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Metformin-Induced Fixed-Drug Eruption Confirmed by Multiple Exposures

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
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Patient: Female, 56
Final Diagnosis: Fixed-drug eruption
Symptoms: —
Medication: Metformin
Clinical Procedure: Discontinued metformin
Specialty: Family Medicine

Objective: Unusual or unexpected effect of treatment





Background: A fixed-drug eruption (FDE) is a reaction characterized by cutaneous lesions that appear due to exposure to a particular drug. Barbiturates, carbamazepine, sulfamethoxazole, and tetracyclines have all been associated with causation of FDEs. Although these drugs are more commonly associated with FDEs, any introduction of a medication has the potential to result in a FDE. Metformin, a commonly used medication to improve glycemic control, has been reported to cause dermatologic reactions in some case reports, but only a single previously documented case report discusses the potential of metformin-associated FDE.

Case Report: We describe a 56-year-old woman who developed a FDE with multiple exposures to metformin. Upon each exposure, small, round, erythematous lesions developed on the palms of the hands and soles of the feet; these lesions resolved each time after discontinuation of metformin. According to the Naranjo scale, there is a definite association between metformin and FDE in this case (score of 8).

Conclusions: This report contributes to the limited documented literature on metformin-induced FDE. Clinicians should be made aware of possible FDEs associated with this commonly used medication.

MeSH Keywords: Diabetes Mellitus, Type 2 • Drug Eruptions • Metformin

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/896424>

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Background

In the United States, 9.3% of the population has diabetes, an incidence that is even higher for those above the age of 45 years [1]. In treating type 2 diabetes (T2DM), metformin is widely recommended as first-line medication therapy due to its ability to improve markers of glycemic control, as well as its oral dosage form and safety profile. It is commonly associated with gastrointestinal adverse effects, yet dermatologic reactions to metformin are uncommon and the literature detailing these events and their management is sparse [2]. Case reports of possible reactions to metformin include erythema multiforme, lichen planus, rosacea, and pseudoporphyria [3–6].

The second most common drug-induced cutaneous reactions are fixed-drug eruptions (FDEs) [7]. Characterized by lesions that appear in response to drug administration, FDEs recur at the same sites when a patient is re-challenged with the same offending medication [8]. Lesions most commonly affect the lips, palms of hands, soles of feet, and groin areas, and are often small and well circumscribed. Barbiturates, carbamazepine, sulfamethoxazole, and tetracycline are most often associated with this type of reaction [9].

A case involving a 41-year-old woman implicated metformin as the cause of a FDE, which led to asymptomatic targetoid macules on the lips, face, and arms [10]. Although the patient's medications were discontinued, the outcome of the case was not described and no rechallenge was performed. Therefore, it is difficult to determine the actual cause of the FDE. Re-challenging patients with metformin after they experienced a dermatologic reaction has been described in other reports, including cases of leukocytoclastic vasculitis and psoriasiform drug eruption, and helped to further indicate that metformin was the probable cause [11–13].

We present a patient who developed a FDE upon initiation and rechallenge with metformin.

Case Report

A 56-year-old white woman, weighing 118 kilograms, with a past medical history of T2DM, hypertension, dyslipidemia, allergic rhinitis, arteriosclerosis, and osteoporosis, reported to our ambulatory care clinic. Her medication regimen included: aspirin 81 mg daily, metoprolol tartrate 50 mg twice daily, omega-3 fatty acid 2000 mg daily, cholecalciferol 1000 units daily, and flaxseed oil 1000 mg daily. The patient had self-discontinued prescribed treatments for T2DM due to loss of insurance. With an HgbA1c of 12.3%, she was started on metformin immediate release 1000 mg twice daily, insulin glargine 10 units daily, and insulin lispro sliding scale. Additionally, she was



Figure 1. Erythematous skin around the outer palm of the patient's hand, with slightly pustular lesions.

started on pravastatin 40 mg and lisinopril 10 mg daily. One month later, lisinopril was replaced with valsartan due to development of a cough. Approximately 2 months after starting metformin, she developed small, round, erythematous, slightly pustular lesions on her palms and soles. The patient described the skin involvement as “lesions that would pop like a pimple and then turn into flakey skin.” It was reported that the erythematous skin around the lesions was painful at times, particularly on the soles of her feet. The metformin dose was reduced to 500 mg twice daily and symptoms improved. The patient continued therapy for 4 months after initial outbreak of symptoms, before self-discontinuing due to ongoing symptoms. Upon cessation of metformin, the symptoms dissipated. Due to worsening of blood glucose control following the discontinuation of metformin, bolus insulin doses were increased. In the following months, liraglutide was started and titrated up to 1.8 mg daily as the insulin lispro was titrated down to less than 10 units prior to each meal. At the same time, due to financial reasons, basal insulin was switched from insulin glargine to detemir.

