Auricular erythermalgia showing excellent response to itraconazole: a case report

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***Abstract*:** Erythermalgia, a rare painful disorder, is characterized by recurrent pain attacking, warmth, and erythema that mainly involves the distal extremities. Red ear syndrome shares similar clinical features of erythermalgia afflicting the external ear with unilateral/bilateral distribution. The treatments of both diseases are still difficult without controlled therapeutics available up to date. A 12-year-old boy was referred because of 3 years of recurrent attacking of painful erythema and warmth that involved the ears alone, the episodes occurred several times daily with duration of dozens of minutes to hours for each flare. The symptoms could be relieved by cold water and triggered by heat stimuli as well as exciting and movement, and showed mild response to gabapentin, celecoxib, and topical lidocaine compounds in combination, but moderate to blocking injection of botulinum toxin to nervus auricularis magnus. However, systemic itraconazole 200 mg daily resulted in an excellent response after 5-week treatment, leading to milder erythema, warmth and burning sensation, shorter duration, and fewer relapses. The treatment continued for 6 months and then itraconazole was decreased to 100 mg daily for another 6 months until it was stopped, with maintenance of good conditions. In 3 months of follow-up after the treatment ceased, the patient had only 7 to 8 attacks over 10 days presenting as tolerable erythema that lasted for less than 10 min and relieved spontaneously, with absence of warmth and no need of treatment. We considered the patient to be a variant of erythermalgia rather than a red ear syndrome. The results showed that erythermalgia might involve the ears alone and itraconazole might be a potential agent for its treatment.

Keywords: erythermalgia, erythromelalgia, itraconazole, red ear syndrome, treatment

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Introduction

There are a few rare kinds of diseases, such as erythromelalgia (EM, also called erythermalgia),[1–5] red ear syndrome (RES),[6–8] and facial flushing, which may present as episodic auricular erythema associated with pain and warmth.

EM, a rare, recurrent, and chronic disease, is characterized by the classic triad of attacking redness, warmth, and burning pain.[1–5] It always involves the extremities symmetrically, mainly the hands and feet, and may extend to other body parts such as face, neck, ears, nose, tongue, and scrotum.[1–5] Sole involvement of EM on vulvae, ears as well as on checks had also been reported respectivelys.[2,4,5] Its triggering factors include touch, exertion, heat stimuli, movements, stress, raging, and so on.[1–5] However, cooling and elevating the afflicting limbs always alleviate the symptoms.[1–5]

RES, first described by Lance[6] in 1994, is characterized by recurrent, unilateral/bilateral, paroxysmal episodes of erythema, pain and burning sensation, and warmth of the external ears, sharing the similar clinical features, triggering factors and resemblant diagnostic criteria of EM. Its lesions may extend to the adjacent areas, but

are absent for extremity involvement. RES is classified as primary type that commonly occurs more often in younger individuals who may associate with migraine and paroxysmal hemicrania, and secondary form that is frequently seen in adults with female predominance accompanied by cervical disorders.[7,8] Some authors including our groups considered that RES might be a variant of EM.[5,9]

Facial flushing, triggered by multiple factors including a broad range of benign and malignant conditions, is a phenomenon of physiologic or a pathologic reaction presenting as visible facial reddening of the skin accompanied by a sensation of warmth, but it is always absent for pain. Flushing may be episodic or persistent. The lesion, resulted from the cutaneous vasculature and an increased vascular capacitance for dilation over the lesional area, usually involves the face, ears, neck, and upper chest.[10,11]

The diagnostic criteria of diseases mentioned above are based on their clinical manifestations; no identifiable criteria for their diagnosis are available up to date. Herein, we reported a refractory case presenting with episodic warmth, redness, and burning pain involving the ears alone that showed excellent response to itraconazole therapy.

