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## CASE REPORT

# Non-ionic iodinated contrast-induced sialadenitis with parotid gland sparing in patient of hepatocellular carcinoma

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## SUMMARY

61-years-old male patient presented with complain of neck swelling and soreness following contrast-enhanced (CE) CT examination with resolution of symptoms in 36–48 hours. He is diagnosed with hepatitis C virus and hepatocellular carcinoma (HCC); already treated with radiofrequency ablation for HCC. He had already undergone two CECT examinations before he was referred to our institution for disease staging/treatment. He also underwent three triphasic CT scan examinations at our institution during the course of treatment for treatment response and staging. Patient remained undiagnosed up to his fourth CT scan due to inability to relate symptoms with contrast administration. The patient was offered close monitoring on fifth CT exam and ultrasound of neck revealed enlarged and echogenic bilateral submandibular glands, however, thyroid and bilateral parotid glands appear unremarkable. This represents transient iodinated contrast induced sialadenitis with sparing of parotid glands.

## BACKGROUND

Sialadenitis following intravenous administration of iodinated contrast media is a rare clinical entity with swelling of parotid, submandibular and/or sublingual salivary glands. Although the aetiology is still not fully understood, but predilection of iodine to accumulate in the ductal system of salivary glands following intravenous contrast administration is considered as the miscreant.<sup>1</sup> This condition which is also known as 'iodide mumps', and it is reported following a variety of procedures using iodinated contrast including coronary angiography, radioiodine thyroid ablation and arteriovenous fistulograms.<sup>2</sup>

We report a unique case of an elderly male, with no known drug allergy or reactions, presented with neck swelling after non-ionic iodinated contrast (NIC) administration for triphasic CT examination. He was later diagnosed with transient postiodinated contrast-induced sialadenitis with sparing of parotid glands. No case with such features, to the best of our knowledge, has been reported from our country, Pakistan, to this date.

## CASE PRESENTATION

We report a case of 61-year-old man referred to the Vascular and Interventional Radiology (VIR) clinic of

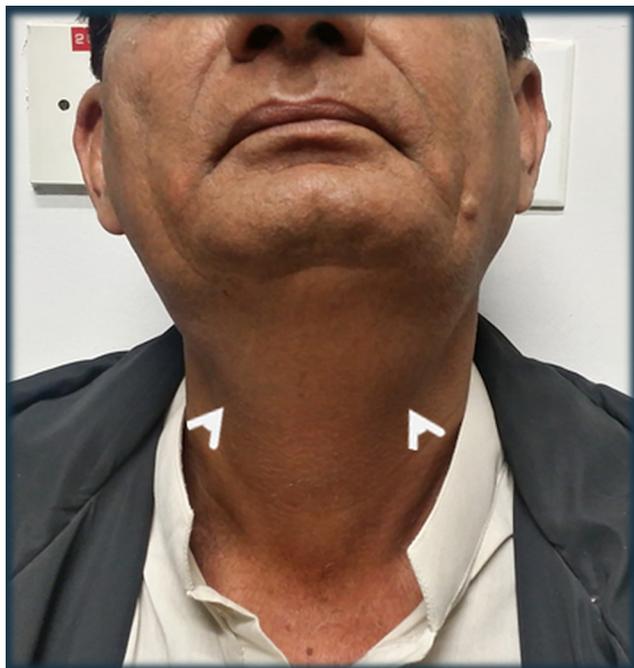
our institute, after being diagnosed with hepatitis C virus (HCV)- induced chronic liver disease (CLD) and hepatocellular carcinoma (HCC). He underwent, total number of five contrast-enhanced (CE) CT examinations. Initial two CECT scans were performed before his referral to our institute. He underwent treatment for HCV induced CLD with pegylated interferon and ribavirin; however, he did not undergo any treatment for HCC, before being referred to our institute. He was a known case of diabetes mellitus (DM) for last 10 years but was non-hypertensive, no known renal disorder and with no known history of any allergy or drug reaction. He was on injection Humulin 70/30 for his DM, with good glycaemic control. He previously received same iodinated low osmolar contrast medium (Omnipaque) for his CECT scans done outside our institute without any postscan adverse reactions.

