
Iodide mumps after contrast media imaging: a rare adverse effect to iodine

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Background: Exposure to iodinated contrast media may elicit a variety of adverse reactions. Anaphylactoid and delayed cell-mediated unwanted effects are common; rare adverse reactions include iodine-related sialadenopathy, iododerma, and acneiform eruptions.

Objectives: To describe the occurrence of iodide mumps in a patient examined using contrast-enhanced computed tomography and to outline differential diagnoses.

Methods: A detailed diagnostic approach, including histologic analysis, skin tests, controlled reexposure, efficacy of premedication, and imaging studies, is presented. The findings unique to this reaction and differential diagnoses are highlighted.

Results: While undergoing repeated contrast-enhanced computed tomography a patient developed recurrent swellings of the sublingual glands, identified as iodide mumps. These swellings resolved within a few days. Imaging studies and histologic analysis showed distinct patterns without inflammation. The important role of iodine in this adverse reaction is demonstrated.

Conclusions: Iodine from iodinated contrast media may rarely elicit noninflammatory edema of the salivary glands. The reaction should be differentiated from other swellings in the head and neck area.

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INTRODUCTION

Allergy to iodine is a commonly suspected clinical problem, but often it is not sufficiently documented. Hypersensitivity reactions to iodine derivatives are currently rare. More common are pseudoallergic reactions to iodinated contrast media, but these reactions depend on the osmolality of the contrast media and not on the iodine molecule. Delayed allergic reactions to iodinated contrast media include exanthemas, in which a T-cell-mediated pathogenesis has been proposed. The eliciting antigens are not known, and recent data indicate that the carrier molecules themselves and not iodine are probably involved. Occasionally, toxic bullous reactions and contact allergy to povidone iodine have been observed. Idiosyncratic reactions where pathophysiologic mechanisms are mostly unknown are only rarely observed and include iodine-induced acneiform eruptions, iododerma, and iodide mumps. Rarely, febrile exanthemas and severe bullous exanthemas have been reported from iodine intake, and patients with dermatitis herpetiformis Duhring and hypocomplementemic vasculitis have had exacerbation of the disease on exposure to high iodine doses.

CASE REPORT

A 71-year-old woman was regularly followed up at the Division of Gastroenterology of University Hospital Basel. She had had chronic hepatitis C for years, and in 2001 a hepatocellular carcinoma was detected and surgically removed. To exclude recurrence, she underwent 6 contrast-enhanced abdominal computed tomographic (CT) scans approximately twice a year. Two days after the sixth scan using ioxithalamate, an ionic monomer contrast medium, she developed bilateral indolent firm swellings of the neck. Three later CT scans using the same contrast medium resulted in similar episodes. Apart from these lumps she was asymptomatic: she did not experience pruritus, dysphagia, dysphonia, tachycardia, or hypotension. A hypersensitivity reaction to the radiocontrast media was suspected, and the patient was referred to the ears, nose, and throat and allergy units of University Hospital Basel.

In 1993 the patient had a mastectomy because of breast cancer. In addition, she has arterial hypertension. Her medications included torsemide, potassium chloride, and calcium carbonate–cholecalciferol, all of which she had been taking for years. There was no personal or family history of allergic diseases, bronchial asthma, angioedema, or food allergy. She denied drug hypersensitivity to any particular drugs. However, she experienced urticaria after having taken an unknown antibiotic several years earlier.

The patient was seen in August 2004, 2 days after the ninth CT scan using ioxithalamate was performed. She was not febrile and did not seem to be in distress. The slightly asymmetrical swelling was located in the region of the submandibular glands; the right side seemed to be more prominent (Fig 1). The overlying skin appeared normal in color and

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texture, and palpation was not painful. The swelling did not result in respiratory distress or dysphagia but caused a pressure sensation in the affected area. Findings from examination of the ears, nose, pharynx, and larynx were normal.

Results of the first laboratory analyses, including renal function and thyroid parameters, were normal. The differential blood cell count showed no left shift or increased eosinophil levels. The slightly elevated hepatic values (bilirubin, aspartate aminotransferase, alanine aminotransferase, γ -glutamyltransferase, and alkaline phosphatase) were preexisting and were attributed to the known hepatitis C.

