OBSERVATIONS

Is Metformin Safe in Patients With Mild Renal Insufficiency?

Among the first million patients who received metformin in the U.S., 47 patients developed metformin-associated lactic acidosis (MALA), with 43 having predisposing factors for lactic acidosis (including moderate to severe renal failure and congestive heart failure) (1). Although there was initial concern, studies have suggested that MALA is secondary to underlying conditions and represents a coincidental finding (2,3). While the current consensus is that the risk of lactic acidosis is negligible when metformin is used as labeled (4), we present a patient who developed MALA in the absence of currently recognized contraindications to metformin.

A 55-year-old man with hypertension, type 2 diabetes, and mild renal insufficiency (measured creatinine clearance 91 ml/min) presented with sudden onset of fatigue, vomiting, and altered mental status after performing strenuous yard work without sufficient hydration. His medications included nifedipine, captopril, hydrochlorothiazide, glyburide, and metformin.

The patient rapidly developed respiratory distress and hypotension necessitating intubation and vasoactive agents. Laboratory studies revealed a serum creatinine level of 9.4 mg/dl, pH 6.98, CO_2 <6 mmol/l, and lactic acid 27 mmol/l. Evaluation using a computed tomography scan and magnetic resonance angiography of the abdomen/pelvis, various cultures and cardiac echocardiogram could not reveal an etiology for lactic acidosis. Serum metformin level (ARUP Laboratories, Salt Lake City, UT) was 8 mg/l (therapeutic range 1–2). Continuous venovenous hemofiltration was initiated immediately. Conservative management was followed by rapid amelioration of his general status. He was extubated within 24 h, continuous venovenous hemofiltration was stopped after 36 h, and he was discharged 6 days after presentation without deficits.

This case is unique in that MALA developed in the absence of currently recognized risk factors or predisposing conditions. Although this patient had mild impairment of kidney function, contraindication criteria for the use of metformin were not met (5). The patient was taking 2 g metformin per day, which is within the recommended therapeutic range.

In our opinion, a threshold serum creatinine level above normal range should not be considered safe for metformin use because renal function can rapidly deteriorate in patients with even mild underlying kidney disease, resulting in accumulation of metformin and development of MALA. We suggest that consideration be given to avoiding metformin in patients with any degree of renal dysfunction.

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DOI: 10.2337/dc06-2155

References

1. Misbin RI, Green L, Stadel BV, Gueriquian JL, Gubbi A, Fleming GA: Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 338:265–266, 1998
2. Misbin RI: The phantom of lactic acidosis due to metformin in patients with diabetes. *Diabetes Care* 27:1791–1793, 2004
3. Salpeter S, Greyber G, Pasternak G, Salpeter E: Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Sys Rev* no. CD002967, 2006
4. Luft FC: Lactic acidosis update for critical care clinicians. *J Am Soc Nephrol* 12:S15–S19, 2001
5. Holstein A, Stumvoll M: Contraindications can damage your health: is metformin a case in point? *Diabetologia* 48: 2454–2459, 2005

Malignant Melanoma Misdiagnosed as a Diabetic Foot Ulcer

A male patient aged 48 years with type 2 diabetes presented with a painless nonhealing ulcer of 18 months duration under his right first metatarsal head. The ulcer was not a typical-appearing neuropathic foot ulcer and had mushrooming granulation tissue and areas of intact epidermis in a lenticular fashion over the wound bed (Fig. 1). The patient also complained of a "knot" in his right inguinal area. An incisional biopsy was taken from the foot lesion, which revealed a poorly differentiated melanoma covered by an intact epidermis and granulation tissue. The incisional biopsy was 0.8-cm thick, and melanoma extended to the deep margin. At presentation, the size and poor differentiation of the tumor made it impossible to assess the subtype of the original melanoma. The S-100 and HMB-45 stains (positive in melanoma cases) were strongly positive. A computed tomography of the chest, abdomen, and inguinal areas revealed metastasis to the inguinal lymph nodes and liver. The patient died 6 months later.

Although rare, melanomas can present as neuropathic foot ulcers in individuals with diabetes (1,2). Melanomas are located on the plantar surface in ~7% of cases (3) with the exception of Japanese patients, in whom the plantar surface is

