

CONCISE COMMUNICATION

Refractory case of adrenergic urticaria successfully treated with clonazepam

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ABSTRACT

Adrenergic urticaria (AU) is a rare type of stress-induced physical urticaria characterized by widespread pruritic urticarial papules. Diagnosis can be made by i.d. injection of adrenaline or noradrenaline, which produces the characteristic rash. Although the lesions of AU typically respond to beta-blockers such as propranolol, the therapeutic options for AU are limited. Here, we report a case of AU that was resistant to beta-blockers and successfully treated with clonazepam. The clinical picture of AU resembles that of cholinergic urticaria (CU), however, positive noradrenaline test and negative acetylcholine skin test were useful for the differential diagnosis of AU and CU. Although his symptoms were resistant to several therapeutic methods including olopatadine (H₁ antagonist), lafutidine (H₂ antagonist) and propranolol, the severity and frequency of his attacks and his subjective symptoms were reduced by oral clonazepam, an anxiolytic benzodiazepine. Dermatologists should be aware that anxiolytic benzodiazepines may be a therapeutic option in AU.

Key words: adrenergic urticaria, anxiolytic drug, beta-blocker, clonazepam, noradrenaline test.

INTRODUCTION

Adrenergic urticaria (AU) is a rare condition that was first described by Shelley and Shelly in 1985.¹ Only 10 cases have been reported in the English-language published work.² AU is characterized by widespread pruritic, urticarial papules triggered by stress, trauma and emotional upset.^{1,2} Although the clinical picture of AU resembles that of cholinergic urticaria (CU), AU can be distinguished from CU by the presence of a white halo of vasoconstriction surrounding small red or pink wheals.³ AU is diagnosed by i.d. injection of adrenaline or noradrenaline, which produces the characteristic rash, and is distinguishable from CU by i.d. skin tests using adrenaline or noradrenaline.^{1,3} The lesions of AU typically respond to beta-blockers such as propranolol.^{1,3} In contrast, CU, first described by Duke in 1924, is characterized by pinpoint, highly pruritic wheals surrounded by large red flares that are typically evoked by stimuli such as exercise or heat, and are associated with an increase in the core body temperature.⁴ Here, we report a case of AU that was resistant to beta-blockers and successfully treated with clonazepam.

CASE REPORT

A 16-year-old male patient presented with a 5-year history of recurrent episodes of punctate pruritic, tingling wheals, heart palpitations and lower limb spasms when he became nervous during class and in the hot environment of a train. At another hospital, the wheals and other symptoms were resistant to H₁ antagonists. Laboratory tests demonstrated normal complete

blood cell counts and biochemical findings, including total immunoglobulin (Ig)E level, specific IgE level and thyroid function. The levels of circulating catecholamines (adrenaline, noradrenaline and dopamine) while the patient was asymptomatic were normal. The wheals were 1–2 mm in diameter resembling goose bumps with large red flares, and were accompanied by a partial white halo surrounding small red wheals.

Based on this history, the patient was first examined for CU. Oral and written informed consent for the study was obtained from the patient. During provocation tests, he could not complete a treadmill exercise test because his punctate urticarial symptoms were induced prior to the exercise test under monitoring by doctors, possibly causing psychological stress (Fig. 1). Moreover, he could tolerate warm bathing for only 1 min because of his punctate urticarial symptoms and tingling sensations in nervous environment under monitoring by doctors. At that time, his differential diagnosis was CU or AU. Autologous serum skin testing showed a positive response. Although an i.d. skin test involving acetylcholine (100 µg/mL) was negative without satellite wheals, it produced local sweating. Thus, acquired idiopathic generalized anhidrosis was excluded.

His clinical history showed that vigorous exercise under a relaxed environment did not induce these symptoms. Additionally, because he had wheals and heart palpitations that were strongly induced by emotional stress rather than the hot environment in the hospital, a diagnosis of AU rather than CU was made. The patient was tested for AU by i.d. injection of noradrenaline (1 µg/mL).^{1,3} The injection resulted in a small erythematous wheal with a halo of blanched skin (Fig. 2a). This

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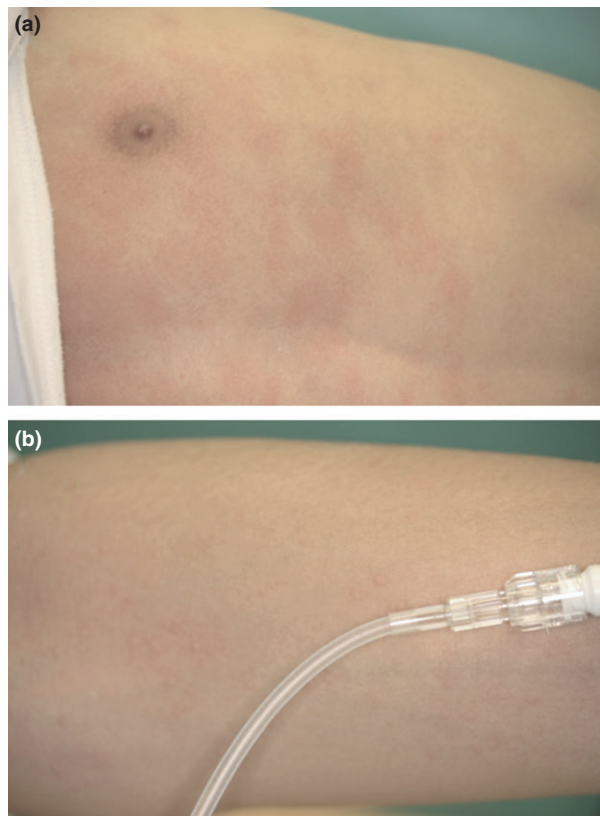


