

associated with wheeze before 3 years of age in all children, unlike in our study. It may be argued that the association between maternal anemia and childhood asthma is explained by residual confounding because we additionally adjusted our results for history of food allergy and vitamin D supplementation in infancy that may explain part of the discrepancy between the studies. Furthermore, we additionally used FeNO and Rint as objective tools to support the diagnosis of asthma and found no association.¹⁰

An important strength of this study is the large study population drawn from the general population and the wide range of potential confounders that have been taken into account. A limitation is that the information on wheezing and asthma diagnosis was obtained by parent-reported questionnaires. This could have led to misclassification of the outcome because physician diagnosis provides more accurate outcome diagnosis. However, only when misclassification was also related to hemoglobin levels would it have influenced our results, and this is unlikely.

In conclusion, this study did not confirm the association between maternal hemoglobin levels during pregnancy and wheezing in early childhood or asthma outcomes at the age of 6 years.

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Acquired C1 inhibitor deficiency: should we monitor for associated antibody deficiency?

Acquired angioedema (AAE) with C1 inhibitor (C1-INH) deficiency usually presents after the fourth decade and is characterized by local swelling that most commonly affects subcutaneous tissue (face, hands, arms, legs, genitals, and buttocks), abdominal organs (stomach, intestines, and bladder), or upper airways (larynx).^{1–3} Unlike the more common spontaneous angioedema with wheals, AAE does not respond to conventional treatments, such as antihistamine or corticosteroids.

AAE is associated with monoclonal gammopathy of unknown significance (MGUS) and B-cell lymphoproliferative disease. Castelli et al² found that in 32 patients with AAE, 13 (40%) had MGUS and an additional 9 (28%) had lymphoproliferative disease. This finding is significantly higher than the 3% rate observed in the general population younger than 70 years.⁴ AAE may occur before or after the occurrence of lymphoproliferative disease. Diagnoses may be separated by several years.⁵

Antibody deficiency, also associated with B-cell lymphoproliferative disease, has not been reported in published cohorts of AAE. We report 3 cases of AAE with antibody deficiency and highlight the need to measure immunoglobulins on a regular basis in these patients.

Patient 1 was a 29-year-old, white, Irish woman who had autoimmune lymphoproliferative syndrome (ALPS) due to a heterozygous nonsense mutation in exon 9 of the *FAS* gene. At 18 months of age, she developed acute lymphoblastic leukemia (ALL) for which she received chemotherapy, with complete remission. At 12 years of age, she underwent splenectomy for hypersplenism, but despite this she developed autoimmune hemolysis at 12½ years of age.

At the age of 28 years, she was investigated for recurrent respiratory infections and found to have low IgG, IgA, and IgM levels (Table 1). There was a poor antibody response to pneumococcal vaccine 23 serotype, pneumococcal conjugated vaccine 13 serotype, and meningococcal conjugated vaccine. She was prescribed intravenous immunoglobulin replacement therapy. A year later, the

Table 1

Laboratory data of the 3 study patients measured at different ages*

Variable	Age, y									Reference range
	Patient 1		Patient 2				Patient 3			
	28	29	55	56	57	59	47	48	50	
IgG, g/L	3.9			6.1	3.3	2.7		5.9	5.0	5.5-16.5
IgA, g/L	5.01			0.79	0.51	0.51		2.18	1.88	0.8-4.0
IgM, g/L	0.66			4.26	3.39	2.41		0.47	0.28	0.4-2.0
C1-INH level, mg/L		50	<45				44			150-350
C1-INH function, %		27	<21				<24			>84
C1q, mg/L		50	<12				<23			50-250
C2, mg/L		<7	<3.6				<3.6			10-80
C3, g/L		0.5	0.37				1.29			0.75-1.65
C4, g/L		<0.02	0.01				<0.02			0.14-0.54

Abbreviation: C1-INH, C1 inhibitor.

*IgG, IgA, IgM, C3, and C4 were measured by turbidimetry. Serum for C1-INH was stored frozen at -80°C before testing. C1-INH level was measured by radial immunodiffusion (The Binding Site, Birmingham, United Kingdom), and C1-INH function was measured by competitive enzyme-linked immunosorbent assay (Quidel Technoclone, Surrey, United Kingdom).

patient developed acute-onset swelling of her left hand and arm, lasting for 4 days despite corticosteroid therapy. Blood tests revealed low C4 and C1-INH levels (Table 1), consistent with the diagnosis of AAE. She was treated with tranexamic acid prophylaxis, with C1-INH for acute swellings. She requires ongoing granulocyte colony-stimulating factor (lenogastim) for neutropenia and at the age of 29 years started additional immunosuppression with mycophenolate mofetil because of neutropenia and thrombocytopenia.