Review of her medical records revealed that thyroid dysfunction had been postulated and that for 5 days before the seventh CT scan the patient had received carbimazole to block thyroid iodine uptake. Despite this intervention, the lumps had occurred again, following the same time pattern and evolution. Then a hypersensitivity reaction with an angioedema was suspected. Before the eighth CT scan, the patient was pretreated with an intravenous application of an antihistamine (clemastine, 2 mg) and an H_2 -receptor antagonist (ranitidine, 50 mg). These measures did not prevent a relapse of somewhat larger lumps. There was no history of intake of angiotensin-converting enzyme inhibitors and no evidence of C1-esterase inhibitor deficiency in her family.

Angioedema is typically located on the face or oral mucosa and presents with an initially asymmetrical, nonpitting edema lasting for a few days. However, this patient's lumps were firm and circumscribed, located in the subcutaneous tissue, and the delayed onset and long duration of the swelling are not typical of angioedema. Inspection of the oropharyngeal cavity did not reveal any clinical signs of infection. There were no painful lymph nodes, the thyroid gland was neither enlarged nor painful, and there were no signs of crepitations.

Subcutaneous emphysema, goiter, lymphadenopathy, and tumors were excluded by means of ultrasound imaging; however, it revealed bilateral diffuse swelling in the area of the submandibular glands (Fig 2). A fine-needle puncture showed normal cytologic findings. After obtaining informed consent, an open biopsy of the lump was performed. It showed normal glandular tissue, mild edema, and no cellular infiltrate. The swelling resolved without treatment within a few days.

Results of skin tests to common respiratory allergens and latex were negative. Results of skin prick and intradermal

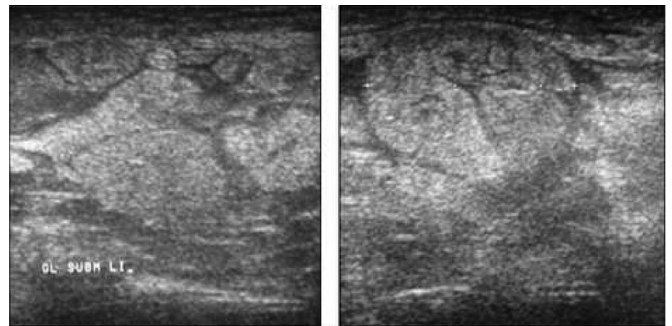


Figure 2. Ultrasound imaging of the left (A) and right (B) submandibular glands: diffuse swelling and prominent internal low-echoic septa.

tests with a series of ionic (amidotrizoate sodium, ioxithalamate meglumine, and ioxaglate meglumine) and nonionic (iopamidol, iohexol, iopentol, iomeprol, iopromid, iobitridol, iotrolan, and iodixanol) iodinated contrast media, read at 20 minutes and at 24 and 48 hours, were negative.¹ Also, results of a lymphocyte transformation test using ioxithalamate, iopamidol, iodixanol, and ioxaglate were negative.²

Her C-reactive protein level and leukocyte count were normal. Her total IgE level (80 kU/L) was within the reference range, and specific IgE for latex was negative. The IgG antibodies for parotitis epidemica were positive; IgM antibodies were negative. Coagulation parameters (international normalized ratio, 1.6; reference value, <1.3), fibrinogen, factor II, factor V, factor VII, and complement factor C3 values were all low (27 mg/dL; reference range, 50–90 mg/dL), whereas C4 (26 mg/dL; reference range, 10–40 mg/dL) and C1-esterase inhibitor concentrations and function were normal. Based on these examination findings, the different forms of angioedema, an infection, an affection of the thyroid gland, and a tumor were all considered to be unlikely.

The patient gave informed consent for all the following investigations. A tenth indicated CT scan was performed using iopromide, a nonionic monomer contrast medium. It resulted again in swelling of the submandibular and parotid glands, verified by means of magnetic resonance imaging (MRI) 2 days after CT (Figs 3 and 4). However, gadolinium-enhanced MRI of the abdomen showed that there was no evidence of pancreatic involvement. Pancreatic amylase (32 U/L; reference range, 13–63 U/L) and lipase (118 U/L; reference range, 21–67 U/L) levels were the same before and after the CT examination. Contrary to the CT scans using ioxithalamate and iopromide, no adverse reaction occurred after the gadolinium MRI. Finally, to confirm suspected hypersensitivity to iodine, oral potassium iodide was given in increasing doses (5, 25, and 50 mg/d) across 3 days. Again, the patient developed swelling after the third day. Ultrasound imaging confirmed an enlargement of the submandibular glands only.

