

Idiopathic pure sudomotor failure and cholinergic urticaria in a patient after acute infectious mononucleosis infection

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Summary

Idiopathic pure sudomotor failure (IPSF) is a subgroup of acquired idiopathic generalized anhidrosis, which is characterized by early age of onset, acute or sudden onset, concomitant sharp pain or cholinergic urticaria over the entire body, absence of autonomic dysfunction other than generalized anhidrosis, raised serum IgE level, and marked response to steroid. The aetiology of IPSF is still not well understood, but is thought to be caused by interference in cholinergic transmission in the eccrine glands of skin. IPSF after viral infection has rarely been reported in the literature. We describe a patient who developed generalized anhidrosis and cholinergic urticaria accompanied by heat intolerance after infectious mononucleosis infection. This is the first such case, to our knowledge, and the patient was successfully treated with steroid pulse therapy.

Acquired idiopathic generalized anhidrosis (AIGA) is an uncommon cause of hypohidrosis/anhidrosis, which is characterized by generalized absence of sweating without other autonomic or neurological dysfunction. Three subgroups of AIGA have been identified: idiopathic pure sudomotor failure (IPSF), sweat-gland failure, and sudomotor neuropathy.¹ IPSF is the commonest type of AIGA, and its features include early age of onset, acute or sudden onset, concomitant sharp pain or cholinergic urticaria over the entire body, absence of autonomic dysfunction other than generalized anhidrosis, raised serum IgE level, and marked response to steroid therapy.² The aetiology of IPSF is still unknown.

Infectious mononucleosis (IM) is caused by the Epstein–Barr virus (EBV), and the classic triad of presentation is fever, lymphadenopathy and

pharyngitis. Neurological complications such as encephalitis and meningitis occur in 5% of patients.³ Anhidrosis/hypohidrosis without other autonomic dysfunction after EBV infection has not been reported, to our knowledge. We present a patient with IPSF that developed after IM infection.

Report

A 22-year-old Taiwanese man presented with heat intolerance and hypohidrosis, associated with tingling pain and papular weals, mainly distributed over the trunk and limbs with sparing of the face and neck. The clinical symptoms were exacerbated by heat and physical exercise. Three weeks previously, the patient had been diagnosed with IM, based on the findings of intermittent fever for 2 weeks, lymphadenopathy, positive IgM and IgG antibodies to EBV capsid antigen, positive IgG antibodies to EBV nuclear antigen, and 21% atypical lymphocytes on full blood count. On physical examination, the patient appeared healthy, with the exception of generalized dry skin.

A thermoregulatory sweat test using the starch–iodine method revealed normal sweating on the forehead, neck and axilla, and only pinpoint sweating on

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the upper chest, back and bilateral palms. No sweating was noted on the abdomen or limbs. Intradermal injection of pilocarpine 1% 0.1 mL elicited sweating on the back, but a negative response on the arm (Fig. 1). Skin biopsies were taken from hidrotic (left palm) and anhidrotic (left arm) regions.

On histological examination of the palm specimen, the eccrine glands and ducts were found to have a normal structure, with only mild perivascular lymphocyte infiltration. However, the specimen from the left arm had a mixed inflammatory infiltrate of lymphocytes and eosinophils around the blood vessels and eccrine glands (Fig. 2a,b). No deposits of immunoreactants were seen on direct immunofluorescence. Using immunohistochemical staining, the main infiltrating cells in both regions were found to be CD3-positive lymphocytes (Fig. 2c,d). Toluidine blue failed to detect any mast cells.

Laboratory investigations gave normal results for full blood count, thyroid function tests, fasting blood sugar, serum levels of protein, electrolytes, creatinine, glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, autoantibodies and complement. However, the patient had a very high level of immunoglobulin E (4393 IU/mL; normal range 66.4–109.0 IU/mL).

Neurological examinations of both motor and sensory systems and autonomic function tests with heart-rate variability and sympathetic skin responses all gave normal results, as did magnetic resonance imaging of the head.

The patient was diagnosed as having IPSF with cholinergic urticaria. He was initially treated with oral antihistamine [loratadine 5 mg + pseudoephedrine sulfate 120 mg (Clarinase; Schering-Plough, Kenilworth, NJ, USA) twice daily for 2 weeks] but without benefit. He was then given methylprednisolone 500 mg daily intravenously for 3 days, followed by oral antihistamine as before for 1 month. The heat intolerance and cholinergic urticaria improved significantly. Another thermoregulatory sweat test was performed 1 month after steroid pulse therapy, which showed larger and more confluent areas of sweating on the patients trunk and limbs. Once treatment was concluded, follow-up was continued on an outpatient basis for a further 2 months, and there was no recurrence of heat intolerance according to the patient.

