Labial angioedema in an elderly woman with hypogammaglobulinemia, grass allergy and urticaria: a case report

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Abstract

This is the clinical case of an elderly woman with stabilized polypathology, suffering from a grass allergy, multiple intolerances, episodes of urticaria, and recurrent labial angioedema. The diagnostic work-up, carried out over many years, failed to yield definitive conclusions, as increases in eosinophils, elevated immunoglobulin (Ig) E, and autoimmune phenomena were all ruled out. Only in later life was a mild hypogammaglobulinemia discovered, specifically an IgG2 subclass deficiency. According to the recent DANCE classification, the labial angioedema was interpreted as idiopathic histaminergic angioedema, which was also suggested by the fact that, after initiating long-term therapy with a second-generation antihistamine, the clinical manifestations did not recur. Although we investigated possible links between chronic urticaria, angioedema, and hypogammaglobulinemia, the case remains partially unresolved, as reports of IgG subclass deficiency associated with angioedema are extremely rare. Only targeted genetic analyses could better define this inborn error of immunity, especially considering that hypogammaglobulinemia was also found in a family member.

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Introduction

Angioedema (AE) is a condition mediated by complex and partially unknown etiopathogenetic mechanisms. Clinical presentation is often crucial to distinguish between histaminergic and bradykininergic forms. The duration of the episodes, the response to antihistamines or corticosteroids, and associated conditions often point to the underlying mechanism. AE may occur alone or alongside wheals. Histaminergic AE is often associated with superficial urticaria: approximately 40% of patients with urticaria develop AE.[1,2] It may be triggered by allergic, pseudoallergic, or anaphylactic reactions. Bradykinin-mediated AE is more common in the elderly, often due to angiotensin-converting enzyme inhibitors (ACEIs). Acquired C1-inhibitor deficiency, another bradykinin-mediated form, predominantly affects older adults. In contrast, hereditary AE persists throughout life. Drug-induced AE disproportionately affects older adults, often caused by ACEIs, aspirin, or non-steroidal anti-inflammatory drugs. Second-generation antihistamines, with omalizumab if necessary, are effective and well tolerated in older adults with mast cell-mediated urticaria.

However, these therapies are ineffective for bradykinin-mediated AE, making an accurate diagnosis essential to avoid airway obstruction and unnecessary or ineffective treatments. We describe the case of an elderly woman with longstanding allergic manifestations involving both skin and mucosa, recently diagnosed with hypogammaglobulinemia.

Case Report

An 82-year-old woman presented in February 2024 with lower lip edema, accompanied by red mucosa and blisters (Figures 1 and 2). Her medical history is extensive. Her maternal grandmother had bronchial asthma. A brother suffers from juvenile-onset allergic asthma, eczema, diabetes, and hypogammaglobulinemia. The patient developed allergic asthma at the age of 22, triggered by

grasses and mites. An intradermal test once led to anaphylactic shock. Her condition was managed with triamcinolone and desensitization therapy. Surgical history includes excision of cutaneous melanoma, quadrantectomy, and radiotherapy for breast ductal cancer. Medical history includes bilateral carpal tunnel syndrome, two pneumonias, bilateral sensorineural hearing loss, cervical and knee arthrosis, osteoporosis, psoriatic nail changes, gastroesophageal reflux disease, cholelithiasis, renal microlithiasis, and carotid atheromasia. Vaccination history comprises 5 COVID-19 vaccine doses; tested positive for COVID twice. Chronic therapy includes omeprazole, berberine, red rice extract, zolpidem, cholecalciferol, melatonin; as needed: etoricoxib, betahistine, hyaluronic acid infiltrations. Known allergies are chloramphenicol, tetracyclines. Old allergy tests showed a positive patch test for nickel; total immunoglobulin (Ig) E was normal [49 UI/mL; (nv<200)], with sensitization to *Lolium perenne* and *Phleum pratense*. Complement components C3c, C4, and C1-inhibitor (48 mg/dL; nv 15-35) were normal (Table 1).

Four years ago, she had a single episode of bronchial asthma, treated briefly with beclomethasone/formoterol inhalers. In the same year, she experienced a skin reaction attributed to food allergy (diffuse urticaria on the abdomen, 5-6 cm red patches with mild pruritus), requiring emergency care and intravenous corticosteroids. Resolution was slow (Figures 3 and 4).