DISCUSSION

The differential diagnosis of neck swelling includes a variety of causes (Table 1). Life-threatening causes include soft



Figure 1. Frontal (A) and lateral (B) aspects of submandibular swellings: firm, nonpainful bilateral lumps.

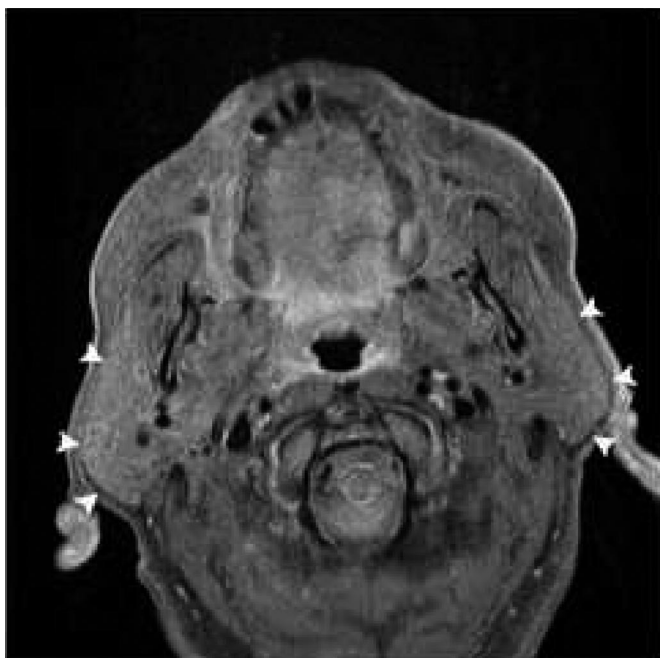


Figure 3. T1-weighted, contrast-enhanced, and fat-suppressed axial image reveals swelling of both parotid glands (arrowheads), leading to bilateral preauricular lumps.

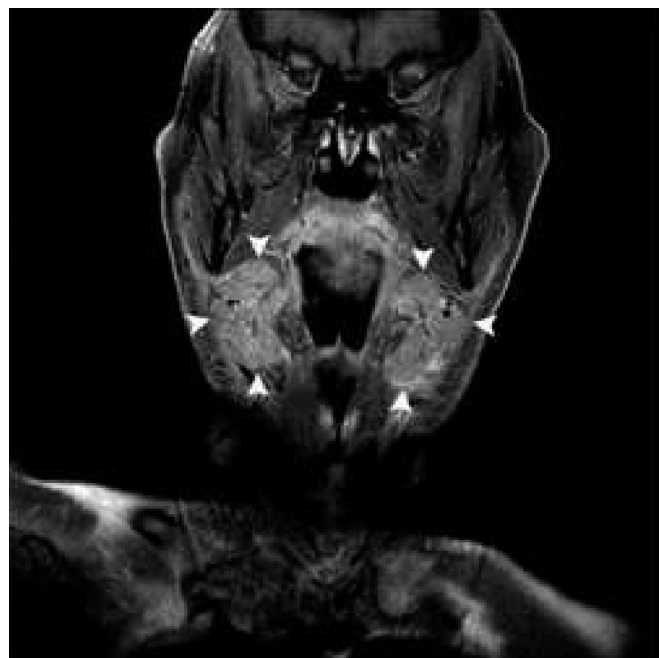


Figure 4. T1-weighted, contrast-enhanced, and fat-suppressed coronal image reveals symmetrical swelling of both submandibular glands (arrowheads).

tissue infection and angioedema from drugs, particularly non-steroidal anti-inflammatory drugs, antibiotics, and radiocontrast media; food allergens; and allergy from insect stings. In cases with isolated angioedema without urticaria, angiotensin-converting enzyme inhibitors and a deficiency in the complement cascade can be responsible.

The neck swelling in this patient was initially attributed to a hypersensitivity reaction. An allergic origin could be excluded by means of history, skin tests, and in vitro tests. Genetically determined hereditary angioedema types I and II and acquired angioedema types I and II can be detected by decreased concentrations or dysfunction of C1 inhibitor.^{3,4} In the present patient, her complement C3 level was decreased, most likely due to her hepatic disease, but normal C1-esterase inhibitor levels and function, clinical presentation, and evolution made hereditary or acquired angioedema unlikely. The submandibular localization of the subcutaneous swelling, the normal thyroid function test results, and the ultrasound imaging findings excluded an affection of the thyroid gland or extrathyroidal tissue, such as a tumor.