Case report

A 12-year-old boy, without any other associations, was referred because of 3-year history of spontaneously recurrent, paroxysmal, and excruciating erythema and warmth involving both ears alone. The daily episodes were about 5 times in Spring, 7 even up to 15 in Summer and Autumn, and only 1 to 2 in Winter, each lasted dozens of minutes to hours. The flares had nocturnal predominance especially when lying down. The symptoms could relieve spontaneously and alleviated more rapidly at daytime than night hours. Warmth, movement, stress, exciting, and climbing stairs could trigger or worsen the attacks, whereas cold water, staying in cold room or in front of the electric fan, and sitting up at night hours might lead to a rapid relief for the flare. However, cleaning teeth, eating, drinking, brushing hair, and neck movement had no influence for the attacks. His medical and family histories were unremarkable. Palliative treatments such as ibuprofen and aspirin showed no beneficial for the symptoms.

Physical examination showed that both ears were mildly red (Figure 1(a) and (b)) with lower temperature (35.2°C for both) than the face (36.2°C) during the interval between the episodes. However, a rapid climbing of stairs for about 5 min led to evident reddening (Figure 1(c) and (d)) associated with marked warmth and pain for both ears, with normal range of heart rate and blood pressure. The temperature was 37.6°C, 37.2°C, 37.0°C, and 36.8°C for the left and right ears, the face, and peri-ears, respectively, during the ongoing episode. Dermoscopy test showed more obvious angiotelectasis during the flare than the interval between the episodes. Laboratory tests for complete blood cell count, biochemistry profiles, antinuclear antibodies, and auto-antibodies were either within normal limits or negative. Magnetic resonance imaging showed mild posticous cervical spondylopathy. Whole-exome sequencing of gene was not performed.

The patient was diagnosed with auricular erythermalgia. However, the disease showed mild response to combinative therapeutics of systemic gabapentin and celecoxib as well as topical lidocaine compounds. Twice blockade injections of botulinum toxin type A to nervus auricularis magnus resulted in moderate relief for the pain, but no change for the attacking frequency and reddening. Whereafter, the patient administrated itraconazole 200 mg daily after his parents signed the written informed consent and the Institutional Review Boards of the First Affiliated Hospital, Gannan Medical College, China, approved the ethics approval (LLSC-2020101009). The symptoms started ameliorating after about 2 weeks of treatment, and had an excellent improvement 5 weeks later, showing 1 to 2 attacks daily with minutes of duration. Itraconazole was decreased to 100 mg daily 6 months later that was used for another 6 months till it was stopped. During the later stage of treatment, the patient kept good condition with 7 to 8 attacks over 10 days, presenting as milder erythema and pain with absence of warmth, that was tolerable and could be controlled more easily than before; and non-attack period for 1 to 3 days might happen sometimes. No adverse effects including liver and renal damages presented. In 3 months of follow-up after stopping of treatment, the attacks had no significant changes as the patient did before, which lasted for less than 10 min and relieved spontaneously, with absence of warmth and no need of treatment.

