Eruptive Xanthomas Associated With Olanzapine Use

Howard Y. Chang, MD, PhD; Todd W. Ridky, MD, PhD; Alexandra B. Kimball, MD, MPH; Elizabeth Hughes, MD; Anthony E. Oro, MD, PhD

Background: Since their introduction to the US market, atypical antipsychotic drugs, such as olanzapine, have been widely prescribed for the management of psychosis and have increasingly been used in dermatologic settings for the treatment of psychogenic dermatoses. Mild hyperglycemia and hypertriglyceridemia have been documented from the use of these medications, but the range of effects on metabolism and the effects on skin are poorly characterized.

Observation: We describe 3 patients who developed eruptive xanthomas, 1 of whom had relative insulin insufficiency, after starting olanzapine therapy. These cases further support the association of severe dyslipidemia with olanzapine use in selected patients.

Conclusion: With the increasing use of atypical antipsychotic agents in the dermatologic setting, the dyslipidemia that develops in association with olanzapine use emphasizes the need for periodic metabolic studies in high-risk patients.

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SINCE THEIR introduction to the US market, atypical neuroleptic agents, such as olanzapine, have been widely prescribed for the management of psychosis. They are considered atypical because of their altered affinities for serotonin and dopamine receptors, and they have an improved adverse effect profile compared with older agents.1-4 While effective, the agents have repeatedly been shown to cause mild hyperglycemia and hypertriglyceridemia.5-11 Although the effects on glucose and lipid metabolism are well documented, the range of glucose and lipid abnormalities is less well characterized. In some individuals, initiation of treatment has been shown to induce latent diabetes, ketoacidosis, and hyperosmolar coma.9,12-16

Atypical antipsychotic agents are increasingly being used in the primary care setting. In a study from the United Kingdom, they make up 1% of all primary care drug expenditures, and the number of prescriptions has increased 6-fold over a 5-year period.17 In dermatology, these drugs have shown efficacy in the treatment of psychogenic dermatoses such as delusions of parasitosis and chronic prurigo nodularis.18-20 The current treatment of choice is the antipsychotic medication pimozide. However, pimozide’s effectiveness is limited by extrapyramidal symptoms such as tardive dyskinesia and akathisia, as well as cardiotoxic effects at high dosages.20-22 These adverse effects are not associated with the use of atypical antipsychotic drugs, making them an attractive treatment alternative. However, the use of atypical antipsychotic agents is relatively recent, and their dermatologic effects are not well established. Herein, we describe 3 unrelated patients who developed eruptive xanthomas after starting olanzapine therapy, illustrating the potential for severe dyslipidemia to develop in association with drug use.

REPORT OF CASES

CASE 1

A 31-year-old white man with schizophrenia presented with a 5-week eruption of hundreds of yellowish umbilicated papules on his arms, legs, and trunk. He was also taking several long-term psychiatric medications, including clomipramine, citalopram, trihexyphenidyl, methylphenidate, and buspirone and had begun taking olanzapine 8 weeks earlier. He had a family history of diabetes mellitus but no personal history of diabetes or glucose intolerance. Multiple 2- to 6-mm, yellowish, erythematous, firm, nontender papules were noted on his trunk and extremities but spared his palms and soles (Figure 1A, C, and F). Acanthosis nigricans was noted on
Figure 1. Eruptive xanthomas after the initiation of olanzapine therapy. The lesions appear diffusely on the trunk (patient 1, A; patient 3, B), extremities, including the elbows, and ears (patient 1, C; patient 3, D and E). The lesions show koebnerization at the site of injury, eg, a cat scratch on the wrist (F). Acanthosis nigricans was seen in the flexural regions of the arms, legs, and feet (patient 1, G and H [arrows]).
the inner aspect of his arms and the dorsal aspect of both feet (Figure 1G and H).

A punch biopsy specimen confirmed the diagnosis of eruptive xanthomas (Figure 2). Laboratory studies revealed severe hyperglycemia and hypertriglyceridemia (Table), and the patient was sent to the emergency department for evaluation and treatment of new-onset diabetes mellitus. He had no detectable antibodies to pancreatic islet cells or insulin, but the insulin C peptide level was elevated at 3.6 ng/mL (1.2 nmol/L) (reference range, 0.6-2.7 ng/mL [0.2-0.9 nmol/L]). His hyperglycemia was rapidly reversed with intravenous insulin, and glyburide therapy was initiated. His hyperglycemia and hypertriglyceridemia were normalized, and the xanthomas resolved after 1 month despite the continuation of olanzapine therapy.

CASE 2

A 21-year-old man with schizophrenia presented with a 2-month history of a progressive eruption of firm, yellow-white papules on his arms, trunk, and face (Figure 1B, C, and E). Olanzapine therapy had been initiated several weeks earlier. He was also being treated with fluoxetine, bupropion, buspirone, and gabapentin. He had no family history of diabetes mellitus. His skin contained hundreds of 2- to 3-mm, white-yellowish, firm papules on the helix of his ears, back, arms, and legs.

A punch biopsy specimen from a right shoulder lesion demonstrated lipid-laden macrophages that were diagnostic for eruptive xanthomas. Metabolic workup revealed markedly elevated serum glucose and triglyceride levels (Table), and the patient was started on a regimen of gemfibrozil and fenofibrate to control his hyperlipidemia. He was subsequently confirmed to have type II diabetes by serial abnormal glucose tolerance test results and a hemoglobin A1c level of 16.4%. Metformin therapy was subsequently initiated. However, the patient was poorly compliant with both therapies, and to date he still has hyperlipidemia and persistent eruptive xanthomas.

