JOURNAL OF
CUTANEOUS IMMUNOLOGY
AND ALLERGY

TYPE Case Report
PUBLISHED 23 September 2026
DOI 10.3389/jcia.2026.17427

OPEN ACCESS

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RECEIVED 21 July 2026
REVISED 30 August 2026
ACCEPTED 10 September 2026
PUBLISHED 23 September 2026

CITATION
Shimada Y, Ono H, Tochigi M, Taga F, Shimizu A, Kawano M, Asahina M and Sano K (2026) Case Report: Sjögren's disease diagnosed following generalized anhidrosis.
J. Cutan. Immunol. Allergy 9:17427.
doi: 10.3389/jcia.2026.17427

Case Report: Sjögren's disease diagnosed following generalized anhidrosis

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Sjögren's disease typically presents with initial symptoms such as dry mouth, dry eyes, fatigue, and joint pain. This report describes a case of Sjögren's disease diagnosed following the onset of generalized anhidrosis. The patient had experienced anhidrosis and elevated body temperature for the past 10 yrs. Physical examination revealed no skin rash or cholinergic urticaria. The Minor's test revealed anhidrosis over 98% of the body surface area. Although idiopathic anhidrosis was initially suspected, a detailed medical history revealed a history of dry eyes, dry mouth, and extensive dental caries. Laboratory tests showed positive antinuclear antibodies and anti-SS-A/Ro antibodies, while serum carcinoembryonic antigen levels and thyroid function were normal. Salivary gland scintigraphy and biopsy confirmed the diagnosis of Sjögren's disease. Histopathological examination of the anhidrotic areas revealed no obvious inflammatory cell infiltration or glandular atrophy characteristic of Sjögren's disease, but showed hydropic degeneration of the sweat glands and disruption of the two-cell-layer structure of clear and dark cells. These characteristic pathological changes are observed in acquired idiopathic generalized anhidrosis. However, this patient was a woman in her 50s who lacked typical features of acquired idiopathic generalized anhidrosis, such as elevated serum carcinoembryonic antigen levels and cholinergic urticaria. She did not respond to a half-pulse steroid therapy. Taking these factors into account, it was determined that this case was clinically diagnosed generalized anhidrosis associated with Sjögren's disease. This case represents a valuable example of a diagnosis of Sjögren's disease arising from the atypical initial symptom of generalized anhidrosis. In patients with anhidrosis, particularly those suspected of having acquired idiopathic generalized anhidrosis, it is extremely important to conduct a detailed medical history and systematic evaluation to ensure that underlying autoimmune diseases are not overlooked.

KEYWORDS
carbonic anhydrase II, GCDFP15, generalized anhidrosis, hydropic degeneration, Sjögren's disease

Introduction

Sjögren's disease (SjD) typically presents with three initial symptoms: dry mouth and eyes, fatigue, and joint pain. These three symptoms (dryness, fatigue, and pain) are observed in over 80% of (SjD) patients. Approximately 55% exhibit autonomic nervous system symptoms, and decreased sweating function has been reported as a statistically significant finding compared to healthy controls [1], but generalized anhidrosis as an initial symptom is extremely rare. Here, we report a case of SjD diagnosed following the presentation of generalized anhidrosis.

Case report

A 50-year-old Japanese woman presented to our department with the chief complaint of decreased sweating throughout her body. She had a history of a pituitary tumor. Ten years prior, she had noticed decreased sweating but had not sought medical attention. During summer, she experienced heat retention even in air-conditioned rooms and managed this with cold compresses. At her initial dermatological visit, there were no skin rashes and she reported no episodes suggestive of cholinergic urticaria. On further questioning, she reported a prior history of oral and conjunctival dryness and numerous treated dental caries. Minor's test revealed anhidrosis covering 98% of her body surface area (Figure 1).

