

Iodinated Contrast Medium-Induced Sialadenitis: Proposal of Management Algorithm

Based on A Case Series Analysis

García-Moguel I¹, Mielgo Ballesteros R¹, Sotomayor Contreras A¹, Alonso Sánchez J², Barranco R^{1,3}, Barrionuevo E¹, Crespo JF¹

¹Department of Allergy, Hospital Universitario 12 de Octubre, Madrid, Spain; Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain

²Department of Radiology, Hospital Universitario 12 de Octubre, Madrid, Spain; Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain

³RETIC ARADyAL, Instituto de Salud Carlos III, Madrid, Spain

Corresponding author:

Ismael García-Moguel

E-mail: ismaelgmoguel@gmail.com

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Iodinated contrast medium (ICM)-induced sialadenitis (ICMIS) was first described in 1956 by Sussman and Miller [1] and fewer than 80 reported cases have been identified to date [2]. However, in a large trial to assess ICM reactions, approximately 1-2% of patients were reported as having symptoms suggestive of mumps [3]. Although the pathogenesis remain unclear, accumulation and high concentration of ICM in the salivary glands could triggers local inflammatory oedema which leads to obstruction of the salivary duct [4]. It is known that 98% of ICM is excreted by kidneys and 2% via the salivary glands, lacrimal glands, and sweat [5]. For this reason, some authors hypothesize that the risk increases with impaired renal function owing to reduced elimination of ICM [6], leading to high serum iodide levels (> 10 mg/100 mL or 11,000 $\mu\text{m}/\text{mL}$) [7-9]. However, given that these plasma iodine levels are similar in asymptomatic patients, there may be a certain idiosyncratic component ICMIS [10]. A correct diagnosis at onset is important in order not to preclude future uses of ICM [11]. However, the literature contains no specific recommendations for a systematic diagnostic approach to this.

The aim of this study was to describe a case series of patients with ICMIS confirmed by ultrasound, the largest case series to date. Moreover, an algorithm to investigate suspected ICMIS is proposed. The study population included 8 patients with symptoms of ICMIS who were referred to the Allergy Service of the Hospital Universitario 12 de Octubre from 2016 to 2021. Patients underwent skin testing with iopromide, iohexol, ioversol and iodixanol, iopamidol, diatrizoate meglumine and diatrizoate sodium (Gastrografin®), and graded intravenous challenge tests (GCT) with the culprit or an alternative ICM, as described elsewhere [12].

Two patient received the ICM directly during the radiologic procedure. An ultrasound on a high-grade ultrasound machine was carried out in each patient to confirm the diagnosis of sialadenitis. The study was approved by the Ethics Committee for Clinical Research of Hospital Universitario 12 de Octubre-Madrid, Spain.

Table 1 depicts the baseline characteristics of 8 patients with several episodes suggestive of ICMIS. None of the patients had impaired renal function, although 3 patients had urinary tract diseases. Two patients had active tumors at the time of diagnosis out of the renal system.

Sialadenitis occurred from 1 to 24 h (median; 12h) after ICM administration and took 4 to 84 h (median; 36h) to resolve. All patient experienced neck swelling, 2 patient developed tender glands and 1 patient also developed erythema on the neck, although this resolved spontaneously after a few minutes. Two patients received symptomatic treatment after the reaction, 1 with nonsteroidal anti-inflammatory drugs (NSAIDs), and 1 with systemic glucocorticoids. One patient had a positive intradermal test with iopromide (immediate reading) Bilateral involvement of the submandibular gland was recorded in all cases. (See table E1 and Figure E1 supplementary material).

Given the similarity to angioedema, these patients are frequently referred to the Allergy Clinic to rule out an allergic reaction to ICM. There have been reports other symptoms such as oedema at other locations, pain, dyspnea and skin lesions [2]. Thus, we first rule out IgE-mediated reactions. We perform skin tests with the ICM involved in the reaction and a panel of ICM used in our clinic, as described elsewhere [12]. If the skin tests are positive for the ICM implicated or another ICM in the panel, the patient should be diagnosed with IgE-mediated angioedema. Further, a GCT with one of the ICM that yielded a negative result in skin tests should be performed to provide a safe alternative. If skin tests are negative, GCT should be performed with involved or available ICM. After the GCT, the patient should be informed about the possibility of neck edema and advised to attend the emergency room for radiological assessment to assess salivary gland involvement (see figure E2 supplemental material).

Based in our experienced and literature reviewed we do not recommend scheduling this radiological procedure, because the time to onset and resolution differ for each patient [2].

In our series, we observed that a patient had a positive test result with the contrast involved, thus suggests an IgE-mediated mechanism, although when the challenge test was performed with an alternative contrast ICMIS was confirmed by ultrasound. In this case, the skin test may have yielded a false positive, or a dual mechanism.

High-resolution ultrasound was the most frequently described imaging test in the literature for assessment of the salivary glands. In acute inflammation, the glands are enlarged and hypoechoic due to edema [2, 4], and the Doppler images reveal hypervascularity. Computed tomography, radiographs and Magnetic resonance been performed in other cases [2].

The course of this reaction is benign, and symptoms generally resolve within 2 hours to 4 days [2-11]. A longer time to resolution was significantly associated with advanced age, longer time to onset of symptoms, and gland tenderness [2]. In the present study, only advanced age may be associated with the resolution time. Treatment for ICMIS is generally symptomatic and includes hydration and administration of anti-inflammatory drugs with NSAIDs and corticosteroids. Corticosteroids may be used if the patient develops severe symptoms that do not resolve rapidly, although the role of the latter is controversial and treatment with dialysis has been proposed for non-responders [2]. Pre-treatment has not been shown to prevent episodes of sialadenitis [2]. None of the patients in the present study had severe symptoms and most symptoms resolved without treatment. Given the benign nature of this adverse effect of ICM; after diagnosis of ICMIS, we recommend performing radiological tests with ICM if it necessary to the diagnosis or follow-up of the patient, assessing the risk and benefit of performing these.

In summary, although ICM-induced sialadenitis has been considered as a self-limiting condition that does not necessitate any intervention, its common presentation as neck swelling could disguise an allergic reaction.

Therefore, we propose an algorithm for the systematic management of patients with symptoms compatible with sialadenitis, which include both the exclusion of a potential IgE-mediated reaction and the confirmation of sialadenitis by a suitable imaging test.

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Conflict of interest

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Table. Baseline characteristics of patients with symptoms suggestive of iodinated contrast media (ICM)-induced sialadenitis.

Patient no.	Sex	Age	Renal impairment	Renal diseases	History of Cancer
1	M	85	No	No	prostate, pleura
2	M	74	No	No	bladder
3	F	66	No	Recurrent Lithiasis	
4	F	62	No	No	lung
5	M	67	No	No	bladder
6	M	67	No	No	lung
7	F	65	No	No	liver
8	F	56	No	No	lung