Clinically, only the submandibular glands were enlarged; the other salivary glands were normal. Sialolithiasis is the most common noninfectious disorder; in 70% to 80% of patients it affects the submandibular gland. Sialadenosis, observed in alcoholism, avitaminosis, diabetes mellitus, and eating disorders, is a noninfectious, chronic, symmetrical, painless swelling of the salivary glands. The parotid gland is most often affected. Two common causes of infections are acute bacterial sialadenitis, typically due to *Staphylococcus*

aureus, and viral parotitis or mumps, due to endemic paramyxovirus infection. Rarely, soft tissue cervicofacial emphysema may develop in association with ears, nose, and throat or dental surgery.⁵

After excluding these differential diagnoses, we diagnosed a pathologic condition referred to as “iodide mumps” or “iodine sialadenopathy.”⁶ This disorder presents as acute or delayed swelling, predominantly in the submandibular and parotid glands. Today, iodide mumps is most often related to iodinated ionic and nonionic contrast media. More than 90% of the cases occurred after the use of ionic agents,⁷ possibly

Table 1. Differential Diagnosis of Swelling in the Head and Neck Area

Angioedema
Exposure to, eg, drugs or latex
C1-esterase inhibitor deficiency (hereditary or acquired angioedema)
Thyroid disorders
Acute thyroiditis
Goiter
Salivary glands
Mumps
Sialadenitis
Obstructive sialolithiasis
Miscellaneous
Subcutaneous emphysema
Soft tissue infection of the neck
Lymphadenopathy
Tumors

Table 2. Some Iodine-Containing Drugs and Foods³⁵

Compound	Iodine content
Iodinated salt	15 mg/kg
Erythrosine (E 127, Red Dye FD&C #3)	577 mg/g (average daily iodine intake, 10 μ g) ³⁶
Iodinated contrast media	Eg, 150–370 mg/mL (bound elementary iodine, free iodide up to 25–50 μ g/mL)
Amiodarone	75 mg per 200-mg tablet
Potassium iodide tablets	65 mg per tablet
Kelp tablets	0.05–0.15 mg per tablet
5% Lugol solution (aqueous)	Iodine, 56 mg/mL; iodide, 85 mg/mL
Iodine tincture (ethanol)	Iodine, 65 mg/mL; iodide, 19 mg/mL
Povidone-iodine (eg, Betadine)	Polyvinylpyrrolidone-iodine, 10 mg/mL

reflecting the previously more common use of these compounds. Most occurred after intravenous administration for excretory urography or angiography. Only 1 case was reported after oral administration.⁸ The incidence seems to be very low: during the past 50 years more than 40 cases of iodide mumps, mostly to contrast media, have been published. However, occasional single cases were reported until recently.^{9,10} On the other hand, an epidemiologic study of more than 17 million individuals prophylactically treated with potassium iodide after the Chernobyl reactor accident found no cases of iodide mumps.¹¹

The pathomechanism of this hypersensitivity reaction to inorganic iodine is unclear. Iodine-containing drugs are known to induce immediate and delayed hypersensitivity reactions and neutrophilic inflammation, such as vasculitis and iododerma.^{12,13} Although iodide mumps occurs only in a few exposed individuals, it is probably not related to an immunologically mediated mechanism. Noninflammatory histologic findings¹⁴ and negative immediate and delayed skin and in vitro test results support this theory. In some patients, renal insufficiency¹⁵ or high osmolarity of radiocontrast media may play a role.¹⁶ However, reactions to low-osmolar contrast media have also been observed. In the present patient, pretreatment with corticosteroids and antihistamines and a trial with carbimazole did not prevent the reaction. Radiocontrast media contain mainly covalently bound iodine and, depending on exposure to light and radiographs, only a little free iodide (up to 25–50 μ g/mL) (Catherine Christiansen, Amersham Health, personal communication, Oslo, Norway). In the present patient, exposure to oral potassium iodide resulted in a rapid recurrence, supporting a crucial role of the iodide content itself. High blood concentrations of iodine may induce swelling of the salivary glands.¹⁷ It is known that 98% of iodine is renally eliminated and that the rest is eliminated through the salivary, sweat, and lacrimal glands.¹⁸ Therefore, its concentration rapidly increases with impaired renal excretion. The high doses given in contrast medium examinations further increase concentration.