Blood tests showed that carcinoembryonic antigen (CEA), thyroid function, and blood glucose were within normal ranges, and hepatitis B and C serologies were negative, ruling out hypothyroidism, diabetes, and active infection. CEA levels are elevated in acquired idiopathic generalized anhidrosis (AIGA) [2], but no such elevation was observed. Antinuclear antibody and anti-SS-A/Ro antibody were positive, raising suspicion of SjD, and the patient was referred to a rheumatologist. Subsequent tests confirmed reduced glandular function: Saxon test: 0.636 g (normal value ≥2 g/2 min), gum test: 3.98 mL (normal value ≥10 mL/10 min), Schirmer's test: 3 mm in the right eye and 2 mm in the left eye (normal value ≥5 mm/5 min). Imaging studies revealed decreased uptake in the submandibular and parotid glands and fatty infiltration of both parotid glands on salivary gland scintigraphy. Histological examination showed lymphocyte and plasma cell infiltration around the salivary gland ducts. Histopathological examination of the anhidrotic area using Minor's test revealed hydropic degeneration of the sweat glands. Based on these findings, the patient was diagnosed with generalized anhidrosis and SjD. After a 3-day course of intravenous methylprednisolone (500 mg/day), oral prednisolone 25 mg/day was initiated and gradually tapered. One year later, the patient noticed slight sweating in her hands and head. The patient is satisfied with the treatment for Sjögren's disease and the management of heat retention. Table 1 provides a timeline of the events.

Discussion

AIGA is a rare condition characterized by anhidrosis affecting more than 25% of the body surface area without other neurological abnormalities or sweat gland pathology; approximately 90% of cases occur in young men, and it is most common among Asian men [3, 4]. In this case, the AIGA diagnostic criteria were met. However, in diagnosing anhidrosis, the most important challenge is differentiating AIGA from secondary anhidrosis. To confirm the diagnosis, secondary causes, particularly autoimmune diseases, drug-induced causes, endocrine/metabolic disorders, and neurodegenerative diseases, must be ruled out. In this case, AIGA was initially suspected, but a detailed medical history and physical examination revealed a history of dental caries and dry eye, leading to an early diagnosis of SjD.

It has been reported that anhidrosis caused by SjD arises through two primary mechanisms: direct autoimmune inflammation of the sweat glands [5] and autonomic dysfunction [6]. In anhidrosis resulting from direct sweat gland damage, lymphocytic autoimmune hidradenitis plays a central role. Pathological examination reveals dense lymphocytic and plasma cell infiltration around the secretory portions of eccrine sweat glands, accompanied by glandular atrophy [7]. In anhidrosis caused by autonomic dysfunction, dysfunction of the postganglionic sympathetic cholinergic system is observed, and abnormal reduced sweating along dermatomes may be detected using the Quantitative Sweat Axon Reflex Test [6]. Histopathological examination in this case revealed hydropic degeneration of the sweat glands on hematoxylin and eosin staining, without glandular atrophy or marked inflammatory cell infiltration.

Sweat glands are composed of clear cells, dark cells, and myoepithelial cells [8]. In normal sweat glands, the secretory coil exhibits a bilayered architecture, with dark cells located in the inner layer and clear cells arranged in the outer layer. In this study, sweat glands were evaluated using carbonic anhydrase II (CAII), a marker of clear cells, and GCDFP15, a marker of dark cells [9]. Sano et al. reported that hydropic degeneration of clear cells, followed by cellular breakdown, frequently occurs in the anhidrotic skin of patients with AIGA, ultimately resulting in collapse of the bilayer architecture and glandular atrophy [10]. In the present case, the sweat glands showed hydropic degeneration without overt atrophy or accompanying inflammatory cell infiltration. This hydropic degeneration was associated with disruption of the bilayer structure, characterized by aberrant CAII expression in clear cells and sparse, markedly reduced GCDFP15 expression in dark cells (Figures 2, 3). Unlike previously reported pathological features of anhidrosis in SjD, the absence of infiltration of inflammatory cells and absence of sweat gland atrophy was an atypical pathological appearance. However the absence of inflammatory cell infiltration suggests that any preceding inflammatory process may have subsided during the 10-year disease course. It is also conceivable that inflammatory cytokines released by infiltrating immune cells caused irreversible damage to the sweat glands and adjacent autonomic nerve fibers, thereby contributing to the development of anhidrosis.

No standard treatment has been established for SjD-associated anhidrosis [11]. In contrast, pulse corticosteroid therapy has been reported to be effective in AIGA, with an overall response rate of approximately 73%, and early intervention is considered particularly important [10].