CASE 3

A 50-year-old Filipino woman with schizophrenia presented with a 3-month history of an eruption of multiple painless papules on her arms, shins, and abdomen. Her antipsychotic therapy had been changed from risperidone to olanzapine some months before the visit, and she was also taking trihexyphenidyl and diphenhydramine. She had no family or personal history of diabetes mellitus. Her skin contained many 2- to 4-mm, orange-yellow, firm papules on her abdomen and the extensor surface of both arms and shins.

A punch biopsy specimen obtained from an abdominal lesion showed a dermal infiltrate of foamy cells and confirmed the diagnosis of eruptive xanthoma. The metabolic workup revealed severe hyperglycemia and hypertriglyceridemia (Table). Simvastatin therapy was initiated, but the patient was subsequently unavailable for follow-up.

The skin has long been known to reflect the metabolic state of the body, with derangements giving rise to a

### Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No./Age, y/Sex</th>
<th>Diagnosis</th>
<th>Family History of Diabetes</th>
<th>Dosage of Olanzapine, mg</th>
<th>Time at Onset, mo</th>
<th>Triglycerides, mg/dL</th>
<th>Cholesterol, mg/dL</th>
<th>Serum Glucose, mg/dL</th>
<th>Xanthomas</th>
<th>Acanthosis Nigricans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/30/M</td>
<td>Schizophrenia</td>
<td>Yes</td>
<td>10</td>
<td>6</td>
<td>3220</td>
<td>607</td>
<td>370</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2/21/M</td>
<td>Schizophrenia</td>
<td>No</td>
<td>Unknown</td>
<td>2</td>
<td>5907</td>
<td>544</td>
<td>358</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3/52/F</td>
<td>Schizophrenia and anxiety</td>
<td>No</td>
<td>10</td>
<td>3</td>
<td>7210</td>
<td>1090</td>
<td>Not determined</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

SI conversion factors: To convert triglycerides, cholesterol, and glucose to millimoles per liter, multiply by 0.0113, 0.0259, and 0.0555, respectively.

Figure 2. Histologic features of eruptive xanthomas in patients taking olanzapine. A, Low-power field showing dermal cell proliferation of lipid-filled cells. B, Higher-power view revealing the benign-appearing cellular proliferation of lipid-filled macrophages seen in xanthomas (arrow).

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variety of dermatoses. Atypical antipsychotic agents such as olanzapine are known to cause mild hyperglycemia and hypertriglyceridemia. This case series shows that, in select individuals, olanzapine therapy can cause insulin insufficiency, hyperglycemia, and dyslipidemia, leading to eruptive xanthomas. These adverse effects can be most easily explained by olanzapine’s effects on insulin action, which is known to regulate glucose and lipid metabolism.23

Olanzapine is believed to act in part by serotonin reuptake inhibition. Serotonin has been shown to have a dual role in glucose utilization, acting centrally to reduce the response to high glucose levels and peripherally on pancreatic β cells to reduce insulin secretion.24,27 This antagonism results in relative insulin insufficiency, exacerbating metabolism of glucose and lipids. Studies in patient 1 revealed an insulin insufficiency with high insulin C peptide levels and acanthosis nigricans. Glyburide, an insulin-releasing agent, was able to clear the xanthomas in a short time despite continued olanzapine therapy, which is is certainly consistent with olanzapine acting on the pancreas.28

The present series adds to the list of drugs associated with eruptive xanthoma due to hypertriglyceridemia, including isotretinoin29 and indomethacin.30 The frequency of dyslipidemia with the use of clozapine and olanzapine appears to be relatively high (about 30%) and may explain the appearance of eruptive xanthomas. Other new drugs, such as retinoid protease inhibitors for human immunodeficiency virus, have also been shown to induce hyperglycemia and dyslipidemia, although, to our knowledge, there have been no reports associating the development of xanthomas with their use.31

Because atypical antipsychotic agents are increasingly being prescribed by primary care physicians and dermatologists, this case series is of particular importance. Olanzapine has been shown to be effective in the treatment of psychiatric-induced cutaneous disease such as delusions of parasitosis and psychogenic excoriation. The clinical efficacy of atypical antipsychotic agents is similar to that of standard neuroleptic agents, and because their use involves fewer adverse effects, these drugs have been favorably received in dermatology. It is not possible at present to predict which individuals will have the severe metabolic effects that have been seen with the use of this class of drugs. In our series, only 2 of the 3 patients had a family history of diabetes, and none had previous glucose intolerance. Consequently, guidelines for the use of atypical antipsychotic agents have recently been developed.32 They include a detailed patient history and regular measurement of serum glucose concentrations during the first year of therapy. Because of the severe dyslipidemia seen in our patients, we suggest that abnormal triglyceride levels may also be a useful clinical marker of adverse drug effect. Finally, atypical antipsychotic drugs that have similar efficacy in treating disease, with fewer adverse metabolic effects, are being developed. In small controlled studies, it has been shown that ziprasidone does not induce hyperglycemia or hyperlipidemia.33,34 If further testing confirms these initial results, ziprasidone may be a more prudent choice in the dermatologic setting.

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Corresponding author: Anthony E. Oro, MD, PhD, Center for Clinical Sciences Research, Stanford University, 269 Campus Dr, Room 2145, Stanford, CA 94305 (e-mail: Oro@cmgm.stanford.edu).

REFERENCES