Cutaneous Drug Reaction in a Nigerian Adult on Oral Antidiabetic Agents: Reaction or Interaction- A Case Report

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Abstract

Background: Type 2 diabetes mellitus is a condition that comprises presence of insulin resistance. Management involves combination of dietary and lifestyle modifications, with deployment of medications as well. Injectable and oral drugs are available for treatment of type 2 diabetes unlike type 1 diabetes that is majorly managed with the use of insulin, which is administered as an injection. The medications act through different mechanisms to increase insulin sensitivity and combat hyperglycaemia. A number of patients with type 2 diabetes mellitus use an average of 2 oral glucose lowering agents for glycaemic control. Virtually all drugs known for treatment of medical conditions generally have individual side effects and there are documented interactions between combinations of some medications. However, most times, oral glucose lowering agents used in managing patients with type 2 diabetes are well tolerated when combined in appropriate manner.

Case Report: We report a case of an unexpected dermatologic reaction in a middle-aged man with type 2 diabetes mellitus following introduction of an additional glucose lowering agent (dipeptidyl peptidase-4-inhibitor) to the oral regimen already being used by the patient. The skin lesions resolved after the withdrawal of the new agent introduced.

Conclusions and Recommendations: The index case has shown that in the process of clinical optimization of patients, there could be unexpected reactions with introduction of new medication. Hence, clinicians should pay attention to the impact of medications on patients as part of holistic management.

Keywords: Type 2 diabetes, Reaction, Medication

Background

Among one of the life-impacting diseases in the world today is diabetes mellitus, which manifests in a form known as type 2 diabetes mellitus (T2DM) in many adults. [1] This is a condition that is majorly driven by a phenomenon called insulin resistance, which thrives in a setting of overweight, obesity, unhealthy eating habits, and physical inactivity.[1,2] Hence, part of the cornerstone of management of diabetes still remains dietary and lifestyle modifications.[3]

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However, because of the progressive nature of T2DM, medications are also prescribed early on in the disease in order to halt glucotoxicity and the complications that could arise if intervention is delayed.[3,4] Different classes of drugs are available for treatment of T2DM, either as oral formulations or injectables, and these (with the exception of insulin) include the sulfonylureas, biguanides, glinides, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4- inhibitors (DPP-4- inhibitors), ergot alkaloid/ dopamine D2 receptor agonist (bromocriptine mesylate), bile acid sequestrants, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1- receptor agonists (GLP-1 Agonists).[4] Recent advancement in diabetology has emphasized prioritizing presence of atherosclerotic cardiovascular disease or risk factors to chart pathway for treatment, however, conventional guidelines have largely maintained Metformin (a biguanide) as the first line medication in the treatment of persons with T2DM. [5,6] If blood glucose is not

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controlled while on Metformin, a second oral agent is added. [6] A third agent may be necessary if blood glucose targets remain unmet, and this could be an injectable (GLP-1 receptor agonist/insulin) or another oral drug depending on different factors. [6] Most of the drugs when combined for treatment in a stepwise and appropriate manner are well tolerated by patients. Apart from individual side effects, there are no significant drug interactions among the oral antihyperglycaemic agents reported in most clinical settings. Addition of DPP-4-inhibitor to SGLT2 inhibitor and/or Metformin is not an unusual option in clinical practice to achieve euglycaemia and if side effects occur, they could appear typical, for example gastrointestinal side effects to use of Metformin. [6] We hereby report a case of drug reaction/ interaction involving DPP-4 inhibitor and SGLT 2 inhibitor, manifesting as a skin reaction in a patient with T2DM in a private health facility in Nigeria.

Case Report

49 year old male, known with DM for 2 and half years, presented to the outpatient diabetes clinic for a review. He had experienced pin and needle sensation in the hands, coupled with some paraesthesia around the left heel in the preceding one week, but these were noted to have improved after engaging in some exercise. There was no intermittent claudications and he had no osmotic symptoms. Nil past history of foot ulcer or stroke but he had left cataract surgery about a year prior to presentation. He attested to ingestion of herbal preparations at times. There was positive family history of DM, hypertension and chronic kidney disease (CKD). He was not known to have hypertension.