Hydropic degeneration likely represents an edematous change predominantly affecting clear cells and may reflect a milder,

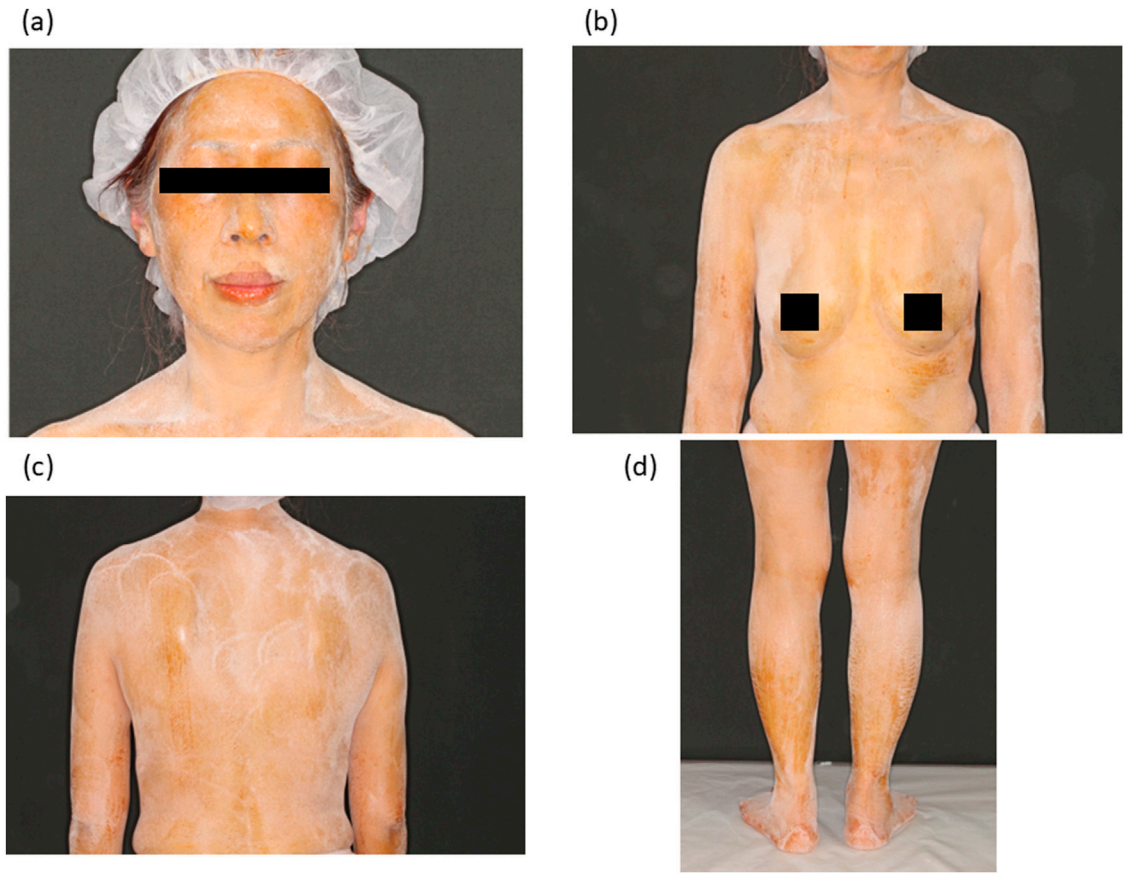

FIGURE 1
Minor's test identified areas of absent sweating across 98% of the body surface **(a–d)**.

TABLE 1 **Timeline of medical consultations and treatments.**

Timepoint (Event)	Clinical findings	Diagnostic workup & treatment	Clinical outcome
10 yrs prior	Generalized hypohidrosis, symptoms similar to heatstroke	None	Gradual progression
day 0 (first visit to a dermatologist)	Oral and conjunctival dryness, noted history of multiple treated dental caries	Minor's test, skin biopsy blood test	Diagnosis: Generalized anhidrosis Referred to rheumatology
day 135~ (first visit to the reumatologist, examination period)	Not applicable	Saxon, gum, schirmer tests Salivary gland scintigraphy/biopsy	Diagnosis: Sjögren's disease
day 265 (therapy induction)	Not applicable	Intravenous PSL (500 mg/day 3 days)	No significant improvement in sweating was observed
day 268~ (tapering phase)	Not applicable	Oral PSL (25 mg/day, tapered)	
1-year follow-up	No obvious skin rash	Oral PSL (5 mg/day, tapered)	The patient noticed slight sweating on her hands and head