Nine months following the discontinuation of metformin, the patient presented to the ambulatory care clinic requesting a rechallenge of metformin. Her motivating factors for rechallenge were the cost of insulin and the inconvenience of multiple daily injections. Since the previous skin reaction did not pose a health threat, and the addition of metformin could allow for the discontinuation of insulin lispro, metformin was restarted. Metformin immediate release was slowly titrated over 6 weeks to a dose of 1000 mg twice daily. When a daily dose of 2000 mg was reached, she experienced diarrhea and split her morning dose in half (500 mg with breakfast and 500 mg with lunch). The diarrhea resolved. She tolerated this regimen for almost a month, when lesions appeared on her palms (Figure 1). The patient self-reduced the dose to 500 mg twice daily. The skin involvement remained, but she wanted to



Figure 2. Small, round, erythematous lesions on the sole of the foot (surrounded by dry skin).

continue therapy because the improvement in blood glucose allowed for the discontinuation of bolus insulin. One month later, lesions also developed on the soles of her feet and migrated onto the dorsal side of the foot (Figure 2). She experienced intermittent pain while walking and was bothered by the appearance. Given her previous history and the current dermatologic symptoms, her primary care physician diagnosed her with a FDE secondary to metformin. The patient was trialed on a reduced metformin dose, but she continued to experience a rash and pain with continued therapy. Metformin was then discontinued and the insulin regimen was intensified to maintain adequate glycemic control. The patient is now maintained on basal insulin along with liraglutide.

With each metformin exposure, the patient denied acute illness and recent changes in use of medications, soaps, lotions, perfumes, laundry detergent, or other topical products. No supportive care with topical or systemic agents was administered because the dermatologic findings resolved upon discontinuation of the agent.

Upon further questioning, the patient recalled a similar dermatologic drug eruption on her hands that occurred 15 to 20 years ago, at the time of T2DM diagnosis. She was taking metformin extended release 2000 mg once daily, and, throughout the first year of therapy, she developed a similar dermatologic reaction. She was referred to a dermatologist, who provided local steroid injections every 2 weeks, but she does not recall a physician's diagnosis. She elected to stop receiving steroid injections because they were only providing partial relief. Subsequently, metformin therapy was self-discontinued, and the dermatologic involvement spontaneously resolved.

Discussion

Several factors, including the temporal relationship, suggest metformin as the cause of a FDE in this patient. She experienced the same dermatologic reaction of erythema and blistering on the palms and soles upon metformin initiation in subsequent years. In both instances, dose reduction improved symptoms, limiting the outbreak to the palms. However, treatment discontinuation was required because the effects became intolerable. Symptoms resolved after treatment discontinuation. Additionally, there are no other identified causes of this clinical manifestation. Two scales were utilized to evaluate the likelihood that metformin was responsible for the FDE. The Naranjo scale resulted in a score of 8, indicating a definite association between metformin and the FDE observed in this patient [14]. An algorithm developed by Kramer et al. resulted in a score of +4, which corresponds to a probable association [15]. The difference in strength of association seen between the 2 scales is related to a higher emphasis on the lack of previously reported cases of this reaction with metformin, a well-studied medication. While it is unusual that new adverse reactions are identified with medications that have been available for longer periods, it is not impossible. Furthermore, metformin has been previously implicated in other dermatologic skin reactions, including 1 case of possible a FDE. Based on this evidence, it is likely that metformin was the responsible medication in our patient.

Conclusions

Metformin is a commonly prescribed oral agent used to improve glycemic control. The adverse effects of metformin are often gastrointestinal, but there have been few reports of dermatologic reactions. To the best of our knowledge, only 1 other case report describes metformin as a possible cause of a FDE. In this case, there is a strong association that metformin was the cause of the FDE. Given the widespread use of metformin, clinicians should be made aware of the possibility of a FDE with this drug.

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