He was using Tab Metformin 2000mg nocte, Tab Empagliflozin 25mg daily prior to the clinic visit and claimed good drug compliance. Empagliflozin was just added at another facility few months prior to his presentation.

His fasting blood glucose (FBG) in the preceding 2 weeks ranged between 120-132mg/dl and the average 2 hour post meal blood glucose was 174mg/dl. Recent investigations showed some derangements in liver function test (LFT): Alanine aminotransferase, ALT- 128 U/L, Aspartate aminotransferase, AST-55 U/L. Electrolytes, urea, creatinine; lipid profile, thyroid function test, full blood counts were normal.

He weighed 81kg, height was 175.60 cm, and he had a body mass index (BMI) of 26.27 kg/m2

Examination showed a middle-aged man, afebrile, anicteric, not cyanosed, nil pale, nil dehydrated, nil pedal edema. Pulse rate was 76/min, while the blood pressure read 130/80mmHg. The hands had no deformity or stiffness; light touch was intact on both hands. Dorsalis pedis and posterior tibialis arteries were palpable bilaterally and 10g monofilament testing on the feet were normal (9/10 on the right and 10/10 on the left). An assessment of T2DM with suboptimal short term glycaemic control; Diabetic eye disease; overweight, keep in view non-alcoholic fatty liver disease (NAFLD) was made. The plan was to do HbA1c, serum calcium, phosphate, urinalysis, urine for microalbuminuria, and repeat LFT. Tab Sitagliptin 50mg daily was added to his medications and he was counselled to see Ophthalmologist and return in 2 weeks for follow-up.

However, he represented prematurely a week after first clinical visit with a 3-day history of peeling of the skin of the hands, worse around the palmar aspect. Similar manifestation was noted on the dorsum of the left foot. There was associated thickening/ dryness of the skin. Affected area became painful after the skin might have peeled off. Nil history of stiffness of the hands and there was no exposure to chemical agents. He had nil fever, pruritus, redness of the eyes, cough, catarrh, lip swelling, or difficulty with breathing. There was no past history of similar skin lesions. He was regular with his medications and had commenced the newly added oral glucose lowering agent (Sitagliptin) 3 days before the peeling of the skin developed. FBG range over 1 week: 103-121mg/dl. Review of investigations requested showed HbA1c of 6.9%, ALT- 64.6 (0-34) U/L, GGT- 165.1 (9.0-39.0) U/L, Microalbumin- 38.2 mg/L (0-18). Urinalysis revealed 4+ of glucose (likely from Empagliflozin use) and trace of protein.

Examination of both hands revealed exfoliation of the skin of both hands, involving the fingers and extending towards the palm. Thickening of the skin on the palm was worse on the right hand. There was no tenderness, deformity or ulceration. Trace of skin thickening and exfoliation was observed on the dorsum of the left foot. His vital signs were stable. Figures 1, 2 and 3 represent the appearance of the skin lesions. A case of exfoliative drug reaction or allergic dermatitis was considered and Tab Sitagliptin was subsequently withdrawn, being the most recent medication he used. He was reviewed by Dermatologist who prescribed steroid (Prednisolone) for a few days. Full blood count was done and this was normal; there was no eosinophilia. Skin biopsy was intended but was not done as the patient opted to see the effect of discontinuation of the new drug before consideration of any procedure. His skin normalized about 3 weeks afterwards, as shown in Figures 4 and 5. Putting these together, the patient could have had a form of skin reaction limited to the hands and feet, that is drug-induced exfoliation, especially in the absence of other features such as macules/papules/pustules/bullae/blisters, erythema, systemic symptoms and no contact with chemicals/agents to suggest other aetiology. At the latest clinic review, he was doing well and he is currently on Tab Empagliflozin 25mg daily, Tab Metformin 1g b.d, Vildagliptin 50mg b.d, Rosuvastatin 10mg daily, Clopidogrel 75mg daily, and Lisinopril 2.5mg daily.

