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### **Iodinated Contrast Medium–Induced Sialadenitis: Proposal of a Management Algorithm Based on a Case Series Analysis**

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Iodinated contrast medium (ICM)–induced sialadenitis (ICMIS) was first described in 1956 by Miller and Sussman [1], and fewer than 80 cases have been reported to date [2]. However, in a large trial to assess reactions to ICM, approximately 1%-2% of patients were reported to have symptoms suggestive of mumps [3]. Although the pathogenesis of this condition remains unclear, accumulation and high concentrations of ICM in the salivary glands could trigger local inflammatory edema, which leads to obstruction of the salivary duct [4]. It is known that 98% of ICM is excreted by the 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 µm/mL) [7-9]. However, given that these plasma iodine levels are similar in asymptomatic patients, there may be a certain idiosyncratic component in ICMIS [10]. A correct diagnosis at onset is important in order not to preclude future uses of ICM [11]. The literature contains no specific recommendations for a systematic diagnostic approach to this condition.

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

**Table.** Baseline Characteristics of Patients With Symptoms Suggestive of Iodinated Contrast Media–Induced Sialadenitis

Patient no.	Sex	Age	Renal impairment	Renal diseases	History of cancer
1	Male	85	No	No	Prostate, pleura
2	Male	74	No	No	Bladder
3	Female	66	No	Recurrent lithiasis	
4	Female	62	No	No	Lung
5	Male	67	No	No	Bladder
6	Male	67	No	No	Lung
7	Female	65	No	No	Liver
8	Female	56	No	No	Lung

the ICM directly during the radiological procedure. A high-grade ultrasound device was used 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.

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

Sialadenitis developed from 1 to 24 hours (median, 12 hours) after administration of ICM and took 4 to 84 hours (median, 36 hours) to resolve. All patients experienced neck swelling, 2 patients 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 corticosteroids. One patient had a positive intradermal test result 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. Symptoms such as edema at other locations, pain, dyspnea, and skin lesions have also been reported [2]. Thus, we first ruled out IgE-mediated reactions. We performed 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 is diagnosed with IgE-mediated angioedema. Furthermore, a GCT with one of the ICM that yielded a negative result in the skin tests is performed to provide a safe alternative. If skin tests are negative, GCT is performed with the ICM involved in the reaction or an available ICM. After the GCT, the patient should be informed about the possibility of neck edema and advised to attend the emergency department for radiological assessment to determine salivary gland involvement (see figure E2 Supplementary material).

Based on our experience and the literature review, 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 suggesting 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 owing to edema [2,4], and the Doppler images reveal hypervascularity. Computed tomography, radiography, and magnetic resonance have also been performed [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 tender glands [2]. In the present study, only advanced age was associated with resolution time. Treatment of ICMIS is generally symptomatic and includes hydration and administration of anti-inflammatory drugs (NSAIDs and corticosteroids). Corticosteroids may be used if the patient develops severe symptoms that do not resolve rapidly, although their role is controversial, and dialysis has been proposed for nonresponders [2]. Pretreatment 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 and its spontaneous resolution, we recommend performing radiological tests with ICM who experience ICMIS if they are necessary for diagnosis or follow-up. If we consider that an adverse effect could occur, we must evaluate the risks and benefits of the test.

In summary, although ICMIS has been considered a self-limiting condition that does not necessitate an 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. Our algorithm includes both the exclusion of a potential IgE-mediated reaction and the confirmation of sialadenitis by a suitable imaging test.

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#### Conflicts of Interest

García-Moguel I has participated on advisory boards and as a speaker and investigator for Novartis, AstraZeneca, Teva, GSK, Sanofi Genzyme, Chiesi, Allergy therapeutics, Leti, Stallergenes, ALK-Abelló, Mundipharma, Pfizer, and Orion Pharma. Mielgo Ballesteros R has participated on advisory boards and as a speaker and investigator for AstraZeneca, Chiesi, and Novartis.

The remaining authors declare that they have no conflicts of interest.

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