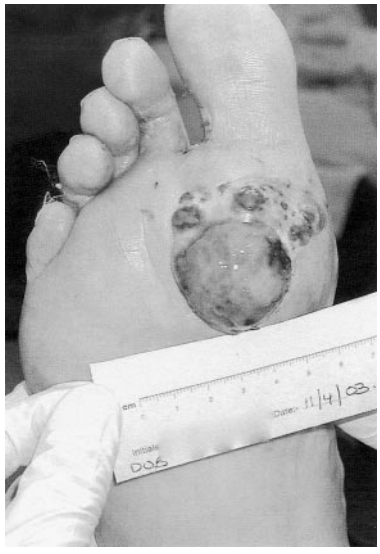

Figure 1—*Malignant melanoma tumor that was misdiagnosed as a neuropathic foot ulcer.*

the most common location (4). Acral lentiginous melanoma is the most common melanoma type that presents on the plantar aspect of the foot (3). This type of melanoma is commonly amelanotic, frequently ulcerates (5), and does not exhibit the classic signs of malignant melanoma associated with the mnemonic aid "ABCD" (asymmetry, border, color, diameter). In a review (6) of 53 lower extremity melanomas, 11 of 18 (61%) misdiagnosed cases were on the plantar foot. All misdiagnosed lesions were histopathologically acral lenginous melanomas. Initial misdiagnoses included nonhealing ulcer, wart, tinea pedis, and onychomycosis. Another retrospective review (7) of palmoplantar melanoma found that misdiagnosis led to a median delay of treatment for 12 months and was associated with increased tumor thickness (5.0 vs. 1.5 mm) and a lower 5-year survival rate (15.4 vs. 68.9%).

We are not supposing that plantar melanoma occurs more frequently in individuals with diabetes. However, we believe there is a greater chance of misdiagnosis given this population's predilection toward plantar ulceration. An individual with peripheral sensory neuropathy is more likely to unknowingly ambulate on a plantar foot lesion, and this increased pressure and trauma can cause a lesion to initially resemble a diabetic foot ulcer. This case and short review emphasizes the importance of performing biopsies on chronic and atypical wounds early in the treatment algorithm of diabetic foot ulcers.

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DOI: 10.2337/dc06-2251

References

1. Gregson CL, Allain TJ: Amelanotic malignant melanoma disguised as a diabetic foot ulcer. *Diabet Med* 21:924–927, 2004
2. Kong MF, Jogia R, Jackson S, Quinn M, McNally P, Davies M: Malignant melanoma presenting as a foot ulcer. *Lancet* 366:1750, 2005
3. Franke W, Neumann NJ, Ruzicka T, Schulte KW: Plantar malignant melanoma: a challenge for early recognition. *Melanoma Res* 10:571–576, 2000
4. Kato T, Tabata N, Suetake T, Tagami H: Non-pigmented nodular plantar melanoma in 12 Japanese patients. *Br J Dermatol* 136:207–211, 1997
5. Dwyer PK, Mackie RM, Watt DC, Aitchison TC: Plantar malignant melanoma in a white Caucasian population. *Br J Dermatol* 128:115–120, 1993
6. Soon SL, Solomon AR Jr, Papadopoulos D, Murray DR, McAlpine B, Washington CV: Acral lentiginous melanoma mimicking benign disease: the Emory experience. *J Am Acad Dermatol* 48:183–188, 2003
7. Metzger S, Ellwanger U, Stroebel W, Schiebel U, Rassner G, Fierlbeck G: Extent and consequences of physician delay in the diagnosis of acral melanoma. *Melanoma Res* 8:181–186, 1998

COMMENTS AND RESPONSES

An Open, Randomized, Parallel-Group Study to Compare the Efficacy and Safety Profile of Inhaled Human Insulin (Exubera) With Glibenclamide as Adjunctive Therapy in Patients With Type 2 Diabetes Poorly Controlled on Metformin

Response to Barnett et al.

In response to the interesting article by Barnett et al. (1), we would like to offer the following comments. Diabetes control has been shown to improve with diet and exercise regimens (2,3). The degree of study participants' compliance with diet and exercise regimens may have confounded the change in A1C reported in the study (1). Also, the independent effect of BMI on both diabetes control and response to therapy has been studied extensively (4). The effect of modification of baseline BMI on diabetes control among various strata of BMI in both study groups needs clarification.

The open-blinded design of the study (1), especially since it involves diabetes education and self monitoring, can significantly impact internal validity due to both performance bias of the subject with respect to compliance with lifestyle modifications as well as detection bias of the health care providers in ascertaining adverse outcomes (5). In addition, the noninferiority design offers no protection against a predetermined idea of equivalence by the investigator, who could allocate similar scores to responses and events of all study subjects (6).

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DOI: 10.2337/dc06-2031

References

1. Barnett AH, Dreyer M, Lange P, Serdarevic-Pehar M, the Exubera Phase III Study Group: An open, randomized, parallel-group study to compare the efficacy and safety profile of inhaled human insulin (Exubera) with glibenclamide as adjunctive therapy in patients with type 2 diabetes poorly controlled on metformin. *Diabetes Care* 29:1818–1825, 2006
2. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C, White RD: Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 29: 1433–1438, 2006
3. American Diabetes Association: Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association (Position Statement). *Diabetes Care* 29:2140–2157, 2006
4. Klein S, Sheard NF, Pi-Sunyer X, Daly A, Wylie-Rosett J, Kulkarni K, Clark NG: Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Di-