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Figure 1: Dorsal aspect of the hands showing skin exfoliation

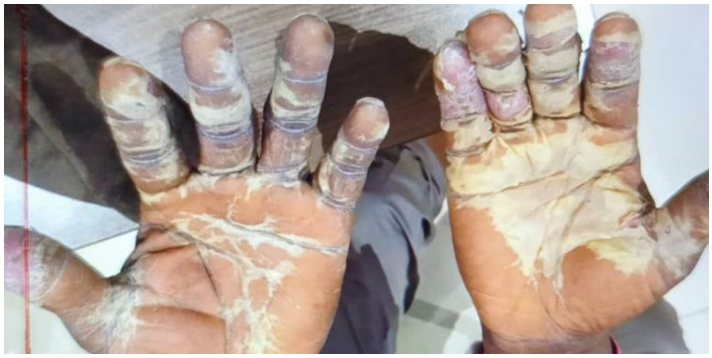

Figure 2: Palmar aspect of the hands few days after introduction of new drug

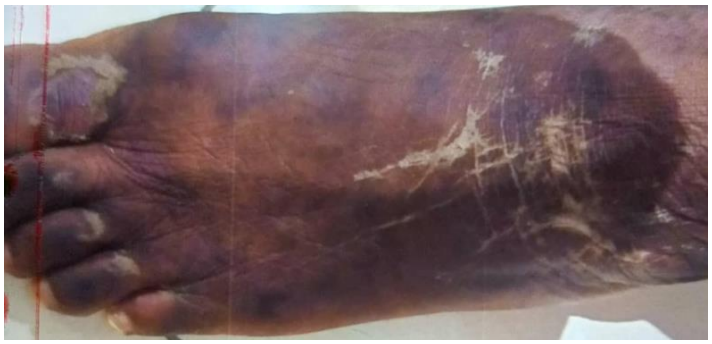

Figure 3: Dorsum of the foot showing skin manifestation after introduction of new drug

