Special Review

Characterization of Iodide-induced Sialadenitis: Meta-analysis of the Published Case Reports in the Medical Literature

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Purpose: To evaluate the patient presentation of postcontrast sialadenitis and factors associated with its duration of symptoms through meta-analysis of case reports.

Background: Acute iodide sialadenitis, or "iodide mumps," is a rare adverse reaction to iodinated contrast causing salivary gland swelling. The condition may be underdiagnosed, with researchers postulating that its true incidence may be close to 1-2%.

Methods and Materials: This study was a meta-analysis performed using PRISMA Reporting Standards. A literature search with no language restriction was performed of the Medline database, primarily through PubMed, using keywords: "iodide mumps," "iodide sialadenitis," "sialadenitis," "salivary enlargement," "contrast reaction," "parotid swelling," and "submandibular swelling." Matching case reports and case series were reviewed, and data regarding the subjects' demographics, renal function, contrast administration, and symptoms were extracted. Uni- and multivariate linear regression analyses were applied to assess the predicting factors of a prolonged symptoms duration.

Results: Sixty-five case reports and case series were identified, with 77 cases of iodide-induced sialadenitis. Two cases were unpublished and from the author's institution. Reported subjects' median age was 63 years, and 61% (47/77) were males. Median time to onset was 16 hours, and symptoms resolved in a median of 3 days after the initial onset. Twenty-seven subjects (35%, 27/77) were reported to have an impaired renal function at baseline. Administration of nonionic, low osmolarity contrast medium was reported most frequently (53%, 41/77). There was no difference in resolution of symptoms among subjects with impaired versus normal renal function. Symptoms were resolved in all cases over a median of 3 days with no statistically significant difference between those who received therapeutic intervention and those who did not ($p = 0.430$). Older age and longer time to onset were significantly associated with longer duration of symptoms in both uni- and multivariate linear regression models, and presence of tenderness demonstrated statistical significance associated with longer duration of symptoms in the univariate model.

Conclusion: Postcontrast sialadenitis is a rare reaction to iodinated contrast media. Older age and a longer time to onset of symptoms are associated with longer duration of symptoms.

Key Words: Iodide; Contrast; Sialadenitis; Pooled cohort analysis; Adverse reaction.

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INTRODUCTION

Acute iodide sialadenitis, or "iodide mumps," is an adverse reaction to iodinated contrast causing salivary gland swelling minutes to days after iodine exposure (Fig 1) *(1,2,15)*. Recovery time is variable, and the incidence of this acute inflammation is unknown *(4)*. In one study of adverse reactions to intravascular contrast material in 337,647 patients, not a single case of iodide mumps was recorded *(7)*. However, further studies have suggested that iodide sialadenitis may be underdiagnosed, with an incidence of 1-2% *(19)*. With a clinical presentation similar to more common entities, variable time to onset, and self-limited

Figure 1. 72-year-old male with impaired renal function who developed bilateral submandibular swelling 12 hours after administration of 140 mL of Isovue 250. (A, B) Frontal and lateral views of the bilateral submandibular swelling. (C, D) Resolution of submandibular swelling after 7 days. (Color version of figure is available online.)

course, radiologists should be aware of iodide mumps as a potential reaction to contrast material.

Originally thought to be IgE-mediated, the swelling symptoms have been mistakenly attributed to angioedema or anaphylaxis *(19)*. While the exact pathogenesis of iodine mumps is still unclear, the current understanding of the condition is a pseudoallergic reaction to contrast related to accumulation of iodine in the salivary gland ducts *(28,38,64)*. The concentration of iodine in the salivary gland has been measured up to 100 times plasma level and may be exacerbated by renal injury causing impaired iodine excretion *(3,64)*. However, iodine mumps has similarly been reported in patients with normal renal function, challenging the notion that renal function is correlated with the entity.

A wide variety of methods have been used to treat iodide sialadenitis, including antihistamines, corticosteroids, hyperhydration, and dialysis in patients with renal failure, none of which have proven efficacy *(3,4,19,28)*.

The purpose of this investigation is an exploratory study to characterize the range of clinical findings of contrast-induced sialadenitis and evaluate factors associated with disease severity using pooled cohort data from published case reports.