Management plan for the patient included radiofrequency ablation (RFA) in perception for small tumour size and unifocal disease process.<sup>3</sup> At our institution, the first triphasic CECT scan was carried out 6 weeks following RFA to assess the treatment response and to rule out residual or recurrent disease process. No antiallergy preparation was given before the procedure due to no known history of allergy or hypersensitivity to any drug. Non-ionic low-osmolar contrast medium (Omnipaque 240) was used as part of standard institute protocol at a dose of 100 mL (1.5 mL/kg body weight). The patient belonged to another city and was sent home postprocedure.

First examination at our institution went uneventful. No history was provided by the patient of any unusual late event including, rash, erythema, shortness of breath or swelling or tenderness in facial or neck region. On follow-up after 3 months, patient underwent second triphasic CECT scan using the same protocol; however, 6 to 8 hours following procedure, patient felt gradual swelling below his chin on both sides of neck with mild soreness. But, he was unable to relate these symptoms to contrast administration as the initial three CECT examination went uneventful. These symptoms resolved gradually over the next 48 to 72 hours. On his next follow-up visit, he reported these complain of neck swelling and soreness. The patient was then offered close monitoring at the time of his third planned CECT at our institute. The procedure was carried out using similar departmental protocol and



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**Figure 1** Patient photograph after 10 hours of CECT examination; demonstrating neck swelling in submandibular region (white arrowheads). CECT, contrast-enhanced CT.

patient was kept under observation following procedure. After the interval of 6 hours, he started to develop bilateral submandibular swelling and soreness which gradually increased up to next 6 hours and became static (figure 1).

On physical examination, he was an average size, middle-aged man, fully oriented in time, space and person with heart rate of 68 beats/min, blood oxygen saturation of 99% and blood pressure of 134/76 mm Hg. On local examination, he had non-tender, bilateral submandibular neck swellings. The submandibular glands were rubbery in consistency, non-tender, partially mobile and had no association with swallowing. No cervical lymphadenopathy, thyroid or parotid gland swelling appreciated.

## INVESTIGATIONS

At the time of his initial presentation at our institute, his renal function test was within normal limits showing serum creatinine and blood urea levels of 0.7 mg/dL (0.8–1.3) and 14 mg/dL (6–20), respectively. The patient had non-detected HCV RNA on polymerised chain reaction with positive HCV antibodies. The liver function tests stating total bilirubin 0.9 mg/dL (0.1–1.2), direct bilirubin 0.2 mg/dL (0–0.2), alanine aminotransferase 52 (<45) and alkaline phosphatase 79 IU/L (54–369). He has diabetes with fasting blood glucose levels of 129 mg/dL (diabetic +>126 mg/dL), random blood glucose levels of 197 mg/dL (diabetic =>160 mg/dL) and haemoglobin A1C 6.7% (diabetic =>6.5%). Other laboratory tests were also within normal limits, which included serology for HBV, serum lipid profile, complete and differential blood counts, bleeding and clotting profile, HIV serology, serum electrolytes and ECG.

The US examination of abdomen revealed mild coarse echotexture of liver with irregular margins, heterogeneous appearing vascular lesion in left lobe of liver in the segment IV and measuring 14×18 mm. The portal vein was dilated without evidence of thrombosis. Splenomegaly was also evident with associated splenic varices; all findings coinciding with a typical picture of CLD, portal hypertension and HCC lesion. The first triphasic CECT scan, at

our centre, after RFA of HCC, demonstrated a solitary low attenuation lesion in the segment IV of liver without any enhancement or venous washout consistent with ablated lesion. No evidence of HCC recurrence also noted after second CECT scan.

After the third CT scan, at the time of initiation of symptoms, complete and differential blood counts were performed showing haemoglobin of 13.8 mg/dL (13.7–16.3), haematocrit 41 (41.9–48.7), platelets  $152 \times 10^9/L$  (150–400) and white cell counts  $5.2 \times 10^9/L$  (4.0–10.0). The erythrocyte sedimentation rate was 14 mm. The coagulation profile revealed prothrombin time (PT) of 12.0 s (9.1–13.1), activated partial PT 29.1 s (22.9–34.5) and international normalised ratio 1.1.

