RESEARCH LETTER

A Case of Acquired Idiopathic Generalized Anhidrosis with Anti-mucin 7 Seropositivity

Marie KITAMURA[#], Kazuki M. MATSUDA[#*], Hirohito KOTANI, Ayumi YOSHIZAKI and Shinichi SATO
Department of Dermatology, The University of Tokyo Graduate School of Medicine, 7-3-1, Hongo, Bunkyo-ku, Tokyo 1138655, Japan.
**E-mail: matsudak-der@h.u-tokyo.ac.jp*
[#]Contributed equally.
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To the Editor,

Acquired idiopathic generalized anhidrosis (AIGA) is a rare disorder marked by the sudden onset of widespread anhidrosis, frequently associated with cholinergic urticaria (1). It is classified into 3 subtypes based on the affected areas: sudomotor nerve impairment, idiopathic pure sudomotor failure (IPSF), and idiopathic sweat gland failure. Mucin 7 (MUC7) is a low-molecular-weight, secreted glycoprotein predominantly expressed in the exocrine glands such as the salivary glands and the eccrine sweat glands (2). It plays a critical role in maintaining oral health by contributing to the lubrication of the oral cavity, facilitating the clearance of pathogens, and supporting mucosal defence mechanisms. Its clinical relevance has been explored in the context of oral diseases, respiratory infections, and as a biomarker in certain systemic conditions. Herein, we report a case of IPSF with seropositivity to MUC7 and discuss the potential involvement of anti-MUC7 autoantibodies in its pathogenesis.

A 28-year-old woman presented to our dermatology department with painful wheals and decreased sweating, first noticed during bathing and exercise 3 months earlier. Initial treatment with oral antihistamines and autonomic nervous system modulators at another clinic was ineffective. Her medical and family histories were unremarkable, except for her grandfather's history of gastric cancer and grandmother's diabetes mellitus. Upon admission in June 2023, thermoregulatory sweat test by Minor method using the iodine–starch reaction revealed widespread anhidrosis affecting 89% of her body without dermatomal patterns, sparing areas such as the axillae and palms (**Fig. 1**A). In an acetylcholine intradermal test, sweat induction was observed in hidrotic areas but not in anhidrotic areas (Fig. 1B). Histological examination of skin biopsies from hidrotic and anhidrotic areas showed no inflammation or structural abnormalities in the eccrine glands in haematoxylin and eosin staining (Fig. 1C). Laboratory tests showed no significant abnormalities, including thyroid and autoimmune markers encompassing SS-A and SS-B autoantibodies. Commercial testing for anti-ganglionic acetylcholine receptor autoantibodies yielded negative results. Genetic testing for mutations associated with Fabry's disease was performed after obtaining written informed consent (approval number: 2023051G) and yielded unremarkable results. Neurological evaluations, including autonomic nervous system assessments such as the heart rate variability test and myocardial sympathetic nerve scintigraphy, revealed no abnormalities.

We further performed an indirect immunofluorescence assay using the patient's serum and a normal skin sample, which revealed IgG deposition within the eccrine glands (Fig. 1D). Proteome-wide autoantibody screening utilizing wet protein arrays, as previously described (3), identified seropositivity to 135 autoantigens, including 8 secreted proteins (Fig. 1E and Table I). Among these, MUC7 exhibited the strongest seropositivity. Comparable levels of seropositivity to MUC7 have been observed in certain cases of systemic lupus erythematosus (SLE) and systemic sclerosis (SSc), as documented in the comprehensive autoantibody database (UT-ABCD; Fig. 1F) (4). Additionally, data from the Human Protein Atlas revealed that MUC7 is specifically expressed in the eccrine sweat glands, as well as in the salivary glands (Fig. 1G) (5).

Diagnosing the case as IPSF, methylprednisolone (mPSL) pulse therapy (1 g/day for 3 days) was initiated, resulting in a marked improvement in sweating and symptom relief. The Dermatology Life Quality Index (DLQI) score, which has been shown to correlate with AIGA severity (6), decreased from 9 to 4 after the first cycle. Recurrent symptoms 4 weeks later were managed with a second mPSL pulse, further reducing the DLQI score. Additional pulses administered at 8 and 16 weeks sustained remission, with scores eventually improving to 2.

AIGA is thought to involve an autoimmune mechanism, as evidenced by the high efficacy of immunosuppressive therapies including mPSL pulse therapy and its association with autoimmune conditions (1). Emerging research has identified autoantibodies against specific targets, including muscarinic receptors, in AIGA. However, the prevalence of such antibodies is low, and their role in the pathogenesis of AIGA has not been clearly established. Autoantibodies targeting mucin have been previously reported in inflammatory bowel diseases and autoimmune gastritis (7). Anti-MUC7 autoantibodies may disrupt the skin microbiome by impairing the antimicrobial activity of MUC7, potentially leading to host sensitization to fungi, a phenomenon previously observed in cholinergic urticaria (8). Notably, anti-MUC7 autoantibodies have been detected in systemic autoimmune rheumatic diseases such as SLE and SSc