Patient 2 was a 55-year-old, white, Australian woman who reported episodes of localized cutaneous swelling, along with a history of irritable bowel syndrome and several operations for abdominal pain (cholecystectomy, hysterectomy, and appendectomy). She was diagnosed as having AAE (Table 1) and treated with tranexamic acid, with full resolution of symptoms.

At the age of 58 years, she became severely anemic (hemoglobin, 3.9 g/dL), with a positive Coomb test result and blood film consistent with hemolytic anemia. A bone marrow biopsy specimen revealed nodules of low-grade B-lymphoplasmacytic lymphoma. Peripheral blood immunophenotyping confirmed light chain restriction, and a small (<1 g/L) monoclonal IgM κ paraprotein was detected. She received cyclophosphamide and prednisolone but required splenectomy at the age of 59 years because of recurrent hemolytic anemia.

After splenectomy, she required emergency hospital admission on 2 occasions for *Streptococcus pneumoniae* sepsis. She had low pneumococcal antibodies despite pneumococcal conjugated vaccine 13 serotype and an immunoglobulin deficiency with low IgG levels (Table 1), despite discontinuation of immunosuppression. She has required long-term intravenous immunoglobulin.

Patient 3 was a 47-year-old, white man who presented with spontaneous facial and recurrent hand swelling. Tests confirmed AAE (Table 1). He was prescribed tranexamic acid prophylaxis. Acute episodes were treated with icatibant or C1-INH.

Additional tests revealed low-level monoclonal IgG λ paraproteins (<2 g/L) and a bone marrow biopsy specimen indicative of MGUS. The paraprotein level has remained stable after 6 years of follow-up. During the follow-up period, he developed mild immunodeficiency with low IgG and IgM levels (Table 1).

Pneumococcal antibodies were low (antibodies to 5 of 13 serotypes tested were protective) with inadequate response to pneumococcal vaccine 23 serotype (7 of 13 protective) and no further improvement after pneumococcal conjugated vaccine 13 serotype. He has not required treatment for the MGUS or the antibody deficiency.

Both C1-INH deficiency and antibody deficiency are subject to considerable diagnostic delay. B-cell lymphoproliferative disorders and their treatment are well-recognized causes of antibody and C1-INH deficiency. It is therefore no surprise that the two should coexist. Initial symptoms of antibody deficiency can be relatively subtle and may be missed initially (patient 2), resulting in life-threatening infection. It is therefore important to monitor for this complication in AAE so that vaccination, antibiotic prophylaxis, or, in severe cases, immunoglobulin replacement can be given.

Immunoglobulin Fc portions have complement- and phagocyte-binding properties.⁶ These properties are enhanced when the immunoglobulin forms an immune complex. AAE may arise when a monoclonal protein, often present in small quantities, has complement-fixing activity sufficient to deplete C1-INH, the only regulator of the early classic pathway. Monoclonal gammopathies may be associated with additional immunologic consequences, such as autoimmune hemolytic anemia (patients 1 and 2).

Lymphoproliferative disorders are usually acquired (patients 2 and 3). However, patient 1 had ALPS, an inherited defect in lymphocyte apoptosis. This is the first report, to our knowledge, of acquired C1-INH deficiency occurring in association with ALPS, although urticaria with angioedema has previously been described in a 26-month-child.⁷

Patients 2 and 3 presenting with symptomatic AAE were diagnosed as having lymphoproliferative disease and, subsequently, antibody deficiency. Patient 1 was diagnosed as having antibody deficiency only after receiving chemotherapy for ALL; thus, it is not possible to know whether the antibody deficiency is secondary to ALPS, the leukemia, or the treatment. Patient 2 had received a short course of cyclophosphamide and prednisolone, whereas patient 3 did not receive any chemotherapy. In practice, it is likely that multiple factors contributed to the antibody loss.

We describe 3 patients with AAE, lymphoproliferative disease, and antibody deficiency. In light of the potential risk for humoral immunodeficiency, clinicians should consider intermittent immunoglobulin measurements in patients with confirmed AAE.

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Radiocontrast-induced iodide sialadenopathy and neutrophilic dermatosis

Iodinated radiocontrast medium (iRCM) can cause immediate or delayed hypersensitivity reactions; however, iodine itself rarely causes acute sialadenitis (iodide mumps) and painful neutrophilic cutaneous nodules (iododerma). We describe a case of acute sialadenitis associated with a Sweet syndrome–like eruption after administration of iRCM.

A 78-year-old man with a medical history of hypertension, chronic renal insufficiency (estimated glomerular filtration rate, 28 mL/min/1.73 m²), diabetes mellitus, and hypothyroidism presented with sudden-onset abdominal pain radiating to the back. Physical examination revealed a pulsatile, nontender central abdominal mass.

Plain computed tomography revealed a large saccular aneurysm (87 × 94 mm) below the level of the renal arteries to the aortic bifurcation. Computed tomographic angiography of the abdomen was performed 2 days later, during which the patient received 100 mL of Ultravist 370, containing 769 mg/mL of iopromide (equivalent to 370 mg/mL of iodine).