potentially reversible stage of sweat gland injury compared with glandular destruction or atrophy. Recovery of sweating function may therefore still be possible if appropriate treatment is initiated before irreversible structural damage develops. This distinctive pathological change can be observed in AIGA. Moreover, the absence of inflammatory cell infiltration closely resembles the pathological features of non-inflammatory AIGA [9], in which the initial ductal inflammation may have subsided, leaving residual glandular abnormalities including hydropic degeneration and acinar atrophy. From a pathological perspective, the possibility that SjD was superimposed on pre-existing AIGA cannot be entirely excluded. Nevertheless, the patient was a woman in her 50s, lacked

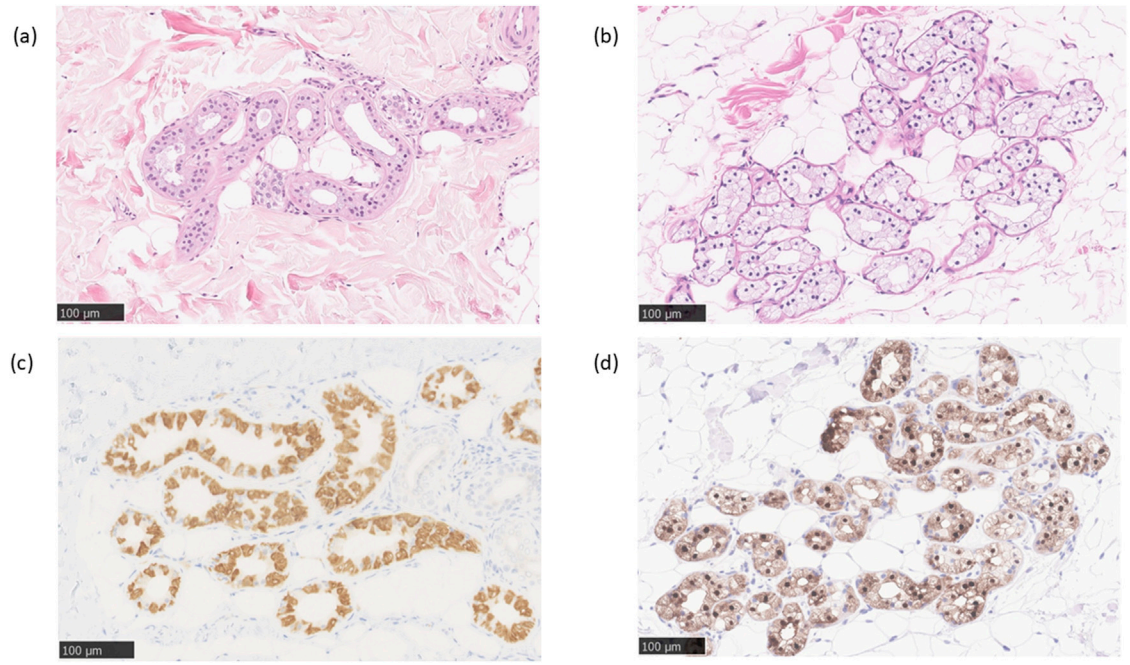

FIGURE 2
Comparison of sweat glands from normohidrotic skin of an AIGA patient and anhidrotic skin of the present case. **(a)** Sweat glands from normohidrotic skin of an AIGA patient. **(b)** Hydropic degeneration of secretory cells is readily apparent in the anhidrotic skin. **(c)** In the normohidrotic skin, CAII-positive clear cells are regularly arranged in the outer layer of the secretory coils. **(d)** Sweat glands from the anhidrotic skin show heterogeneous cytoplasmic CAII staining, with numerous cells exhibiting aberrant nuclear CAII immunoreactivity.

