A Case of Cutaneous Leukocytoclastic Vasculitis Associated With Aripiprazole

To the Editor: Most adverse cutaneous drug reactions of psychotropics are benign and self-limited after drug discontinuation. But, in rare cases, life-threatening complications requiring immediate medical attention may occur. Among these rare adverse effects is leukocytoclastic vasculitis, which can affect the blood vessels of any organ with circulating immune complexes. This rare condition with an incidence rate of about 30 cases per million persons per year[1] is usually mediated by drugs and sometimes becomes life-threatening. In psychiatry, there are reports showing association between some anticonvulsant and antidepressant consumption and leukocytoclastic vasculitis.[1,2]

To date, aripiprazole has displayed a relatively benign profile of side effects, and the only precaution in its black box warning is dementia-related psychosis in the elderly.[3] According to our search, leukocytoclastic vasculitis has not yet been reported following aripiprazole consumption. This article reports a rare case of this complication in a patient receiving aripiprazole.

Case report. Ms A is a 28-year-old married woman with secondary school education and a diagnosis of obsessive-compulsive disorder according to *DSM-IV-TR* criteria. She was hospitalized for refractory obsessive-compulsive disorder. Her disorder had begun with contamination, checking, and ordering obsession that persisted until hospitalization. Over the past 10 years, she had tried a variety of medications, including citalopram, sertraline, paroxetine, fluoxetine, risperidone, trifluoperazine, pimozide, quetiapine, propranolol, buspirone, haloperidol, carbamazepine, and lamotrigine, but never experienced more than a 30% reduction on the Yale-Brown Obsessive Compulsive Scale (YBOCS).[4] During her previous hospitalization 6 months before, she was treated with fluvoxamine 350 mg/d, clomipramine 100 mg/d, olanzapine 10 mg/d, and clonazepam 1 mg/d, but obsession still persisted (YBOCS score = 33). No particular issue was observed during physical examinations or in the results of paraclinical tests including complete blood cell count; thyroid function tests; liver function tests; kidney function tests; fasting blood sugar, cholesterol, and triglyceride levels; pregnancy test; urinalysis; and urine tests for use of methamphetamine, cannabis, and opium. Her medical history contained appendicitis surgery, mitral valve prolapse, benign stomach polyp surgery, abortion once (due to fetal anomalies), and hypothyroidism. For the latter, she has received treatment with levothyroxine (0.1 mg/d) for the last 10 years. Two years ago, she had developed an allergy to sodium valproate and suffered itching and rash, which resolved with termination of use. However, no history of other allergy-related diseases was found (such as asthma and cutaneous allergies). Her family had no history of psychiatric or medical disorders including autoimmune diseases or medication and nonmedication sensitivities.

On admission day, olanzapine was discontinued, and for augmentation purposes, aripiprazole (5 mg/d) was added to her medications, which was increased to 10 mg/d 3 days later. Five days after starting aripiprazole, painful maculopapular erythematous rashes appeared on Ms A's lower extremities, along with petechial, erythematous plaque, urticaria, and myalgia. A day later, the lesions spread to her hands and trunk, accompanied by appearance of palpable papule and purpuric eruptions in the palate. On the fourth day, a few lesions on the lower extremities turned into small wounds. Over these 4 days, Ms A had a mild fever (102.2°F) with a heart rate of 90 bpm and respiratory rate of 16 breaths/min. Examinations of the abdomen, lungs, and cardiovascular and central nervous systems showed results within normal ranges. A diagnosis of classic cutaneous leukocytoclastic vasculitis was made after a dermatology and pathology consultation. All medications were discontinued, underlying diseases were investigated, and hydroxyzine was administered.

A complete blood count revealed mild leukocytosis (white blood cell count = 11.7×10^9/L, with segment = 75%, and eosinophil = 2%), erythrocyte sedimentation rate was 33 mm/h, and C-reactive protein was +1. Results from other assessments were all in the normal range, including rheumatoid factor, antinuclear antibody, antidouble strain DNA antibody, antineutrophil cytoplasmic antibody, complement C3 and C4 levels, serum cryoglobulin, prothrombin time, partial thromboplastin time, creatine phosphokinase, lactate dehydrogenase, and HIV and hepatitis B and C serology. Abdominal ultrasound and plain lung x-ray were also normal.

Ms A's symptoms gradually abated with discontinuation of medications and administration of hydroxyzine, and cutaneous lesions disappeared after 2 months. Fifteen days after discontinuation, fluvoxamine and clomipramine were administered again, but the symptoms did not recur.

Classic leukocytoclastic vasculitis, also known as hypersensitivity vasculitis and leukocytoclastic angiitis, is a small vessel inflammatory disease created by immune complex deposit containing neutrophils in the small vessel wall and release of lytic enzymes. Circulating immune complexes can be identified in a large percentage of patients with leukocytoclastic vasculitis. This type III hypersensitive reaction is usually mediated by drugs, and the resultant inflammatory response leads to leukocyte infiltration, necrosis and fibrin deposition, and, subsequently, the destruction of small vessels.[5]

Lesions are mostly restricted to the skin, but some patients also develop systemic involvement. The majority of cutaneous symptoms consist of palpable purpura in the lower extremities. However, urticarial-like lesions, ulcers, erythematous plaques, nodules, hemorrhagic bullae, Raynaud disease, and digital necrosis may also be seen. Systemic involvement often engages the liver, the kidneys, and the central nervous and digestive systems, which can be life-threatening. In most cases, the disease starts in the acute form, and symptoms abate in the course of a few weeks. But, chronic and recurring trends have also been reported. In mild cases, treatment of vasculitis involves elimination and avoidance of the causes and administration of nonsteroidal anti-inflammatory drugs and antihistamines. In severe systemic cases, corticosteroids with or without immunosuppressive agents might be required. The prognosis depends on the severity of internal organ involvement.[6]

