric lesions all over the body. The patient was on metformin for four months. Punch biopsy of the lesion revealed perivascular polymorphonuclear infiltrate, fibrinoid deposits in the small dermal vessels and fragmented neutrophils consistent with leukoclastic vasculitis. The lesions rapidly disappeared after discontinuation of metformin.[8] Another reported case was of a 29-year-old woman who developed a facial skin rash during the treatment with metformin. Clinical and laboratory findings excluded the presence of systemic diseases. Withdrawal of metformin induced an improvement of symptoms.[9]

Table I. List of established photoallergenic systemic drugs[5]
Systemic photoallergens
Chlorpromazine
NSAIDs (Ketoprofen, Piroxicam, Diclofenac)
Fluoroquinolones
Sulfonamides
Sulfonylureas
Quinine
Quinidine
Pyridoxine

Using the Naranjo Adverse Drug Reaction Probability scale, a probable association between the patient's skin lesions and metformin was established.[10] The lesions erupted in proximity with the initiation of metformin treatment. The distribution of the lesions is typical of a photoallergy. Also, the patient did not have any history that would implicate another drug or a clinical condition to the appearance of the rash. Lastly, after withdrawal of the drug, the lesions gradually disappeared.

Management of photocontact dermatitis is straightforward. Significant improvement is expected within days after discontinuation of the offending agent. Other treatment strategies are supportive only such as antihistamines to relieve pruritus, topical moisturizers, and sun protective agents. Antibiotics may be given if there is evidence of secondary bacterial infection. Corticosteroids have no clear benefit in the treatment of photoallergy.

Other diagnoses that may be considered for this patient are psoriasis, vasculitis and skin infection. Psoriasis also presents with scaly lesions. However, the skin lesions in psoriasis are typically found in the extensor surface of the extremities or in the trunk and do not necessarily follow a pattern of sun-exposure. Also, auspitz sign, though not present in all psoriasis patients, was not observed in our patient. Vasculitis, which may be a manifestation of a systemic disease, produce purpuric lesions or plaques that may be generalized or localized. The apparent absence of a systemic disease in our patient is a point against the diagnosis. Although there was a previous case report regarding a vasculitic reaction attributed to metformin use, exclusive involvement of sun-exposed areas of the skin was not observed. This however does not completely rule out the diagnosis. A skin biopsy would have been ideal to rule out these differentials. Skin or skin structure infection may also produce these lesions but a secondary rather than a primary process is more likely in this case. The patient's disease course is insidious rather than acute, and the distribution of the lesions in sun-exposed areas is not a feature of primary skin infections. A drug-provocation test would have also been of great help in establishing our diagnosis of a drug-induced reaction, unfortunately however, it was not done to the patient.

Conclusion

Metformin is a widely used drug and has numerous benefits especially in diabetics with or without cardiovascular diseases. Though its common side effects have been documented, there are still some adverse drug reactions that tend to be unreported or misdiagnosed, specifically the uncommon ones. The diagnosis of photocontact dermatitis as a side effect of metformin needs to be considered as a differential diagnosis in patients who would present with skin rashes, especially in sun-exposed areas. This would reduce medical errors and medical cost and would result to prompt initiation of appropriate treatment. For this case, a skin biopsy would have been ideal to rule out other skin conditions and a photo-patch test would have made the diagnosis more certain.

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