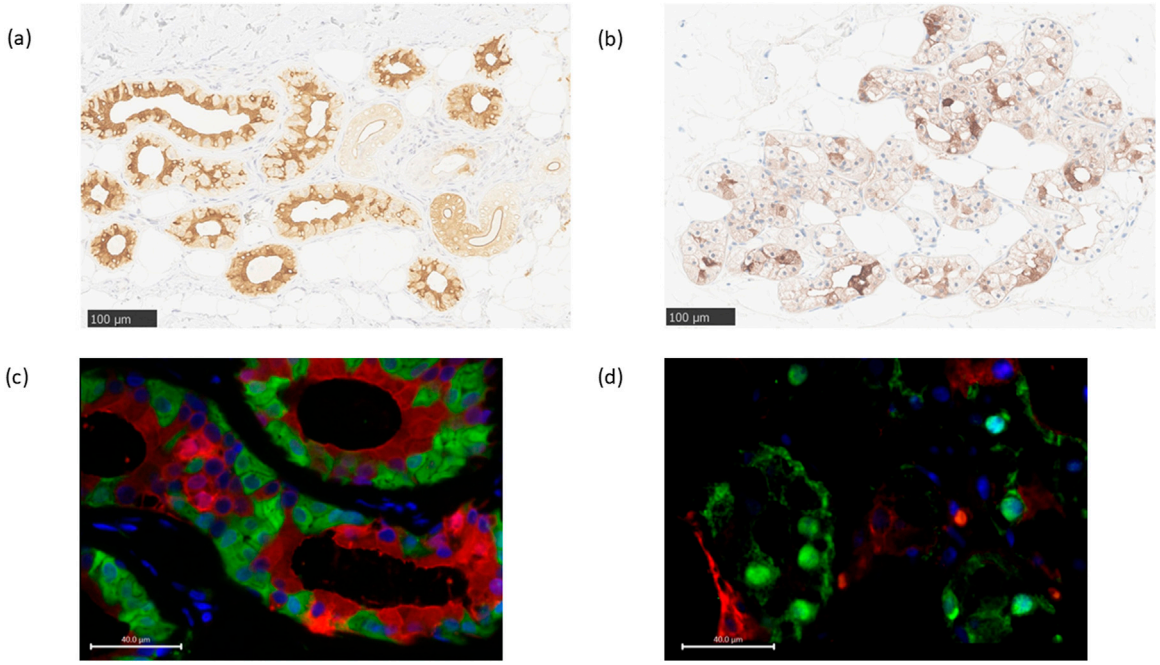

FIGURE 3
Immunostaining for GCDFP-15 and double immunofluorescence staining for CAII (green) and GCDFP-15 (red). **(a)** Immunostaining for GCDFP-15. GCDFP-15-positive cells are observed in the inner layer of normal sweat glands. **(b)** In skin with anhidrosis, GCDFP-15-positive cells are markedly reduced and scattered. **(c)** Double immunofluorescence staining of CAII (green) and GCDFP-15 (red). This demonstrates that the two-layer structure is well preserved in normal sweating skin. **(d)** In anhidrotic skin, the two-layer structure is almost completely disrupted, and the arrangement of the clear and dark cell clusters is disorganized.

features characteristic of AIGA such as elevated serum CEA levels and cholinergic urticaria, showed no response to a half-pulse steroid therapy. Based on clinical progress, it cannot be ruled out that SjD was coexisting with AIGA, but it was diagnosed as SjD associated with generalized anhidrosis.

This case is a valuable example of SjD presenting with the atypical initial symptom of generalized anhidrosis. In patients with anhidrosis, especially those suspected of having AIGA, a detailed medical history and systematic evaluation are essential to avoid overlooking underlying autoimmune diseases and to facilitate early therapeutic intervention.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Department of Dermatology, Kanazawa Medical University, Daigaku 1-1, Uchinada, Ishikawa 920-0293, Japan. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors participated in the study design, interpretation of results, data analysis, and manuscript review. YS, HO, MT, FT, and MK performed clinical diagnosis, testing, and treatment. KS contributed to the immunostaining of sweat glands and the pathological analysis, and YS contributed to the drafting of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Acknowledgments

We gratefully acknowledge the patient. We also thank David Price at English Services for Scientists, based in Hiroshima, for proofreading.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

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