Title

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CLINICAL VIGNETTE

Metformin Vasculitis: A Rare Reaction to a Common Medication

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Case Presentation

A 58-year-old Caucasian female with no significant past medical history on no medications was found to have type 2 diabetes during a routine physical examination. BMI was 40 and her initial Hemoglobin A1C was 13.2. She was started on Metformin 500mg a day. Six days after initiation of Metformin, she phoned the office, stated she was experiencing achy and tingling in her legs, and said a few sores were showing up on her legs. She was advised to continue Metformin with observation of the sores. She returned to the office 10 days after initiation of Metformin and was diagnosed with venous insufficiency. The Metformin dose was increased to 1000mg a day.

After 30 days of taking Metformin, the ulcerated sores had rapidly and severely erupted from foot to knee in both lower extremities. Metformin was stopped and Sitagliptin 100mg was started. A wound specialist was consulted. Vascular work up was normal for arterial and venous blood flow, so it was concluded that the leg sores were not due to vascular insufficiency. Her skin lesion culture was negative for infection. The lesion was biopsied and found to be consistent with drug-induced leukocytoclastic vasculitis.

Within a week of stopping Metformin, the ulcerated lesions began to heal, and no new lesions developed. The patient was on Metformin for almost 30 days before being taken off the medication. For the next 2 weeks after Metformin was stopped, the lesions continued to heal. Canagliflozin 100mg was added to Sitagliptin to better control hyperglycemia. Within days, new lesions began to develop and Canagliflozin was immediately discontinued. While the patient's ulcers were slowly healing, she experienced significant pain and swelling, which were treated with periodic Dexamethasone injections, oral tapering prednisone, Lasix, and pain medication. The patient was resistant to use of insulin from the start and remained hyperglycemic despite daily Sitagliptin. She eventually agreed to insulin Glargine injections, and Sitagliptin was discontinued. It took an additional 3 months for the large ulcerated lesions to heal and eventually close with hyper-pigmentation expected to remain for months.

Physical Examination: Nearly 30 Days on Metformin

Patients was alert, awake, and in tears. Vital signs were within normal limits. BMI 40. Lower extremities showed numerous hemorrhagic, erythematous, and ulcerative lesions in various sizes. The patient's legs were swollen from toes to knees, and tender to exam due to overall inflammation.

Metformin is commonly used as a first line medication for diabetes and for prediabetes management due to its benefit in reducing mortality.[1] Aside from its common gastrointestinal side effects, metformin is often considered a medication without serious side effects. However, it is important for primary care physicians to be aware of rare adverse side effects. Cutaneous adverse effects are rare with metformin use. They can include urticarial, lichenoid reaction, and psoriasiform drug eruption.[2,3] One rare cutaneous reaction is leukocytoclastic vasculitis as seen with our patient. Leukocytoclastic vasculitis may be primary (idiopathic) or secondary to underlying infection, autoimmune disease, malignancies, or medications.[4] The first reported case of metformin-induced vasculitis was in 1986, when a patient presented with purpuric papules with some hemorrhagic vesicles in her extremities and lower abdomen after starting metformin for a few months.[5] Biopsy showed leukocytoclastic vasculitis. Other causes of leucocytoclastic vasculitis were ruled out with negative ANA, hepatitis, protein electrophoresis, and cryoglobulin. The patient recovered with discontinuation of metformin and treatment with prednisone. Metformin was actually re-introduced 2 weeks later, and the patient developed identical eruptions within 2 days, which again resolved after discontinuation of metformin. Similarly, a 2006 case reported a patient presenting with palpable purpura in lower extremities within a few days of starting metformin 850mg daily.[6] Biopsy showed leukocytoclastic vasculitis. Other causes for leukocytoclastic vasculitis were excluded, including negative ANA, ANCA, cryoglobulin, serum protein electrophoresis, C3, and C4. The vasculitis resolved after discontinuing metformin without other treatment. The patient restarted this medication a month later and again developed maculopapular eruptions in her lower extremities. Aside from purpuric papules, another case report showed that metformin-induced vasculitis can cause hemorrhagic bullae as well.[7] Drug-induced vasculitis is understood as an immune mediated reaction. From the few case reports of metformin-induced vasculitis we found, vasculitis often involve the lower extremities, resolve with discontinuation of metformin and recur with rechallenge.

We believe the probable cause of our patient's leukocytoclastic vasculitis was metformin. Our patient was not on any medication prior to starting Metformin. The skin biopsy, which revealed leukocytoclastic vasculitis, was performed while patient had been on Metformin for nearly 1 month, Sitagliiptin for 1 day, and no other medications. Therefore, it is reasonable to conclude that the vasculitis was caused by

Metformin. The emergence of new sores with the initiation of Canagliflozin was also investigated. A literature search did not result in any report of leukocytoclastic vasculitis induced by Canagliflozin. While consultations with multiple endocrinologists, dermatologists, and vascular specialists did not suggest that the vasculitis was caused by Canagliflozin, Canagliflozin was discontinued to eliminate the possibility of further worsening the patient's clinical situation.

Since metformin is a widely used drug for diabetes and prediabetes, it is important for primary care physicians to be aware of rare dermatological side effects and not confuse it with dermatological sequela of uncontrolled diabetes.