MATERIALS AND METHODS

Literature Review and Data Extraction

This study was designed as a meta-analysis of reported cases of iodine mumps using PRISMA Reporting Standards. A search of the English and international published literature was performed of the Medline database, primarily through PubMed, using combinations of the key words: iodide mumps, iodide sialadenitis, sialadenitis, salivary enlargement, contrast reaction, parotid swelling, and submandibular swelling. Titles and study abstracts were evaluated and only reports describing reactions after intravascular-iodinated contrast material were included. Searches of the bibliographies of each report were performed to identify additional relevant cases. Additionally, two cases from the authors' institution were included in the study. To meet the definition of iodide sialadenitis, salivary gland enlargement after intravascular-iodinated contrast must have been reported. A time frame was not chosen between contrast administration and development of iodide sialadenitis, due to lack of literature supporting a specific time window. Studies were excluded if they reported sialadenitis in

patients who had sialadenitis before contrast administration. Articles were published between the years of 1956 (the first published case report) and 2018. Data regarding (a) patient age, (b) gender, (c) renal function, (d) administered contrast volume, (e) contrast type, (f) time-to-onset of symptoms, (g) time-to-resolution, (h) gland involvement, and (j) symptoms were extracted from the reports. When cases reported time as "immediate" or "a few minutes," a value of 0.1 hours was assigned for statistical purposes. Creatinine and blood urea nitrogen levels were collected when available; however, renal function was categorized simply as "impaired" or "normal" in a subset of cases. Imaging findings described in the case reports were recorded. Data were collected by one author and rechecked by another. Articles published in languages other than English were translated by professionals fluent in the language.

Institutional review board approval was obtained for chart review of the cases included from the authors' institutions.

Case Report Quality Assessment

Assessment of quality was performed by one author, and another author performed quality checks for a random subset of articles to compare to the initial author. The authors assigned ratings for (a) adequate description of the patient case (renal function, contrast, onset time, treatment, resolution, tenderness), (b) evidence supporting diagnosis, and (c) other explanations for the patient presentation considered. Ratings included yes, partially, or no. Adequate description of the patient case was rated "yes" if no more than one of age, gender, renal function, contrast type, contrast dose, onset, treatment, resolution time, and tenderness was missing. A rating of "partial" was given if two of the aforementioned categories were missing, and "no" if more than two of those categories were missing. Evidence supporting diagnosis was rated "yes" if the authors logically described supporting data toward the diagnosis, such as imaging, labs and a clear timeline for development of the sialadenitis. This was rated "partial" if the authors simply described the symptomatic development of sialadenitis after contrast administration, and "no" if there was no diagnostic logic described. Other explanations for patient presentation were rated "yes" if the authors performed directed studies for other diseases such as infectious mumps or if they engaged in a discussion of potential differential diagnoses of the entity. This was rated "partial" if the authors did not explicitly target other diseases in additional lab tests (eg, amylase levels), and rated "no" if no alternative diagnoses were provided or no implicit differential diagnosis could be gleaned from the article. The overall quality of the report was rated "good" if it received no more than one "partial" and did not receive a "no" rating. Reports were rated "moderate" if they received two "partial" ratings or one "no" rating, with all other ratings being "yes." Articles were "poor" if they received three "partial" ratings or one "partial" and one "no."

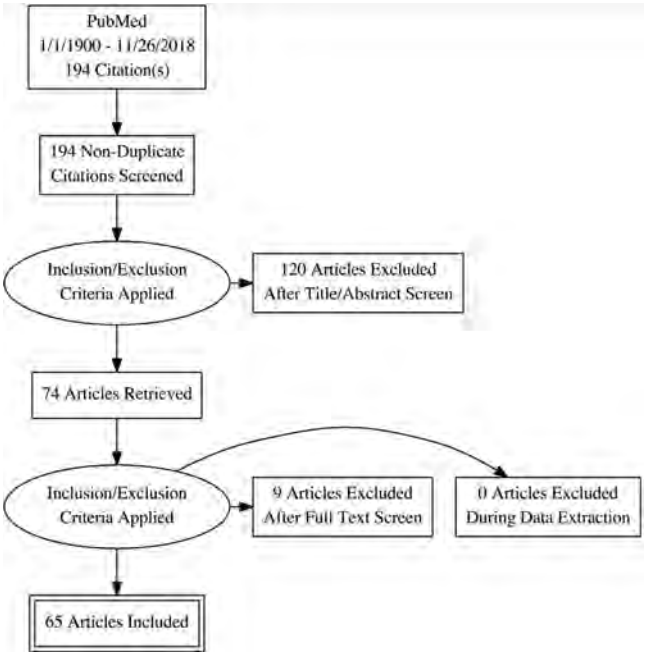

Figure 2. Flowchart describing case selection and literature search.