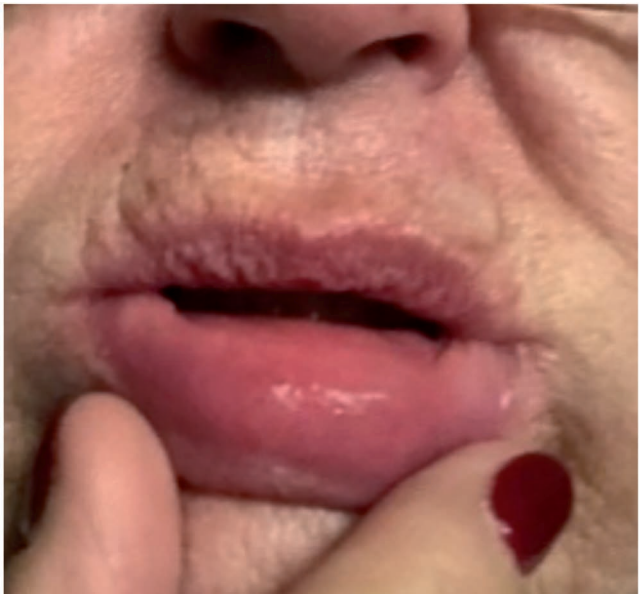

Figure 1. Recent appearance of edema of the lower lip accompanied by red mucosa and blisters.

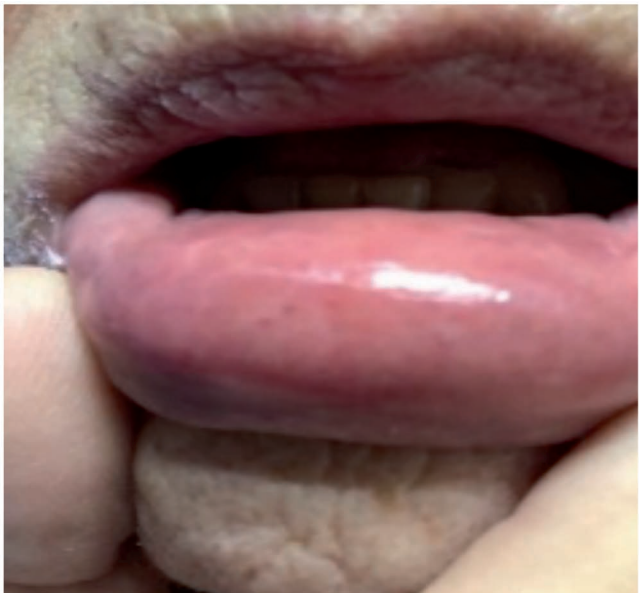

Figure 2. Close-up view of labial angioedema.

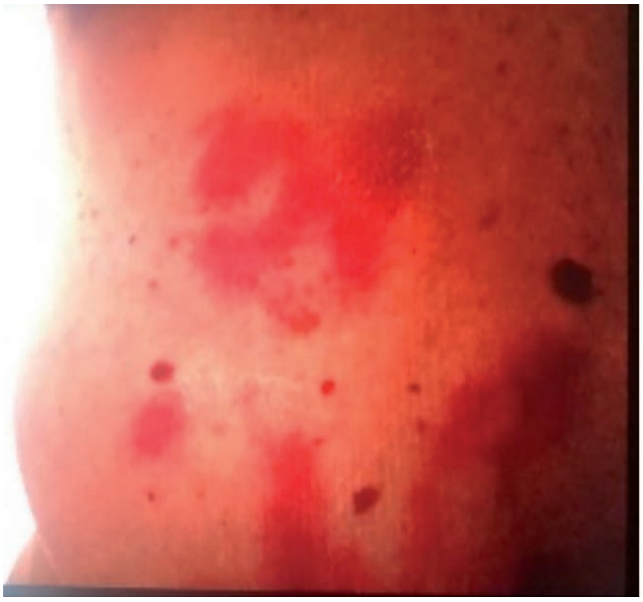

Figure 3. Four years earlier, widespread urticaria, 5-6 cm red patches with mild itching on the abdomen.

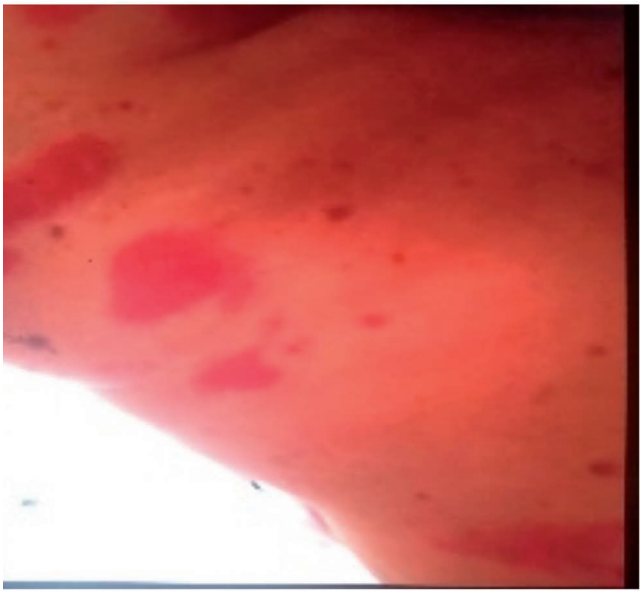

Figure 4. Lateral view of widespread abdominal urticaria.