Since coagulation profile and total leucocyte count turned out to be normal, this ruled out the possibility of infective causes as well as iatrogenic bleeding within the salivary glands. The HCV viral load was also insufficient to attribute as an acute cause. Moreover, the diabetes was well managed, with borderline increased blood glucose levels, to consider as an aetiological factor for transient sialadenitis. Subsequently, the ultrasound of neck was performed revealing bilateral enlarged submandibular glands with relatively increased echogenicity to parotid glands representing sialadenitis (figure 2). Bilateral parotid glands and thyroid gland appear unremarkable (figure 3). No evidence of cervical lymphadenopathy noted.

## DIFFERENTIAL DIAGNOSIS

Sialadenitis can occur in various settings which may include infection (viral and bacterial), such as HCV, HIV/AIDS infection, leprosy, etc. In addition, it is also associated with Sjögren syndrome, diabetes, Wegner's granulomatosis, lymphoproliferative disorders and sarcoidosis. Various drugs like propylthiouracil and organophosphate poisoning<sup>4</sup> are also reported as an inducing factor. The clinical history and laboratory results of our patient were inconsistent with any of the above-mentioned causes other than administration of non-ionic iodinated contrast medium.

## TREATMENT

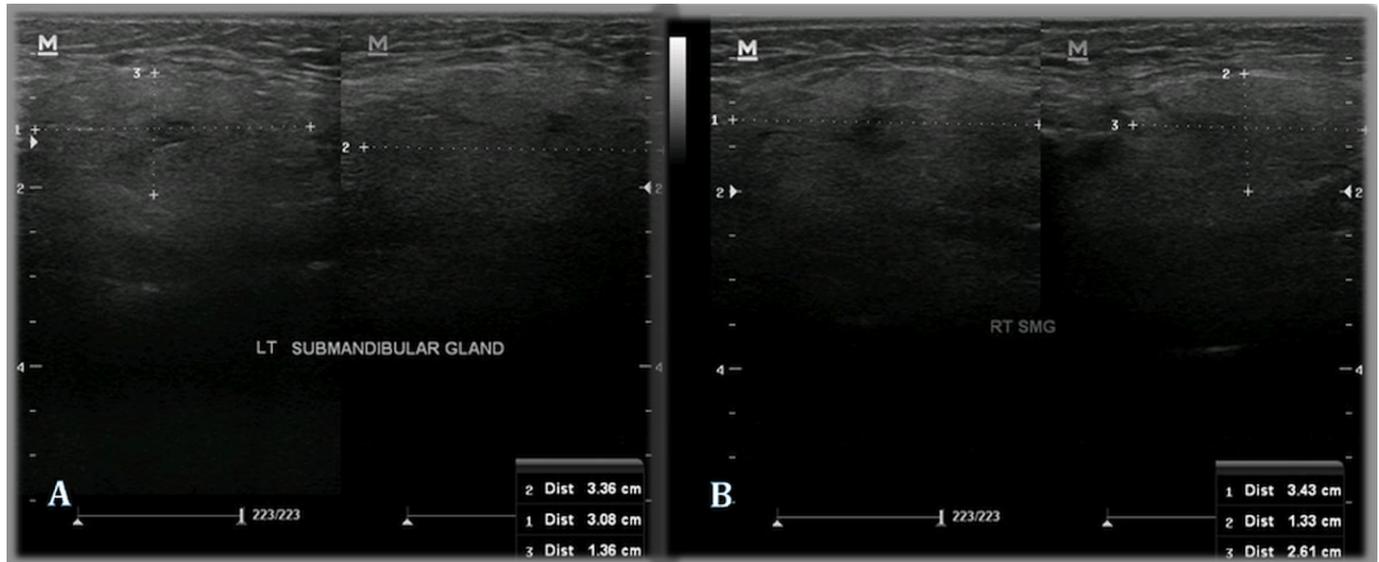
Simple analgesia with tablet ibuprofen was provided at a dose of 400 mg per oral every 8 hourly. Patient was also offered to do ice packing of submandibular region for 10 to 15 min thrice a day.