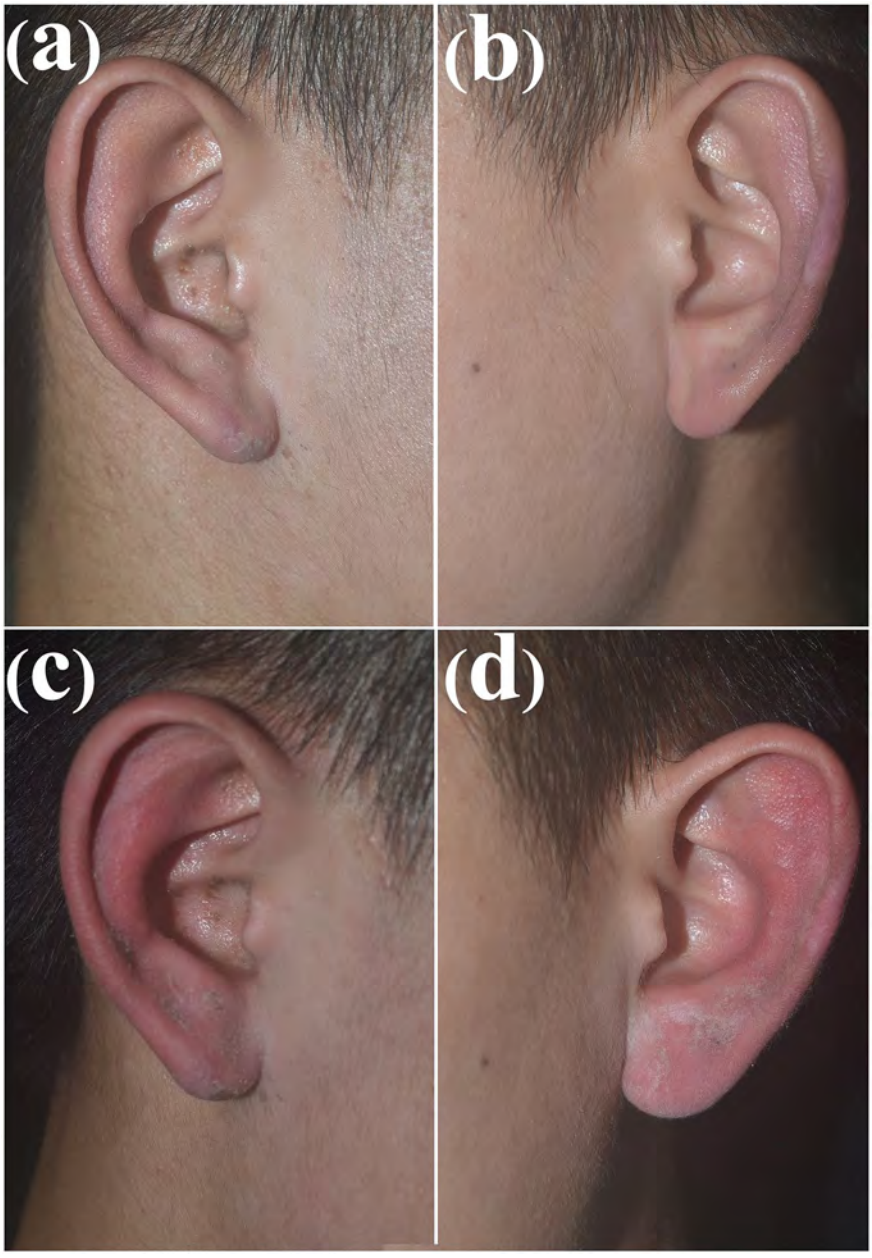

Figure 1. Cutaneous examination shows slightly red for the right (a) and left (b) ears in the interval between the episodes, and evident reddening for both ears (c, d) associated with warmth and tenderness during the attacking after rapid climbing of stairs.

Discussion

Based on the clinical manifestations, we considered the present patient to be an auricular variant of EM rather than RES although limb involvement was absent. As EM is used to describe the conditions fitting Thompson's 5 diagnostic criteria[1] with limb involvement primarily, with or without association of involvement of the face or other areas, and some individuals[2,4,5] fitted the diagnostic criteria[1] but lacked for extremity involvement like in our case, we supported that 'erythermalgia' be better than 'erythromelalgia' to describe such conditions, based on the term's origins.[4,5] We also supported Davis' opinion[12] that EM should be reserved for patients fitting Thompson's diagnostic criteria[1]

with or without other organ involvement, because its broad use may result in neglecting the factors causing flushing.[12] We also sustained that some RES might be a separate entity and some an auricular variant of EM.[4,5] The present condition should be distinguished from relapsing polychondritis, perichondritis, contact dermatitis, erysipelas, and so on. Because of highly disabling, EM might associate with increasing mortality and suicide.[3] Unfortunately, it still poses diagnostic difficulties up to date.