Etiologically, an obvious cause is not found for this kind of vasculitis in almost 50% of cases. However, in other cases, the most common causes are medications and infections (especially hepatitis C) followed by malignancies and vascular collagen disease.[6] Among psychiatric drugs, there are reports of such side effects of the following medications (all as case reports): clozapine,[7] phenothiazines,[8] gabapentin,[9] haloperidol,[10] olanzapine,[11] additives to lithium,[12] paroxetine,[13] fluoxetine,[14] maprotiline,[14] trazodone,[15] carbamazepine,[16] and levothyroxine.[17] There is no report of such side effects with aripiprazole so far. In this study,

the patient had previously used many of these medications and had shown no allergic reaction to any of them.

In conclusion, it is critical to be aware of vasculitis in cases of cutaneous adverse drug reactions in psychiatry. Also, occurrence of any skin complication should warn against aggravation of symptoms or systemic involvement; hence, the patient should be closely and constantly monitored. Symptoms that indicate severe complication include malaise (fever above 104°F), hypotension, enlargement of lymph nodes, arthralgia, sore throat, wheezing coughs, rash, tongue inflammation, generalized erythema, facial involvement, mucous membrane erosions, skin tenderness, blister or full epidermal detachment, palpable purpura, skin necrosis, eosinophil count < 1,000/μL, lymphocytosis with atypical lymphocytes, and kidney and liver dysfunction in tests. As soon as these symptoms appear, medications should be discontinued immediately, and the patient should be hospitalized and completely assessed to find out the causes (medical and nonmedical).[18,19]

References

1. García-Porrúa C, González-Gay MA. Comparative clinical and epidemiological study of hypersensitivity vasculitis versus Henoch-Schönlein purpura in adults. *Semin Arthritis Rheum*. 1999;28(6):404–412.
2. Skonicki J, Warnock JK. Drug eruptions: 6 dangerous rashes. *Curr Psychiatry*. 2008;7(4):101.
3. Alert for Healthcare Professionals. Aripiprazole (marketed as Abilify). US Food and Drug Administration website. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm151088.htm. Updated August 22, 2013
4. Rajezi Esfahani S, Motaghipour Y, Kamkari K, et al. Reliability and validity of the Persian version of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). *Iranian J Psychiatry and Clin Psychol*. 2012;17(4):297–303.
5. Micheletti RG, Werth VP. Small vessel vasculitis of the skin. *Rheum Dis Clin North Am*. 2015;41(1):21–32, vii.
6. Barham KL, Jorizzo JL, Grattan B, et al. In: Burns T, Breathnach S, Cox N, et al, eds. *Rook's Textbook of Dermatology*. Vol 4. 7th ed. Blackwell Science; 2004:49.7–49.9.
7. Penaskovic KM, Annamraju S, Kraus JE. Clozapine-induced allergic vasculitis. *Am J Psychiatry*. 2005;162(8):1543.
8. Carlson JA, Ng BT, Chen K-R. Cutaneous vasculitis update: diagnostic criteria, classification, epidemiology, etiology, pathogenesis, evaluation and prognosis. *Am J Dermatopathol*. 2005;27(6):504–528.
9. Poon DY, Law NM. A case of cutaneous leukocytoclastic vasculitis associated with gabapentin. *Singapore Med J*. 2003;44(1):42–44.
10. Lee AY. A case of leukocytoclastic vasculitis associated with haloperidol. *Clin Exp Dermatol*. 1999;24(5):430.
11. Karmacharya P. Cutaneous leukocytoclastic vasculitis: case report. *Reactions*. 2014;1488:27–28.
12. Lowry MD, Hudson CF, Callen JP. Leukocytoclastic vasculitis caused by drug additives. *J Am Acad Dermatol*. 1994;30(5 pt 2):854–855.
13. Margolese HC, Chouinard G, Beauclair L, et al. Cutaneous vasculitis induced by paroxetine. *Am J Psychiatry*. 2001;158(3):497.
14. Lamer V, Lipozencić J, Turcić P. Adverse cutaneous reactions to psychopharmaceuticals. *Acta Dermatovenerol Croat*. 2010;18(1):56–67.
15. Mann SC, Walker MM, Messenger GG, et al. Leukocytoclastic vasculitis secondary to trazodone treatment. *J Am Acad Dermatol*. 1984;10(4):669–670.
16. Harats N, Shalit M. Carbamazepine induced vasculitis. *J Neurol Neurosurg Psychiatry*. 1987;50(9):1241–1243.
17. Levothyroxine (levothyroxine sodium) and leukocytoclastic vasculitis. Philadelphia, PA: MedsFacts website. http://medsfacts.com/study-LEVOTHYROXINE%20%28LEVOTHYROXINE%20SODIUM%29-causing-LEUKOCYTOCLASTIC%20VASCULITIS.php. Updated 2012
18. Shinkai K, Stern RS, Wintroub BU. Cutaneous drug reactions. In: Longo DL, Fausi AS, Kasper DL, et al, eds. *Harrison's Principle of Internal Medicine*. Vol. 2. 18th ed. New York, NY: McGraw-Hill; 2012:432–440.
19. Warnock JK, Morris DW. Adverse cutaneous reactions to antipsychotics. *Am J Clin Dermatol*. 2002;3(9):629–636.

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