Statistical Analysis

Continuous data are presented as median (min-max) and categorical variables are summarized as frequency (percentage). Univariate comparisons between patients with normal and impaired renal function were done using the Mann-Whitney U, Chi-square, or Fisher's exact tests, as appropriate. Univariate and multivariate linear regression models were used to evaluate the association of different factors with a longer symptom resolution time period. For this purpose, natural logarithm of resolution time was considered as outcome in the regression models. Factors with statistically significant association in the univariate model were selected for the multivariate model. Statistical significance was set at $p < 0.05$. All analyses were done using Stata InterCooled for Mac version 14.2 (StataCorp. 2015. College Station, TX: StataCorp LP.).

RESULTS

In total, 194 citations were found. After title and abstract screening, 120 articles were excluded as they did not describe a case of iodine mumps. Nine articles were excluded after a full text review due to insufficient description of the case. No cases were excluded for data retrieval and analysis. There were a total of 65 case reports and case series studied, with a total of 77 patients *(1–65)* (Fig 2).

Quality of the Cases

Cases overall had moderate to good quality. There were 50 cases rated "good." Twelve cases were "moderate," and only

four cases overall were rated "poor." Most cases reported all categories of data collected (51/77, 66.2%), including (a) patient age, (b) gender, (c) renal function, (d) administered contrast volume, (e) contrast type, (f) time-to-onset of symptoms, (g) time-to-resolution, and (h) gland involvement.

Clinical Characteristics

Demographic and clinical characteristics are summarized in Table 1. Median age was 63 years (range: 8-83) and 61% (47/77) were males. Twenty-seven subjects (35%, 27/77) were reported to have an impaired renal function at baseline. Administration of nonionic, low osmolarity contrast medium was reported most frequently (53%, 41/77). Sialadenitis occurred in a median of 16 hours after administration of contrast medium with no statistically significant difference between ionic, high- and nonionic, low contrast media (median [min-max]: 10 [0.1-96] and 15.5 [0.1-120], respectively; $p = 0.498$). Overall, the time to symptom onset ranged from immediate to five days. The submandibular gland was the most affected solitary gland (48%, 37/77) and in 25% of the cases (19/77) both parotid and submandibular glands were involved. Gland tenderness was reported in 49% (38/77) of the cases. Thirty-nine cases (51%, 39/77) received therapeutic interventions including warm soaks, saline gargle, hydration, sour candy, NSAIDs, antihistamines, steroid, antibiotics, dialysis, or a combination of these modalities. Symptoms resolved in all cases over a median of 3 days with no statistically significant difference between those who received therapeutic intervention (median: 3 [0.1-70]) and those who did not (median: 3 [0.1-72]; $p = 0.430$). Overall, the range of time required for symptoms to resolve was immediate (transient swelling) to 72 days.

Comparison Between Normal and Impaired Renal Function

Only eight cases did not include information about renal function. All case reports with information about renal function ($N = 69$) described function as either normal or impaired, and gave descriptions such as "end stage renal disease" or "kidney function tests were normal." Quantitative creatinine levels were reported in 20 cases. The normal renal function cases had a median creatinine level of 0.9 mg/dL (range: 0.5-1.1, $N = 11$). The median creatinine level for those with impaired renal function was 2 mg/dL (range: 1.2-31.5, $N = 9$). Quantitative blood urea nitrogen levels were provided in 12 cases. The median normal blood urea nitrogen level was 14 mg/dL (range: 13.4-22, $N = 5$) and median impaired blood urea nitrogen was 124 mg/dL (range: 32-372, $N = 7$). Subjects with impaired renal function demonstrated a significantly longer time to onset compared to those with normal renal function (median [range]: 24 [0.1-120] versus 12 [0.1-120], respectively; $p = 0.018$). Otherwise, there was no statistically significant difference between two groups (Table 2).