EM includes two subtypes: primary one, which is mainly caused by mutations of SCN9A, SCN10A, and SCN11A gene; and secondary one, for which its etiopathogenesis is not fully understood yet and may be associated with blood disorders, infections, drugs, connective tissue diseases, neuropathic diseases, and malignancies.[3] Although its mechanisms remain unknown yet, neural or vascular abnormalities or even both are considered to play important roles.[3] As patients with EM always have increased warmth and microvascular blood flux[13] as well as obvious angiotelectasis[4,5] during the episodes, those suggested that vasodilation might play important roles in the symptoms of EM.

The treatment for EM is still difficult and highly individualized although multiple drugs including vascular agents, sodium channel blockers, antidepressants, anticonvulsants, antihistamines, topical application of medications, and so on, alone or in different combinations have been used, showing variable results.[2–5,14] Cooling with cold water or ice over the affected areas was used in patients with poor response to medications, but it might lead to ulcerations and gangrenes in rare instances. Interestingly, our case showed poor response to traditional medications but had an excellent response to itraconazole, suggesting that itraconazole might be a potential agent for the treatment of EM. To our knowledge, no similar report has been described yet.

Itraconazole, a widely used agent for fungal infection diseases, was reported to be able to inhibit the inflammation and angiogenesis[15–17] including infantile hemangioma[18,19] and could reduce the pain of vulvodynia with prolonged treatment resulting in increasing pain reduction,[20] and it was also considered to be an anticancer agent in some conditions.[15,21] Itraconazole could inhibit the proliferation and promote apoptosis of hemangioma cells, reducing the angiogenesis *in vitro* by suppressing the platelet-derived growth factor-β activation and its downstream effectors including PI3K, Akt, 4E-BP1, and p70S6K, *via* downregulating the platelet-derived growth factor-D.[19] It could decrease the expression of tumor necrosis factor (TNF)-alpha and interleukin (IL)-6 as well as vascular endothelial growth factors (VEGFs) and their receptors including VEGF-A, VEGF-C, VEGFR-2, and VEGFR-3 in mice model, showing strong anti-inflammatory and anti-angiogenic effects;[17] and depress the binding of VEGF/VEGFR-2 and restrain the receptor signaling after the ligand stimulation.[22] However, Hara *et al.*[23] considered that the anti-angiogenic effect of itraconazole might be owing to its direct stimulation of apoptosis in endothelial cells, but not caused by inhibition of VEGF signaling. By suppressing VEGF-C expression, itraconazole could inhibit lymphangiogenesis, resulting in decrease of malignant pleural effusion in mice;[24] it also selectively depressed endothelial cells by targeting multiple angiogenic pathways including the VEGF, hedgehog, and mTOR.[17] Its inhibition on the mTOR signaling pathway, especially on mTORC1, resulted in decrease of inflammation-related angiogenesis and nerve growth factor protein expression in Schwann cells, which might be why itraconazole could relieve the pain of vulvodynia.[20] Although the exact mechanisms remain unknown, we speculated that the present result might be *via* itraconazole inhibiting the expression of VEGF and mTOR signaling pathway. Certainly, the exact mechanism needs further study. It also indicated that itraconazole might be a potential agent for the treatment of EM. Of course, the present is only one clinical case description; more case observations and further studies are necessary to determine whether itraconazole is indeed another therapeutic strategy for the treatment of EM.

Conclusions

As RES and EM share similar clinical features and diagnostic criteria, we considered that both RES and auricular EM, at least partly, might have described the same condition. Itraconazole might be a potential agent for the treatment of EM. We support that 'erythermalgia' is better than 'erythromelalgia' to describe the condition that fits Thompson's 5 diagnostic criteria[1] but is absent for limb involvement.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

An informed written consent signed by the patient's parents was obtained before the treatment. The ethics approval was approved by the Institutional Review Boards of the First Affiliated Hospital, Gannan Medical College, China (LLSC-2020101009).

Consent for publication

Written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Author contributions

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Juan-Hua Liu: Conceptualization; Data curation; Project administration; Resources; Validation; Writing – original draft.
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Conflict of interest statement

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