Table 1. Summary table of the main laboratory tests performed over 16 years (from 2009 to 2025).

	Laboratory test					Normal range
	04/2009	05/2022	12/2023	03/2024	02/2025	
Red blood cells (×10^{12}/L)			4.71		4.73	4.50-5.50
Hemoglobin (g/L)			141		144	135-160
White blood cells (×10^{9}/L)			6.62		5.22	4-10
Neutrophils (×10^{9}/L)			3.98		2.83	1.9-8
Lymphocytes (×10^{9}/L)			1.70		1.61	0.90-4.00
Monocytes (×10^{9}/L)			0.67		0.49	0.20-0.96
Eosinophils (×10^{9}/L)			0.23		0.27	0.00-0.50
Total protein (g/L)		65.3		66.2	66.8	66-88
Albumin (g/L)		64.4		63.4	62.9	55.8-66.1
α-1-globulins %		4.3		4.3	4.2	2.9-4.9
α-2-globulins %		9.9		10.3	10.9	7.1-11.8
β-1-globulins %		6.1		6.2	5.9	4.7-7.2
β-2-globulins %		5.2		5.3	5.6	3.2-6.5
γ-globulins %		10.1*		10.5*	10.5*	11.1-18.8
Sodium (mmol/L)			146		143	136-145
Potassium (mmol/L)			4.1		4.0	3.5-5.1
Chlorine (mmol/L)			107		106	98-107
Magnesium (mmol/L)			0.90			0.70-1.05
Complement C3c (g/L)	1.41				1.43	0.90-1.80
Complement C4 (g/L)	0.35			0.31	0.38	0.10-0.40
C1 inactivator (mg/L)	480*			316	395*	210-390
Complement C1q (mg/L)				306	237	165-280
Urica acid (mmol/L)					0.32	0.15-0.35
IgA (g/L)		1.02			1.04	0.80-5.00
IgG (g/L)		7.31			7.66	6.00-16.00
IgG (g/L)			6.83*			7.00-16.00
IgM (g/L)		0.42			0.63	0.40-2.40
IgE total (UI/mL)	49					<200
Specific IgE *Lolium perenne* (kU/L)	3.50*					<0.1
Specific IgE *Phleum pratense* (kU/L)	2.72*					<0.1
Fecal calprotectin (ug/gr)			303.3*		61	<100
Homocysteine (umol/L)					15.10	0-20
ANA (title)				1:80 dotted fine		<1:80
ENA screening				Negative		Negative
Anti-thyroid peroxidase (kU/L)				1.8		<16
Anti-thyroglobulin (kU/L)				<10		<10
Anti-transglutaminase IgA (CU)			1.5			<20
IgG1 (g/L)			4.424			3.800-9.300
IgG2 (g/L)			1.788*			2.400-7.000
IgG3 (g/L)			0.313			0.200-1.750
IgG4 (g/L)			0.300			0.040-0.850
Tryptase (ug/L)			5.1			1.0-11.0
β-2-microglobuin (mg/L)			2.09			0.80-2.34
CPK (U/L)			139			20-180
C-reactive protein (mg/L)	0.82					<5
TSH (mIU/L)					1.38	0.20-4.00
FT4 (pmol/L)					17.10	9.00-22.00
D-dimer (ug/L FEU)					552	<800
ACE (U/L)				54		13-64
Stool antigen test *Helicobacter pylori*				Negative		Negative

IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IgE, immunoglobulin E; ANA, antinuclear antibodies; ENA, antibodies anti extractable nuclear agents; CPK, creatine phosphokinase; TSH, thyroid stimulating hormone; FT4, free thyroxine; ACE, angiotensin converting enzyme; *Altered value.

Later in the autumn, she had labial AE with aphthous stomatitis. An allergist diagnosed her with oral allergy syndrome (OAS) in a patient already allergic to inhalants and nickel.[3] Skin tests were not performed due to her history of anaphylactic shock. She later experienced another episode of facial edema. More recent symptoms included recurrent rhinosinusitis and laryngitis, treated with levofloxacin, antihistamines, corticosteroids, and beclomethasone aerosol therapy.

She also developed high blood pressure and frequent tachycardia with extrasystoles, prompting treatment with bisoprolol. She reported transient diarrhea and tachycardia after ingesting tomatoes.

Over the past 12 years, she has had recurrent episodes of upper lip edema, later extending to the lower lip. On one occasion, she linked the reaction to aspirin. During the most recent episode, in winter 2024 (Figures 1 and 2), treatment with cetirizine and corticosteroids resolved the symptoms in 4 days.