TABLE 1. Demographic and Clinical Summary (Total Cases, $N = 77$)

Variable		Summary[1]
Age		63 (8-83)
Sex	Male	47 (61%)
	Female	29 (38%)
	Not mentioned	1 (1%)
Renal function	Normal	42 (55%)
	Impaired	27 (35%)
	Unknown	8 (10%)
Contrast volume (mL, $N = 58$)		105 (15-500)
Contrast osmolarity	High	22 (29%)
	Low	41 (53%)
	Iso	4 (5%)
	Unknown	10 (13%)
Time to onset (h, $N = 74$)		16 (0.1-120)
Involved gland	Parotid	21 (27%)
	Submandibular	37 (48%)
	Both	19 (25%)
Tenderness	Yes	38 (49%)
	No	25 (33%)
	Unknown	14 (18%)
Treatment after onset (steroids, dialysis)	Yes	39 (51%)
	None	36 (47%)
	Unknown	2 (2%)
Treatment type	Steroid only	10 (13%)
	Antihistamine only	4 (5%)
	Dialysis only	3 (4%)
	NSAID only	6 (8%)
	Antibiotics only	1 (1%)
	Steroid and antihistamine	10 (13%)
	Steroid and diuretic	1 (1%)
	Steroid, antihistamine, dialysis	1 (1%)
	Steroid, NSAIDs, antibiotics, dialysis	1 (1%)
	Saline gargle, warm soaks	1 (1%)
	Sour candy	1 (1%)
Resolution (d, $N = 73$)		3 (0.1-72)

[1] Numerical measures are summarized as median (min-max), and categorical variables are shown as frequency (percentage).

Imaging Findings

Overall, 31 cases included imaging findings. Seven cases used radiograph to exclude sialolithiasis. Seventeen cases described ultrasound findings. Such findings included diffuse swelling of submandibular glands, increase in vascularity, and hypoechoic structures representing prominent ducts. Computed tomography was described in nine cases. Findings included gland enlargement with no evidence of fat stranding surrounding the glands in seven cases. Two cases described inflammatory changes in the surrounding fat and subcutaneous tissues. One case described magnetic resonance imaging showing edema of the salivary glands.

TABLE 2. Comparison of the Reported Subjects' Characteristics and Their Symptoms by Renal Function[4]

Variable[1]		Normal[3] (*N* = 42)	Impaired[3] (*N* = 27)	*p* Value[2]
Age		63 (29-83)	63 (8-83)	0.926
Sex	Male	27 (66%)	15 (56%)	0.393
	Female	14 (34%)	12 (44%)	
Contrast volume (mL)		105 (30-500)	100 (15-240)	0.673
Contrast osmolarity	High	12 (32%)	7 (29%)	1.000
	Low	23 (60%)	16 (67%)	
	Iso	3 (8%)	1 (4%)	
Time to onset (h)		12 (0.1-120)	24 (0.1-120)	0.018
Involved gland	Parotid	13 (31%)	4 (15%)	0.301
	Submandibular	19 (45%)	14 (52%)	
	Both	10 (24%)	9 (33%)	
Tenderness	Yes	19 (56%)	15 (65%)	0.586
	No	15 (44%)	8 (35%)	
Treatment (steroids, dialysis)	Yes	23 (56%)	9 (35%)	0.086
	No	18 (44%)	17 (65%)	
Resolution time (d)		3 (0.1-70)	3 (1-72)	0.793
Creatinine		0.9 mg/dL (0.5-1.1, *N* = 11)	2 mg/dL (1.2-31.5, *N* = 9)	N/A
Blood urea nitrogen		14 mg/dL (13.4-22, *N* = 5)	124 mg/dL (32-372, *N* = 7)	N/A

[1] Numerical measures are reported as median (min-max), and categorical variables are shown as frequency (percentage).
[2] Medians are compared with the Mann-Whitney U test, and the frequencies are compared with the chi-square test or Fisher's exact test, as appropriate.
[3] Renal impairment was defined by the authors of specific case reports. All authors who reported kidney function categorized function as normal or impaired.
[4] Renal function information was unavailable in eight cases.

Factors Predicting Longer Symptom Resolution

Results of uni- and multivariate linear regression analyses for association of evaluated factors for longer symptom resolution time are demonstrated in Table 3. Older age (β: 0.02, $p = 0.007$), a longer time to onset of symptoms (β: 0.01, $p = 0.015$) and gland tenderness on presentation (β: 0.68, $p = 0.015$) were significantly associated with a longer resolution time in univariate regression models. In the multivariate model, patient age (β: 0.02, $p = 0.011$) and longer time to symptom onset (β: 0.01, $p = 0.031$) maintained a significant association with longer symptom resolution time. While gland tenderness' association with delayed resolution was not statistically significant in the multivariate model (β: 0.050, $p = 0.060$), there appeared to be a trend toward significance, and it may have lost significance based on a lower number of cases.