Figures

Figure 1. Ten days after starting Metformin.

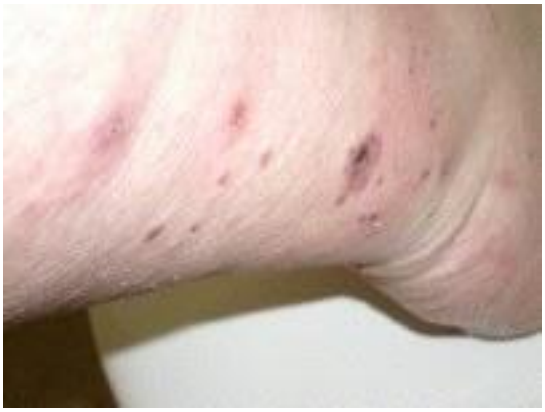
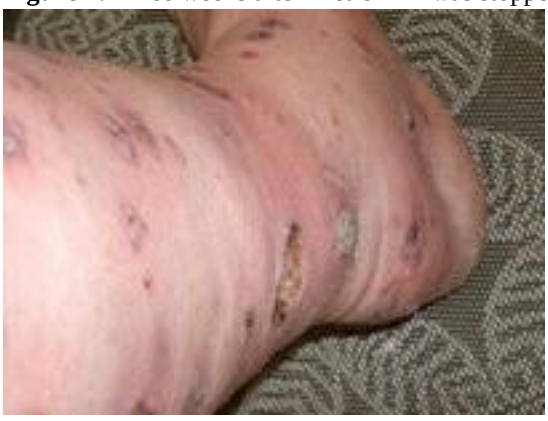


Figure 2. Three weeks after Metformin was stopped.



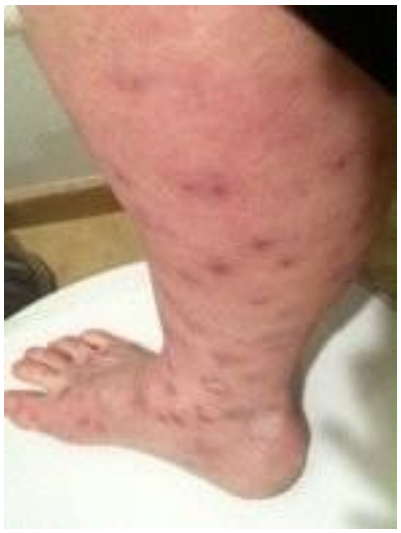


Figure 3. Two months after Metformin was stopped.

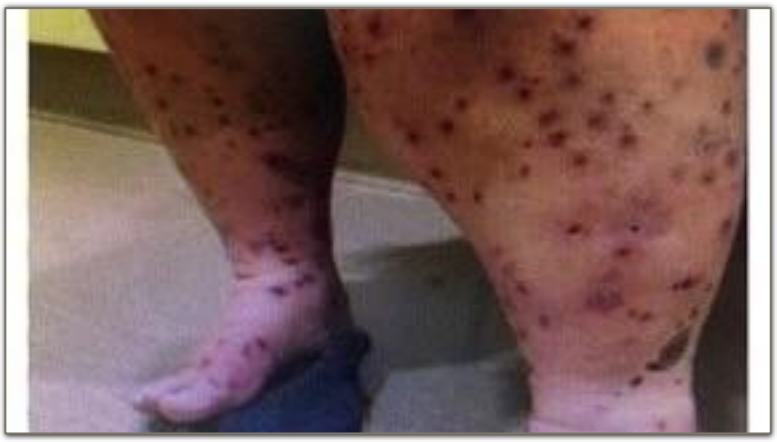
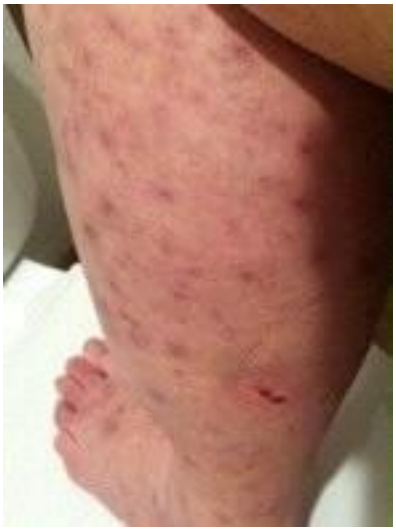
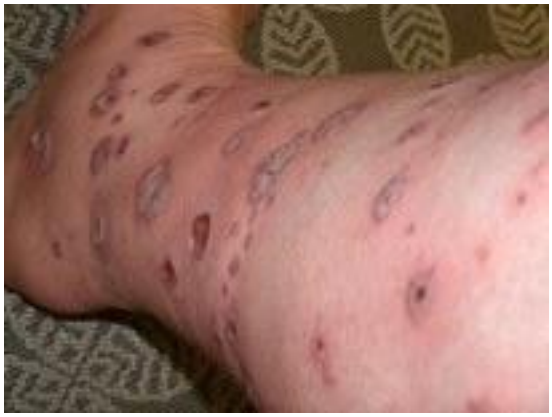


Figure 4. Five months after Metformin was stopped.





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