Anhidrosis/hypohidrosis occurring after acute infection has rarely been reported, and can be divided into two groups. The first group is anhidrosis/hypohidrosis with other forms of autonomic dysfunction, including hyporeflexia, orthostatic hypotension and tonic pupil. The second group is anhidrosis/hypohidrosis without autonomic dysfunction. There have been only four previously reports of anhidrosis without autonomic dysfunction (occurring after typhoid, paratyphoid,⁴ and H1N1 influenza infection⁵), and our case is the first report of anhidrosis/hypohidrosis after IM infection.

Several hypotheses regarding the aetiology of AIGA have been proposed based on the histopathological

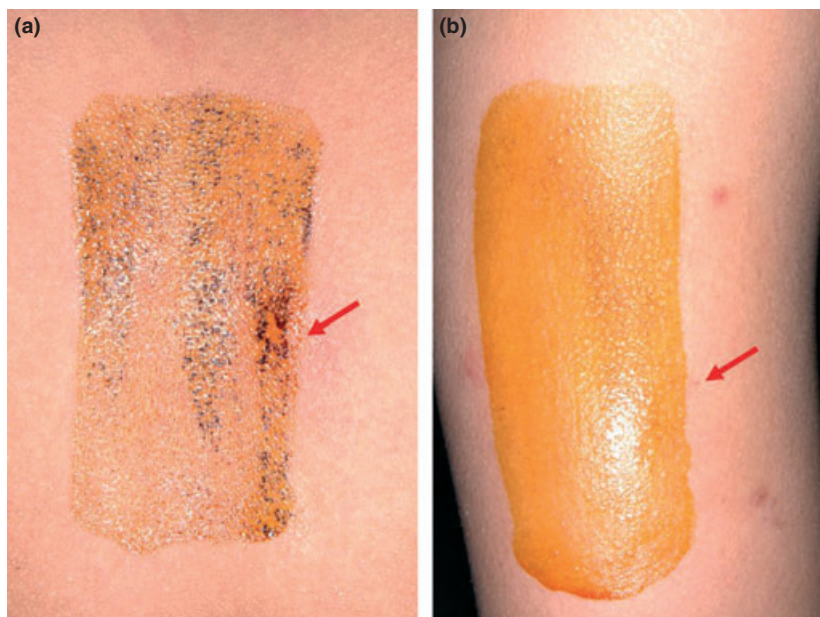


Figure 1 Intradermal injection (red arrows) of pilocarpine 1% 0.1 mL elicited (a) pinpoint-sized sweating on the back, with (b) a negative response on the upper arm.