Figure 1. (a) Clinical images obtained from our patient. (b) Numerous punctate papules surrounded by red flares developed following an increase in body temperature.

noradrenaline-induced urticarial response was blocked by oral propranolol (10 mg) (Fig. 2b). Thus, AU was diagnosed.

Olopatadine (a H_1 antagonist) and lafutidine (a H_2 antagonist) failed to relieve his symptoms. Propranolol (20 mg once a day), which was reported as the most effective therapy for AU, also had no effect on his symptoms. Carvedilol, an α - and β -blocker, reduced the urticarial lesions. However, carvedilol failed to relieve his subjective symptoms, such as the tingling sensation and heart palpitations. He mainly had subjective symptoms, therefore, he was not satisfied with the effect of carvedilol.

Oral clonazepam, an anxiolytic benzodiazepine, was administered at 5 mg three times daily, based on a previous report suggesting that tranquilizers effectively ease AU symptoms.⁵ The severity and frequency of his attacks and his subjective symptoms in a nervous state were dramatically reduced by oral clonazepam. His symptoms of CU also gradually diminished with clonazepam treatment and he was satisfied with the effect of clonazepam.

DISCUSSION

There appears to be some overlap of symptoms in AU and CU, and their differential diagnosis is not easy. A case of AU in a

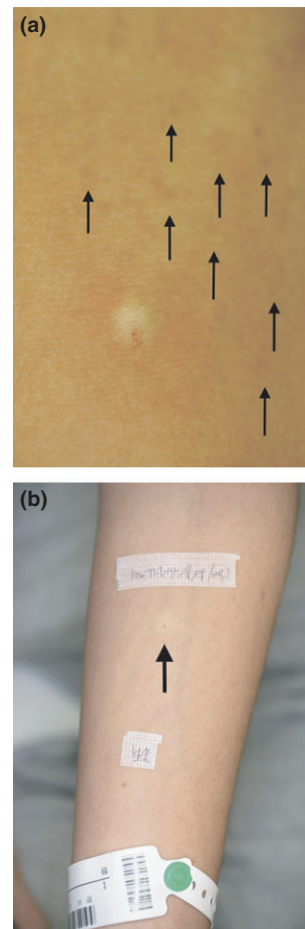


Figure 2. (a) Urticarial response induced by i.d. noradrenaline injection. A small erythematous wheal with a halo was induced by i.d. noradrenaline injection with no other drugs (arrow). (b) The urticarial response induced by noradrenaline injection was blocked by oral propranolol (arrow).

patient with CU has been reported.⁶ Hogan *et al.*² suspected that many cases of AU have been included within the diagnosis of CU because of the similarities in their presentations and limitations of current diagnostic methods, supporting the effectiveness of β -blockers for some cases of CU.^{6,7} Positive noradrenaline test and negative acetylcholine skin test strongly supported the diagnosis of AU but not CU in our case. Although we performed a noradrenaline test among 10 CU patients in our hospital, no patients showed a positive reaction to the noradrenaline test. This high rate of negative noradrenaline test among CU patients may support the use of the noradrenaline test in differential diagnosis between AU and CU (data not shown).

The therapeutic options for AU are limited, although AU typically responds to non-selective β -blockers such as propranolol.^{1,3} H_1 antagonists such as ketotifen and clemastine are not noted to provide symptomatic relief.^{1,3} Our case showed that symptoms of AU are resistant to H_1 and H_2 antagonists. It was remarkable that the anxiolytic benzodiazepine clonazepam was more effective for symptomatic relief of AU than propranolol

and carvedilol. However, because we used 20 mg propranolol once a day, which required relatively few doses compared with past reports, the effectiveness of propranolol may be limited.^{1,3}

Although precise mechanisms of AU remain unknown, AU is suspected to be associated with levels of circulating catecholamines (adrenaline, noradrenaline and dopamine). In our case, the levels of circulating catecholamines during attacks were not confirmed, but lower limb spasms might have been induced by sympathetic activation and high levels of catecholamines. Indeed, the brain noradrenergic system is activated by acute stress.⁸ Propranolol, the primary treatment for AU, is usually a remedy for hypertension and angina pectoris, and in contrast it can readily penetrate the blood-brain barrier and often be effective for improving anxiety, acute panic and post-traumatic stress disorder. We assume that the effectiveness of clonazepam in our case might have been linked to these broad effects of propranolol. However, further analysis of the effectiveness of anxiolytic benzodiazepines for AU is needed.

In summary, dermatologists should be aware that anxiolytic benzodiazepines such as clonazepam may be a therapeutic option in AU.

CONFLICT OF INTEREST: None declared.

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