TABLE 3. Uni- and Multivariate Linear Regression Analysis Showing Association of Different Factors with a Longer Symptoms Resolution Time in Cases Reported with Postcontrast Mumps; Natural Logarithm of Symptoms Duration is Considered as Outcome

	Univariate Model		Multivariate Model[1]	
	β ± SE	*p*	β ± SE	*p*
Age (y)	**0.02 ± 0.01**	**0.007**	**0.02 ± 0.01**	**0.011**
Sex (female)	−0.27 ± 0.26	0.300		
Renal function (impaired)	0.15 ± 0.27	0.580		
Contrast volume (mL)	−0.001 ± 0.002	0.473		
Type of contrast (high-osmolar)	−0.58 ± 0.30	0.054		
Onset time (h)	**0.01 ± 0.005**	**0.015**	**0.01 ± 0.005**	**0.031**
Involved glands (both versus one)	−0.30 ± 0.30	0.314		
Tenderness	**0.68 ± 0.27**	**0.015**	0.50 ± 0.26	0.060

[1] Variables with statistically significant association in the univariate model are selected for multivariate analysis. No interaction was detected between factors in the multivariate model. Statistically significant associations are highlighted in bold.

TABLE 4. Contrast Agents Causing Iodide Sialadenitis as Reported in the Literature (*N* = 65)

Contrast	Number
Conray 280	1
Conray 400	1
Hypaque	2
Hypaque 50%	1
Imeron	1
Iobitridiol	1
Iodixanol	3
Iohexol	5
Iomeron	2
Iopamidol	6
Iopamidol 370	1
Iopromide	2
Ioversol	1
Ioxaglate	4
Ioxithalimate	1
Isovue 250	1
Isovue 370	1
Methylglucamine diatrizoate	1
Metrizoate	2
Omnipaque	2
Omnipaque 240	1
Omnitrast	2
Optiray	1
Renografin	1
Renografin 60%	3
Renografin-76	1
Renovist	4
Ultravist	1
Ultravist 300	6
Ultravist 370	2
Urografin	1
Urografin 30%	1
Urografin 60%	1
Urografin 70%	1

DISCUSSION

The first reported cases of iodide sialadenitis were described by Sussman and Miller in 1956, who coined the term "Iodide Mumps," likening the facial glandular swelling to viral parotitis *(30)*. In fact, the clinical symptomology of iodine mumps overlaps with that of infectious sialadenitis, stone or foreign body duct obstruction, stricture, inflammatory disorders, trauma, and neoplasm. This wide differential diagnosis of acute facial swelling, combined with variable time to onset, self-limited course, and infrequent occurrence of iodine mumps, makes dedicated clinical investigation difficult.

After administration of iodine contrast, the majority (98%) is excreted in the urine, with the remainder eliminated through exocrine secretions such as saliva, sweat, and gastric juices, as well as through the hepatobiliary system *(14,53)*. Salivary glands are known to concentrate iodide up to 30-100 times the plasma inorganic iodide level *(12,22)*. Previous studies have shown that gland enlargement correlates with high plasma iodide levels, with symptoms developing after plasma iodide levels rise above 11,000 μm/100 mL *(8,36)*. The proportion of saliva excretion is greatest from the submandibular gland (69%), which may explain the preferential involvement of submandibular glands in the reported cases (74.0%) *(29,50)*. However, similar plasma inorganic iodide levels are often measured in symptomatic and asymptomatic patients, indicating that acute sialadenitis may be an individual idiosyncratic response *(42)*. One suspected mechanism of iodine mumps involves the toxic accumulation of iodide within the salivary ductal mucosa leading to edema, duct obstruction, and enlargement of the affected glands in patients who are susceptible *(8)*. No statistically significant difference in the overall incidence of iodine mumps was observed between the normal renal function and impaired patients. Hence, normal renal function should not preclude this diagnosis.

Imaging of the glands was performed in 31 patients, including radiographs, ultrasound, CT, and MRI examinations. Characteristic ultrasound findings include diffuse gland edema and enlargement with prominent hypoechoic internal septa (Fig 3) *(30)*. Nonspecific gland enlargement and edema were also documented with computed tomography (CT) and magnetic resonance (MR) *(27)*. While imaging can exclude other causes of gland enlargement, further diagnostic imaging is not indicated given appropriate patient history and could potentially exacerbate symptoms if performed with additional iodinated contrast material.