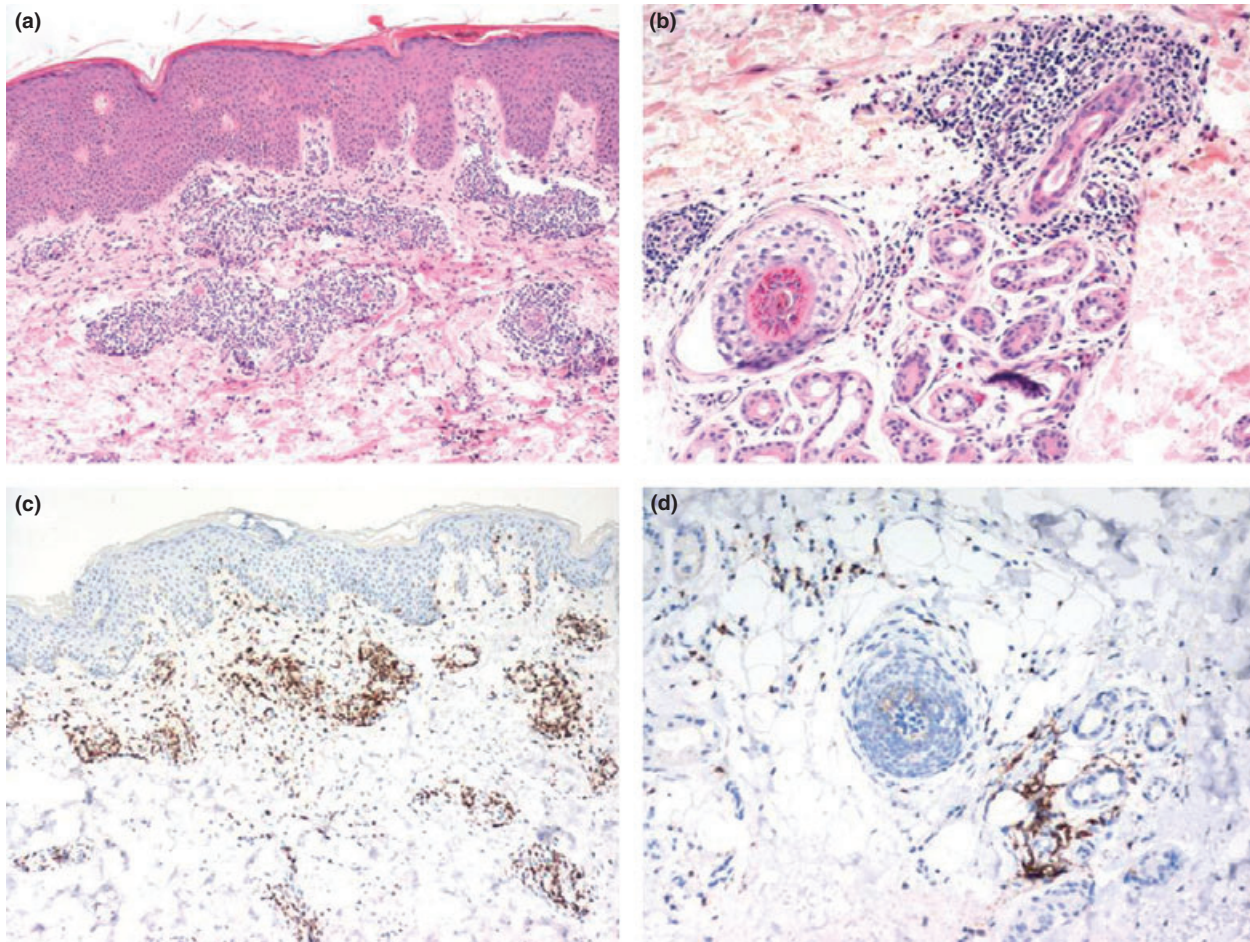


Figure 2 Biopsy specimen taken from an anhidrotic area of the left arm showed mixed inflammatory infiltrate with lymphocytes, eosinophils and scattered neutrophils (a) in the upper dermis and (b) around the eccrine glands. Haematoxylin and eosin, original magnification (a) $\times 100$; (b) $\times 200$. (c,d) Immunohistochemistry revealed that the infiltrating cells around (c) vessels and (d) eccrine glands were positive for CD3. Original magnification (c) $\times 100$; (d) $\times 200$.

findings, including T cell-mediated immune response,⁶ reduced expression of muscarinic acetylcholine receptors in eccrine glands,⁷ and occlusion of eccrine ducts.⁸

Based on the clinical and pathological findings in our patient, we propose that acute IM infection may cause a cross-reactive immune response (possibly initiated by a viral antigen), which interferes with cholinergic transmission in the eccrine glands of skin, thus causing anhidrosis. The pilocarpine test elicited a negative sweating response in the anhidrotic region in our patient, which is consistent with a defect within the cholinergic receptor.

The mechanism of cholinergic urticaria in AIGA is not well understood. Nakamizo *et al.*⁹ suggested that impaired sweat production may cause an elevation of

local acetylcholine levels, which may stimulate cholinergic receptors on mast cells and induce cholinergic urticaria. The distribution of cholinergic urticaria in our patient is corresponded to the anhidrotic region.

In conclusion, we describe a patient with IPSF and cholinergic urticaria occurring after IM infection, the first such case to our knowledge. Clinicians should be aware that anhidrosis may occur after certain bacterial or viral infections. Further studies are needed to clarify the mechanisms involved and the prognosis for such patients. Spontaneous remission occurs in some cases of IPSF, and most patients have an excellent response to systemic steroid. Our patient responded well to a combination of steroid and antihistamine, with no recurrence seen after 9 months of follow-up.

Learning points

- AIGA is an uncommon cause of hypohidrosis/anhidrosis, which is characterized by generalized absence of sweating without other autonomic or neurological dysfunction.
- IPSF is the commonest type of AIGA, and its aetiology is still unknown.
- Anhidrosis without autonomic dysfunction after certain infections has rarely been reported.
- Our case is the first report of anhidrosis/hypohidrosis with cholinergic urticaria after IM infection.
- We propose that acute IM infection may cause a cross-reactive immune response that interferes with cholinergic transmission in the eccrine glands of skin, thus causing anhidrosis.
- Spontaneous remission occurs in some cases of IPSF, and systemic steroid generally produces an excellent response.

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