Sixteen hours later, he experienced submental and parotid area pain, severe enough that light touch or movement was excruciating. During the ensuing hours, these areas swelled markedly. The following day multiple, painful, tender, dark purplish nodules appeared on his scalp. On the third day he had painful blistering swellings on the palms and fingers with hand edema. He was febrile (temperature, 38.2°C). Aneurysm repair surgery was postponed because the patient was acutely unwell (Fig 1).

Vasculitis and endocarditis were considered; autoimmune screening, serum complement, cryoglobulin, blood culture, and echocardiography results were normal. A test result for mumps virus IgM was negative. Eosinophil count was normal throughout. The C-reactive protein level was elevated. A diagnosis of iodide mumps secondary to iRCM exposure and iododerma or Sweet syndrome was made. Treatment with prednisolone, 50 mg, was commenced; by the second day of treatment, he was no longer febrile, the parotid and submandibular swelling had substantially reduced and was less tender, and mastication was tolerable. The scalp lesions subsided almost completely, leaving faint hyperpigmentation. The bullous lesions on the hands turned to a dark purplish discoloration. Some of the hand lesions discharged serosanguineous fluid. The C-reactive protein level, which peaked at 210 mg/L, decreased to 39 mg/L. Aneurysm repair surgery was scheduled.

In the evening of day 5 of prednisolone treatment, the patient experienced sudden pain and collapsed within a few minutes. The resuscitation team found him to be pale and clammy with a distended abdomen, unrecordable blood pressure, and absent pulse. Cardiopulmonary resuscitation failed.

A skin biopsy specimen (taken 2 days after commencing prednisolone therapy) available after his death revealed heavy dermal neutrophil infiltration with superficial dermal edema and early vesicle formation in the papillary dermis. The epidermis was acanthotic and hyperkeratotic with focal spongiosis. Eosinophils were not identified. The overall

appearances were consistent with Sweet syndrome. Dermal microabscesses, a cardinal feature of iododerma, were not seen.

Iodide mumps (sialadenopathy) is generally a benign and self-limiting condition. It has been described after urography or angiography with ionic and nonionic iRCM and is reproducible on repeat exposure.¹ Some cases are painless, whereas others appear to be associated with inflammation, pain, and tenderness. Whether this reaction is idiosyncratic or immunologically mediated remains unclear, but the result of immediate and delayed skin testing with iRCM was negative in one patient.² Importantly, iodide mumps has been reported after exposure to iodide salts, indicating that this is not a reaction to the molecular carrier of iodine but to the iodine or iodide itself.² Iodine is largely excreted by the kidneys; most reported cases of iodide mumps had renal insufficiency.^{3–5} These factors imply that iodide mumps is a physicochemical reaction to excessive iodine, probably in the form of the iodide ion.

Cutaneous hypersensitivity reactions to intravenous iRCM include acute or delayed urticaria, morbilliform rash, and Stevens-Johnson syndrome. These are considered to be caused by hypersensitivity to the iRCM carrier molecule rather than iodine itself. Iododerma is a rare pustular cutaneous reaction that has been reported in association with iRCM but can also be induced by iodide salts.³ Sweet syndrome (febrile neutrophilic dermatosis) has been reported in one individual who received iRCM for intravenous pyelography.⁶

Our patient had cutaneous lesions that might have been consistent with iododerma or Sweet syndrome. Histopathologic findings revealed a heavy neutrophilic infiltrate characteristic of Sweet syndrome. Sweet syndrome typically presents with tender, edematous, and inflamed papules, plaques, and nodules. Less common manifestations in the form of bullous or targetoid lesions have also been described. Our patient displayed these clinical features and fulfilled all criteria for drug-induced Sweet syndrome proposed by Walker and Cohen. There have been no previous reports of glandular swelling occurring simultaneously with Sweet syndrome.

Because iododerma has been reported after iodide salts in patients with renal failure, it is considered likely that it is mediated directly by an inflammatory response to high concentrations of iodides.⁷ In contrast, drug-induced Sweet syndrome is considered a hypersensitivity reaction, although the mechanism is not well elucidated. A cell-mediated immune reaction to antigen with production of cytokines promoting neutrophil activation and infiltration has been suggested.⁸ Pichler et al⁹ have proposed the extended Gell and Coombs hypersensitivity scheme in which type IVa is predominantly mediated by macrophages, type IVb by eosinophils, type IVc by cytotoxic T cells, and type IVd by neutrophils; one example of type IVd is acute generalized exanthematous pustulosis, but drug-induced Sweet syndrome may also be mediated by this mechanism. Therefore, although iododerma and Sweet syndrome are both neutrophilic dermatoses, the inciting mechanism appears to be distinct.