The natural history of iodine mumps is benign and self-limited, which favors a conservative approach with observation, supportive therapy, and patient education *(4,27)*. Based upon this collected cohort of case reports, clinicians faced with this entity often treat it as an immunologic response, administering steroids and/or antihistamines to combat the reaction. The reported efficacy of these pharmacologic treatments is purely anecdotal and, in the absence of a controlled clinical study, likely targeted at the wrong physiologic process *(10,27)*. Allergic skin testing with contrast material in three different cases was negative *(9,26,61)*. Histologic examination of the affected glands through fine needle aspiration and open biopsy showed normal glandular tissue with edema and minor cellular infiltrate, but no evidence of inflammation in one case *(9)*. Laboratory studies including differential blood cell count, thyroid function test, liver function tests, and renal function tests were also normal in that patient *(9)*, as well as others *(4)*. Although recurrence of iodine mumps may occur, the reaction clearly is not a contrast allergy and premedication protocols are not warranted. Analgesia may be helpful as gland tenderness was a dominant symptom in multiple cases *(27,46,47)*, but overall there was no statistically significant difference in days to symptom resolution for those who received therapeutic intervention versus those who did not in our results; this may also explain why prophylaxis was ineffective in patients who had recurrence after repeat contrast administration.

The major limitation of this analysis is that it is a retrospective review based upon data included in the published case reports,

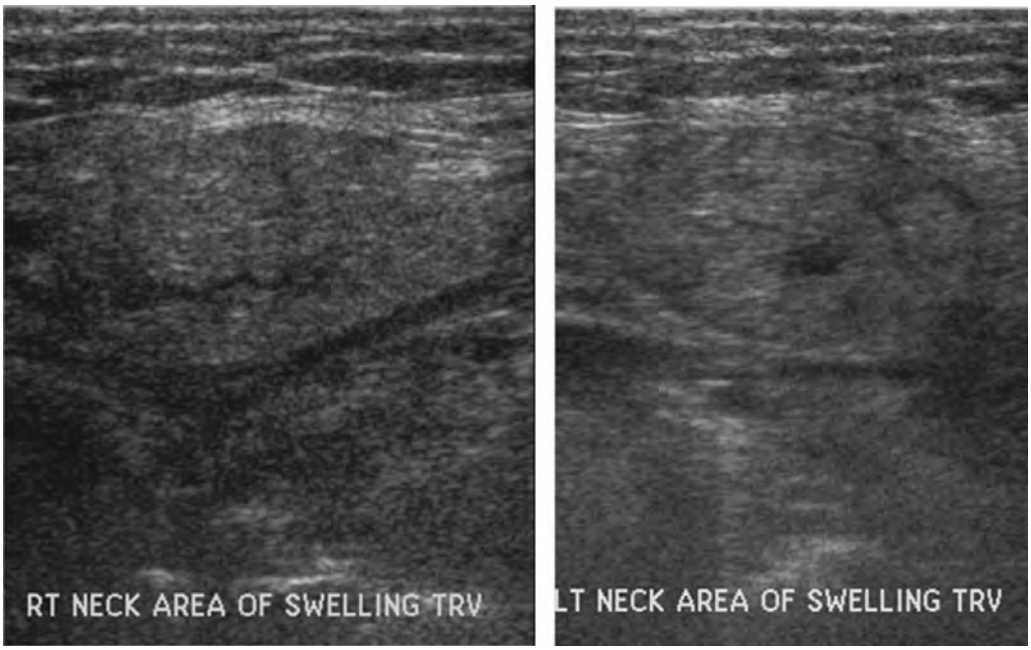

Figure 3. 72-year-old male with impaired renal function who developed bilateral submandibular swelling 12 hours after administration of 140 mL of Isovue 250. Ultrasound images of the submandibular glands showing diffuse gland edema and enlargement.

which introduces a selection bias. Case reports and case series are prone to significant publication bias, as cases with negative findings are rarely published. The quality of the available publications and variable reporting of measures of interest limits the power of the statistical analysis. While patient age and longer time to symptom onset were significantly associated with longer time to symptom resolution, the clinical utility of this information is limited to awareness of these potential trends as management remains conservative. However, pooled analysis of case reports is a useful method to combine evidence of uncommon disorders, and the statistical significance of the reported results provides insight into its characteristics.

CONCLUSION

Iodine mumps remain an uncommon reaction to iodinated contrast. The exact incidence of this reaction is unknown and may be higher than reported given the delayed nature of the symptoms, self-limited course, and lack of physicians' familiarity with this entity. Older age and a longer time to onset of symptoms may be associated with longer duration of symptoms. Steroid and antihistamine prophylaxis do not benefit these patients. Treatment is conservative, including analgesics when necessary. Recurrence is not uncommon in patients who experience this reaction, and appropriate patient education is warranted regarding all iodide-containing compounds.

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