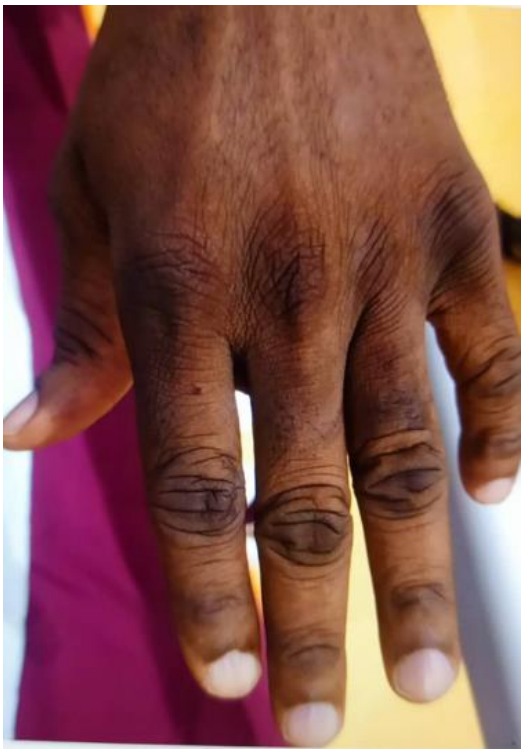

Figure 4: Appearance of the hands after resolution of skin lesion

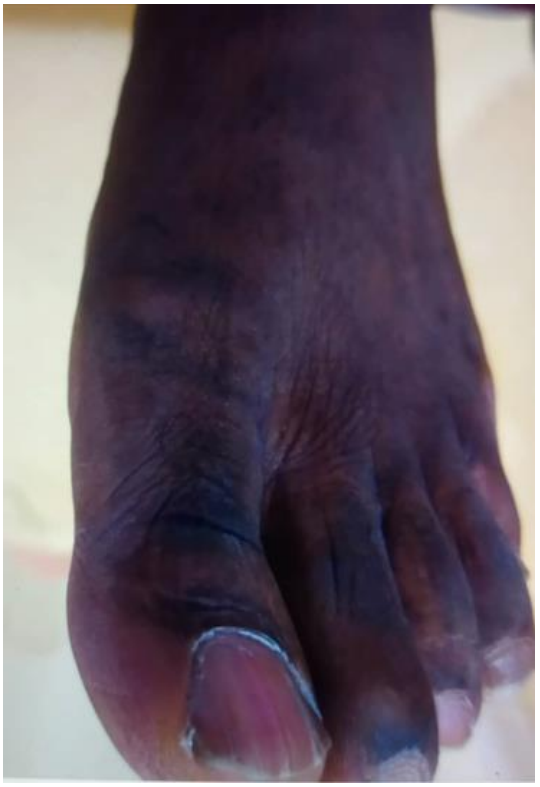

Figure 5: Appearance of the foot after resolution of the skin manifestation

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Discussion

Side effects occur with use of many drugs and these could be described as unintended or unwanted effects, which are majorly negative and may be related to the pharmacological properties of the medication.[7] At the extreme of this is adverse drug reaction, which are usually unpleasant and could be life threatening, accounting for up to 7% of hospitalizations. [7,8]. Generally, 2–3% of all adverse drug reactions arise in the skin. [9] Effects of drug administration on the skin, also known as cutaneous adverse drug reactions (CADRs), are mostly mild, but there could be wide variation in the appearance of the eruptions, which could present as a singular erythematous plaque on the trunk to a full body sloughing of skin, including life-threatening reactions, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). [10] Antibiotics and anti-seizure medications are the most common drugs implicated, with patients developing dermatologic complications in 1% to 5% of treatments. [10,11]

The likely possibility in the index patient is either a side effect of one of the oral agents or drug-drug interaction between 2 or more drugs. While some of the side effects linked to oral glucose lowering agents are gastrointestinal, few cases of dermatologic manifestations have been mentioned, including use of Empagliflozin and Sitagliptin. [10] Ali et al in Trinidad and Tobago reported a case of 5 patients who developed pruritus and rash after introduction of SGLT2 inhibitors (Empagliflozin and Dapagliflozin), with resolution of rash after cessation of medications. [12] Similarly, cutaneous reactions, including bullous pemphigoid, have been reported following use of Sitagliptin, with some appearing after the first dose, [13] comparable to this patient who developed the skin lesions within 4 days of use of Sitagliptin. Furthermore, Nakatani in Japan reported a case of a rash in a patient placed on Metformin and Sitagliptin 6 months after initiation of therapy, with cessation of rash after withdrawal of Sitagliptin.[14]

Mechanisms of manifestation of adverse effects include development of drug-specific IgE, serum-sickness-like reactions in response to drug-antibody complexes, direct release of inflammatory mediators, or involvement of the immune system by mechanisms that are poorly understood. [15] There could be idiosyncratic adverse drug reactions, which are heterogeneous and are not predictable from the pharmacological actions of the drug. [15] Many of these reactions occur as a result of pharmacogenetic differences in drug bioactivation and drug or metabolite detoxification or clearance. [15]

The index case could either be viewed as a drug reaction from Sitagliptin or interaction between Empagliflozin and Sitagliptin or rarely between Sitagliptin and Metformin. Since patient is currently on Vildagliptin, which is tolerated, one could deduce that the experienced dermatologic manifestation could have been due to exposure to Sitagliptin. DPP-4 inhibitors stimulate insulin secretion in a glucose-dependent manner and inhibit glucagon secretion, thus limiting hypoglycaemia and improving hyperglycaemia. [16, 17] On the other hand, SGLT2 inhibitors reduce glucose reabsorption from glomerular filtrate and increase excretion of glucose into urine and hence, one could reason that the lack of similar mode of action between SGLT2 inhibitors and other agents suggests that they can be given in combination with any of the existing classes of glucose-lowering agents, including DPP-4 inhibitors.[17] Also, research has shown that combining DPP-4 inhibitors with SGLT2 inhibitors could produce advantages beyond lowering glucose, such as beneficial effects on cardiovascular and renal risk factors, including albuminuria, and reducing body weight and systolic blood pressure.[17] However, any observed undesirable effect on patients with this drug combinations needs to be attended to when such arises, as it is possible that the index patient developed an allergic/hypersensitivity reaction to Sitagliptin, which is uncommon, thus emphasizing the need for individualized care.

Conclusion

As the prevalence of diabetes continues to rise globally, newer therapeutic agents with options for drug combinations are being developed in order to mitigate effects of morbidity and mortality that could arise from uncontrolled diabetes. It is important to note that clinicians should continue to encourage follow-up of patients and also observe the effects of medications prescribed on the patient as a whole.

Conflicts of interest: None declared.

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