Recent lab results: specific IgE for shrimp and tomato <0.10 kUa/L; normal PTH, calcitonin, cortisol, ACTH, renin, aldosterone, eosinophils and basophils within the normal range, C4, C1q, and C1-inhibitor normal, normal B, T, and NK lymphocytes, antinuclear antibody weakly positive (1:80, fine speckled), extractable nuclear antigen screening negative, normal β2-microglobulin and thyroid-stimulating hormone, and negative anti-thyroglobulin and anti-thyroperoxidase antibodies (Table 1).

Differential diagnoses considered were i) chronic spontaneous urticaria; ii) OAS; iii) recurrent histaminergic AE due to hypersensitivity; iv) idiopathic histaminergic AE evolving into granulomatous cheilitis;[4,5] and v) mast cell activation syndrome (MCAS).[6]

Further testing revealed: mild hypogammaglobulinemia (10.5%; nv 11.1-18.8); total IgG 6.83 g/L (nv 7-16); IgG subclasses – IgG-2: 1.78 g/L (nv 2.4-7.0); negative anti-tTG IgA and anti-endomysium Ab; fecal calprotectin initially elevated (303 µg/g stool; nv<100), later decreased to 61 µg/g; tryptase 5.1 ug/L (nv 1.0-11); plasma ACE 54 U/L (nv: 13-64); negative stool test for parasites, occult blood, coproculture, and urine colture; negative *Helicobacter pylori* stool antigen (Table 1). The patient was started on continuous second-generation non-sedating H1-antihistamine drug (cetirizine 10 mg daily) for 5 months, with only short reaks. No AE or urticaria recurred, though she experienced minor ulcerations on the tongue. She received autologous platelet-rich plasma infiltrations in her knees, without AE recurrence. She adheres to a nickel-free diet: no tomatoes, dried fruit, legumes, chocolate, or wine.

Discussion

This is a complex case involving an elderly woman with a long-standing history of allergic diseases and hypersensitivity reactions. Notably, she exhibited neither eosinophilia nor elevated IgE. A recent diagnosis of selective IgG2 deficiency adds to the complexity. Her episodes of labial AE never coincided with respiratory symptoms or urticaria. The symptoms began 12 years before diagnosis.

While an evolution toward granulomatous cheilitis cannot be ruled out, ACE and calprotectin were normal, and a lip biopsy was not recommended.

Regarding MCAS, baseline tryptase was normal, though no post-episode sample was collected. According to the classification by Cicardi *et al*.,[7] this case aligns with recurrent idiopathic or hypersensitivity-related histaminergic AE. C4, C1q, and C1-inhibitor were consistently normal, and autoimmune/neoplastic diseases were excluded.

The DANCE international consensus introduced five types and endotypes of AE with standardized terminology.[8,9] This patient may fall under mast cell-mediated AE (AE-MC) or AE of unknown mechanism. Isolated histamine-mediated AE is an uncommon form of chronic urticaria. AE, with or without wheals, is seen in 30-50% of patients with chronic spontaneous urticaria.[1,2] Although AE and urticaria often co-occur, they need not be simultaneous.

Recurrent histaminergic AE, even in the absence of hives, supports the diagnosis of chronic urticaria.[10] AE is not an indicator of severity but is linked to a longer disease course.[11] Rare cases in the literature describe those associated with immunodeficiency.[12,13]

In elderly patients, AE or urticaria may represent the first manifestation in a small subset.[14] Older individuals with AE-MC show a higher prevalence of autoimmune disease and a lower rate of autoallergic forms. Some studies report an association between AE and autoimmune thyroiditis or hyperuricemia in the elderly.[15,16]

In the suspected inborn errors of immunity (IEI), next-generation sequencing using a targeted gene panel is recommended.[17] However, this was not applied in our case.

Experimental studies have found pathogenic variants in *TNFRSF13B/TACI*, *CARMIL2*, *STAT1*, *STAT3*, and *ORAI1* genes in young patients with immunodeficiency.[18,19] In particular, *STAT1* gain-of-function mutations are associated with a wide range of IEIs phenotypes. This line of investigation could also be extended to elderly patients, like ours with IgG2 deficiency, to explore possible pathogenic variants associated with AE, urticaria, and non-specific allergic phenomena, especially in the absence of classic atopic markers such as high IgE or eosinophilia.

Conclusions

The diagnosis of recurrent histaminergic AE without wheals in this complex case of acquired idiopathic AE was one of exclusion, supported by the positive response to prolonged antihistamine therapy. The last onset of hypogammaglobulinemia with selective IgG2 deficiency is currently considered unrelated, as there is insufficient evidence in the literature to support a direct association with AE.

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