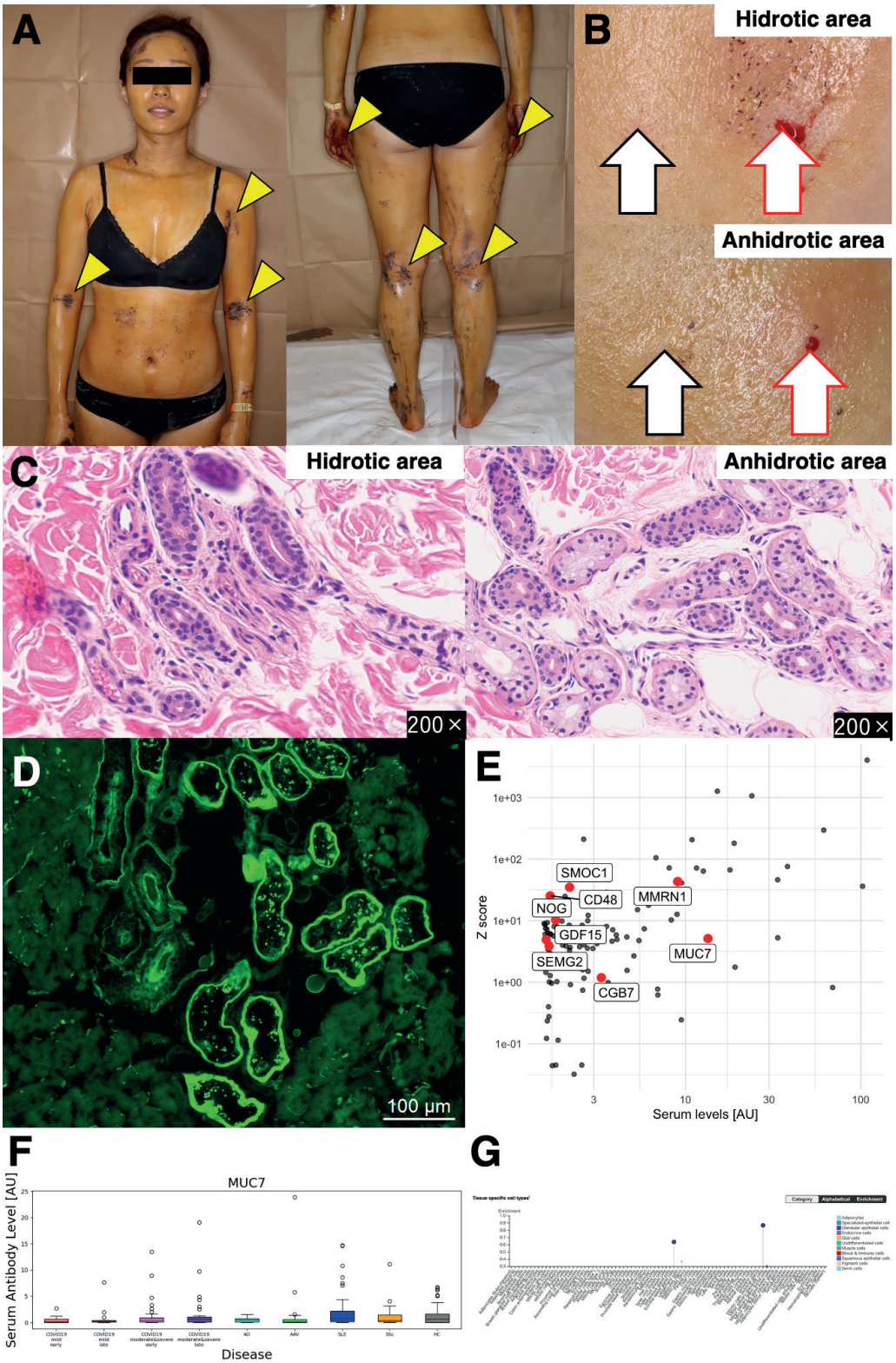

Fig. 1. Clinical, histopathological, and immunologic features of the presented case. (A) Thermoregulatory sweat test by Minor method visualized hidrotic areas (yellow arrowheads). (B) Acetylcholine intradermal test in hidrotic and anhidrotic area. Sweating was induced by acetylcholine intradermal injection (red arrows) only in the hidrotic area. Normal saline (black arrows) did not induce sweating in either area. (C) Histopathological images from a skin biopsy of the hidrotic and anhidrotic area. No morphologic change in the eccrine sweat glands with minimal inflammation was observed in both areas. (D) Indirect immunofluorescence engaging the patient's serum and a normal skin sample revealed IgG deposition within the eccrine glands. (E) A scatter plot illustrates autoantibody levels detected from the patient's serum. The X-axis shows absolute serum levels, while the Y-axis represents Z scores compared with sex and age-matched healthy controls (n=12). Secreted autoantigens are highlighted in red. AU: arbitrary unit. (F) A box plot illustrates the serum levels of anti-MUC7 autoantibodies in various conditions. The data were referenced from the autoantibody comprehensive database (UT-ABCD). (G) A lollipop chart shows the expression levels of MUC7 among human tissues. The data derive from the Human Protein Atlas.

Table I. Autoantibodies targeting secreted proteins in the presented case

Autoantigens	Serum levels [AU]	Z-scores
MUC7	13.432	5.118
MMRN1	9.026	43.034
CGB7	3.312	1.184
SMOC1	2.184	34.79
NOG	1.817	10.215
CD48	1.692	25.25
SEMG2	1.668	3.877
GDF15	1.606	4.894

(Fig. 1F), which are often accompanied by sicca symptoms. Given the differential expression of MUC7 in the exocrine glands (Fig. 1G), experimental studies, including antibody transfer models in mice, are essential to establish a causal relationship between these autoantibodies, anhidrosis, and sicca symptoms. Additionally, identifying other molecular targets relevant to the diverse subtypes of AIGA could further illuminate its complex pathophysiology and guide more targeted therapeutic strategies.

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Ethical approval information: This study was approved by the University of Tokyo Ethical Committee (Approval number 2023051G).

Data availability: All data are incorporated into the article and its online supplementary material.

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