## OUTCOME AND FOLLOW-UP

The symptoms started to resolve spontaneously after 36 hours following procedure. These were almost completely resolved within next 50 hours (figure 4). Patient did not complain of any additional delayed signs or symptoms. His routine follow-up visit at VIR clinic is scheduled after 3 months. Spontaneous and complete resolution of symptoms exclude systemic or infectious etiology.

## DISCUSSION

Sialadenitis, inflammation of the salivary glands has multiple reported aetiological factors; like diabetes and HCV infection in our case. However, HCV-infected patients may frequently have histological signs of Sjögren syndrome like sialadenitis with mild or even absent clinical symptoms and even Sicca syndrome.<sup>5</sup> Ohoka *et al*<sup>6</sup> demonstrated that latent sialadenitis is frequently observed in chronic HCV infection, but it is not directly related to HCV per se. They demonstrated that serum S-isoamylase levels were elevated in patients with HCV infection, which remain elevated even after HCV was eradicated. Moreover, in situ hybridisation also did not show the presence of HCV-RNA in the salivary gland in such patients.



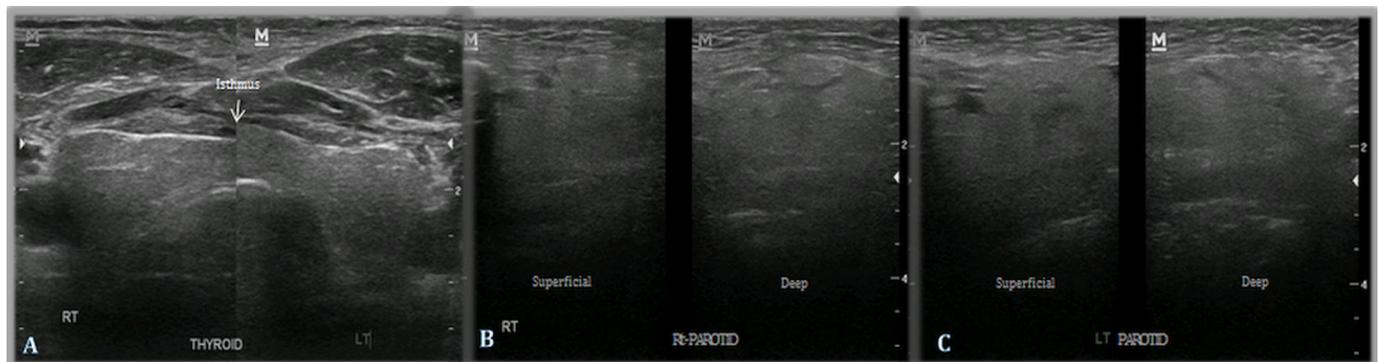
**Figure 2** Ultrasound examination of neck. (A) Left submandibular gland and (B) right submandibular gland ultrasound show enlarged (left gland measures 3.36×3.08 cm and right gland measures 3.43×2.61 cm) and echogenic submandibular glands representing sialadenitis.

The term ‘iodide mumps’ was first brought into attention by Miller and Sussman in 1956 who were the first to describe sialadenitis following administration of intravenous iodinated contrast medium in intravenous urography.<sup>7</sup> The excretion of contrast is mediated by kidneys, the concentration of which can significantly increase in the blood in the settings of renal pathology with deranged renal function leading to in vivo accumulation of iodide in salivary glands which may possibly explain the occurrence of iodide mumps in patients with pre-existing renal disease. But the cases of iodide mumps had also been reported with no pre-existing renal pathology in patients with normal renal function tests as we report in our case as well. The underlying aetiology is still not clearly understood. Idiosyncratic reaction can be considered as one possible phenomenon. Other possible mechanism is the tendency of iodine to accumulate in ductal system of salivary glands where the concentration can reach up to 100 times to that of plasma.<sup>1</sup> These high concentrations trigger local inflammatory response causing inflammation of the ductal mucosa leading to ductal obstruction and thus resulting in the swelling of salivary glands.<sup>8</sup> Ben-Ami *et al*<sup>9</sup> reported that repeated exposure to iodinated contrast media can cause iodide mumps in susceptible patients. This concept also explains event in our case as it happened after fourth CECT scan.