Ultrasound findings showed diffuse swelling and prominent internal low-echoic septa, described in iodide mumps.¹⁸ Histologic analysis showed only mild edema and minor cel-

lular infiltrates without evidence of inflammation, making an inflammatory process also unlikely.¹⁴

The course of iodide mumps is self-limiting, and no treatment is necessary. In some patients, however, complications have been observed, including associated enlargement of the thyroid and lacrimal glands, erythema of the skin, allergic vasculitis, pancreatitis, and facial nerve palsy, requiring decompression.¹⁹ In the present patient, pancreatic involvement could not be demonstrated. Despite the usually benign course, we suggest that these patients should not receive any medication containing free iodide because the possibility of a more severe reaction or complication cannot be excluded.

Other idiosyncratic reactions to iodine with an unknown pathomechanism include acneiform eruptions, iododerma,^{12,20,21} and leukocytoclastic vasculitis.¹³ These illnesses are more common in patients with renal insufficiency, multiple myeloma, lymphoma, polyarteritis nodosa, and arthritis.^{22,23} Nowadays such reactions have also become rare. In some skin disorders acute exacerbations have been observed after the intake of iodine. These reactions have been reported for dermatitis herpetiformis Dühring,²⁴ bullous pemphigoid,²⁵ and hypocomplementemic vasculitis.²⁶ Possibly a nonspecific immune stimulation is the cause of such reactions.

Other hypersensitivity reactions to iodine-containing compounds are more common. Contrast media may cause immediate adverse reactions,²⁷ such as urticaria, angioedema, laryngeal edema, bronchospasm, and shock, and delayed adverse reactions, such as maculopapular exanthema.^{1,28} The former are not attributable to specific IgE antibodies to iodine or contrast media molecules. Therefore, the terms *anaphylactoid* and *pseudoallergic reactions* are applied. The exact mechanism is not known. However, agents of high osmolarity are more likely to cause reactions than are low-osmolar preparations.²⁹

Iodine salts, commonly used in former times for skin and mucosal disinfection, were well-known elicitors of contact allergy. In his studies on iodine idiosyncrasy published in 1911, Bruno Bloch identified iodine-induced contact dermatitis as a delayed-type hypersensitivity reaction.³⁰ In povidone-iodine, on the other hand, iodine is compounded and slowly released in a free form. The incidence of contact allergy is very low.³¹ However, irritant, sometimes bullous

dermatitis from exposure to povidone-iodine, may occur. Rarely, anaphylactic reactions from exposure to povidone-iodine, due to the povidone molecule but not the iodine, have been observed.^{32,33}

Delayed reactions to radiocontrast media include nonspecific complaints, such as flulike symptoms, fever, pain, fatigue, and vomiting. Maculopapular exanthemas, appearing with a delay after application of contrast media, have been reported more often in recent years. Some of these reactions seem to be based on T-cell-mediated mechanisms. The time pattern and evolution, and the positive patch and delayed intradermal and lymphocyte stimulation test results,³⁴ support this model.

Finally, iodine as an elicitor (Table 2)³⁵ is often implicated in some other disorders, and allergy from seafood is often suspected to be due to iodine. Even physicians are not always aware of the different types of iodine hypersensitivity, ignoring the fact that it is not contraindicated to administer radiocontrast media to patients with allergy only to topical iodine.³⁶ Also, the content of iodine in seafood is typically too low to elicit any of the adverse reactions described previously herein.²² However, sea algae may contain high iodine concentrations,³⁷ and there have been few reports of exanthema from such food.³⁸ Also, erythrosine (E 127, Red Dye FD&C #3) contains high levels of iodine (577 mg/g). However, the average daily intake of iodine through this source is estimated to be only 10 μ g³⁹ because its bioavailability is low.⁴⁰

In conclusion, iodine-containing drugs may induce a variety of hypersensitivity reactions. Iodine sialadenopathy or iodide mumps is among the rarest adverse reactions. It presents with self-limiting indolent swelling of one or several salivary glands. Its pathomechanism is not known, but individual factors seem to play an important role. Iodide itself seems to be involved in the elicitation. Therefore, all drugs that contain releasable iodide are contraindicated in such patients. Potential complications include affection of other excretory glands, particularly the pancreas, and, rarely, cutaneous manifestations.

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