Iodine mumps have been reported in patients with no history of drug or food allergy. Moreover, the cases have been reported from various countries of the world excluding the possibility of any race specificity of this pathology.

So far, almost 40 cases of contrast-induced sialadenitis have been reported in the published English literature majorly from USA, UK, Israel and Switzerland. One case has been reported from Indian subcontinent, from the state of Tamil Nadu, India in 2015, where the patient underwent coronary CT angiography for angina.<sup>10</sup> Another case was reported from mainland China in August 2015<sup>11</sup> in the setting of coronary angioplasty, but no case has been reported so far from Pakistan though with isolated involvement of submandibular glands and sparing of parotids to the best of our knowledge.

Katayama *et al* reported that the use of NIC can significantly reduce the occurrence of potential life-threatening adverse effects of contrast agents.<sup>12</sup> However, cases of iodide mumps have been reported following administration of both ionic and non-ionic iodinated contrast media. This represents no specific benefit of safe considered NIC in preventing from minor complications such as sialadenitis. Dose of contrast medium in the previously reported cases is also variable, and so far, no specific dose has been defined to prevent the occurrence of iodide mumps.



**Figure 3** Ultrasound examination of neck. (A) Thyroid gland, ultrasound reveal normal both lobes and isthmus (arrow) of thyroid gland without any lesion; (B) Right parotid gland, and (C) left parotid gland ultrasound show normal size (>2 cm) and parenchymal echogenicity of both deep and superficial lobes of parotid glands.



**Figure 4** Patient photograph after 52 hours of CECT examination and symptomatic treatment, demonstrating resolution of neck swelling from submandibular region. CECT, contrast-enhanced CT,

Sialadenitis is typically demonstrated from few hours up to 5 days following contrast administration,<sup>10 11</sup> as in our case, where it started after 6 hours of contrast administration. It usually involves bilateral parotid, submandibular and sublingual glands with cases of unilateral parotid gland involvement have also been reported. However, the isolated involvement of submandibular glands with parotid sparing as in our case is indeed unusual. Moreover, establishment of no clinical features following first triphasic CT examination with interval development of symptoms following subsequent CECT examinations also justifies the increase in possibility of iodine mumps following repeated exposures in susceptible individuals as was observed in our patient as well.

Our case is unique for multiple reasons; first, he had no known history of any drug allergy. Second, the symptoms in our case started only after the fourth CECT examination, however, he stayed completely normal until after the third CECT. Furthermore, previously reported cases of the same entity primarily involved parotid and submandibular glands with no previously known case to our knowledge primarily affecting submandibular glands and with parotid sparing. Lastly, only three cases of ‘iodide mumps’ have been reported from our region; in a patient with renal impairment in Hong Kong in 2008,<sup>13</sup> from mainland China in August 2015<sup>11</sup> and in patient who underwent coronary CT angiography for angina workup from India in 2015.<sup>10</sup> There is a small limitation to our case that we did not perform the fine-needle or trucut biopsy of submandibular gland at the time of swelling.

Most studies have shown that contrast-induced sialadenitis is a self-limiting pathology requiring no specific intervention. Few cases have been treated symptomatically with corticosteroids and

analgesics, but clinical data in this regard is insufficient to prove the efficacy of these medications.<sup>14</sup> Possibly, with the advent of new sophisticated NIC agents in future, its correlation can be established with type of contrast medium, but this dimension demands further research.

### Learning points

- ▶ Contrast-induced sialadenitis is a rare clinical entity which can occur following administration of iodinated-contrast medium irrespective of route of administration, type of procedure, dose or the type of contrast medium.
- ▶ The symptoms are usually self-limiting and should be expected to resolve without any specific intervention.
- ▶ Due to widespread use of iodinated contrast media in radiology and various imaging modalities, any signs and symptoms suggesting this entity following contrast administration should be looked for to prevent any undue anxiety on patient’s behalf.

**Contributors** MA diagnosed the case in VIR Clinic. MBHC and MA did initial literature search, selected the images and proof read/edited the final manuscript. JS wrote initial manuscript with the help of MBHC. SZB edited the manuscript, organised the images and wrote figure captions. All of the authors contributed to the intellectual context and approved the final version.

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