

Case Report

A Case Report of Chemical Pneumonia after Trans-Arterial Chemoembolization for Hepatocellular Carcinoma during Covid-19 Outbreak

Rimondi A^{1,2*}, D'Ambrosio R¹, Crespi S³, Bergna I^{1,2}, Iavarone M¹ and Lampertico P^{1,2}

¹Department of Gastroenterology and Hepatology, CRC "A.M. e A. Migliavacca" Center for Liver Disease, Milan, Italy

²Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

³Department of Radiology, University of Milan, Milan, Italy

***Corresponding author:** Roberta D'Ambrosio, Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Via F. Sforza 35, 20122 Milano, Italy. Tel: 393387709867 ; E-mail: roberta.dambrosio@policlinico.mi.it

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Abstract

Due to the dramatic outbreak of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection in Italy, management of patients with Hepatocellular Carcinoma (HCC) has become challenging. Palliative treatments, such as transarterial chemoembolization (TACE) and radioembolization (TARE) have been maintained in selected patients, in order to optimize the risk-benefit ratio, by minimizing risks related to hospitalization.

Although considered safe procedures, these palliative treatments are associated with generally underestimated complications.

Here we report the case of a 78-year-old patient who developed respiratory failure after TACE procedure while being hospitalized during Coronavirus Disease 2019 (COVID19) outbreak. Clinical decisions and outcomes are therefore described.

Keywords: TACE; Chemical Pneumonia; Hepatocellular Carcinoma; COVID 19; Respiratory Failure

Abbreviations: SARS-CoV-2: Severe Acute Respiratory Coronavirus-2; HCC: Hepatocellular Carcinoma; TACE: Transarterial Chemoembolization; TARE: Transarterial Radioembolization; CPT: Child-Pugh Turcotte; HCV: Hepatitis C Virus; LUF: Lipiodol Ultrafluid; EPI: Epirubicin; CT: Computed Tomography; AFP: Alpha-fetoprotein; S: Segment; Sat: Saturation; COVID-19: Coronavirus Disease

Introduction

A 78-year-old woman was diagnosed with multifocal recurrence of a previously resected HCC on compensated (CPT-A) cirrhosis due to untreated Hepatitis C Virus (HCV) infection. She could not benefit from Direct-Acting Antivirals (DAA), since in Italy treatment is currently not reimbursed in patients with active HCC outside liver transplant waiting list. She had no comorbidities, and TACE was planned by our multidisciplinary team. After the first c-TACE [Lipiodol ultrafluid (LUF) plus Epirubicin (EPI)], abdomen CT-scan showed three residual nodules [11 mm in liver segment (S) 7, 10 mm in S5 and 10 mm in S6] with typical HCC pattern and Alpha-Fetoprotein (AFP) lowering from 260 to 85 ng/mL. The next TACE procedure occurred to be planned during peaking Italian SARS-CoV-2 outbreak at the very beginning of April 2020. The patient was still motivated to undertake HCC treatment, aware of the risks associated with current pandemic, albeit mitigated by protocols implemented in our Coronavirus disease (COVID-19)-free department. She underwent two SARS-CoV-2 na-

sopharyngeal swabs, 5 and 3 days before hospital admission, which both tested negative. At admission, blood tests showed mildly increased liver enzymes, however with normal bilirubin and liver function tests.

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After checking S7, S6 and S5 lesions vascular supply, the hypertrophic right inferior phrenic artery was selectively catheterized, and LUF 2 mg emulsified with EPI 5 mg was injected (Figures 1a,1b). TACE procedure was immediately interrupted due to appearance of not previously described pulmonary shunts (Figure 1c).

Thereafter, HCCs were treated with standard doses of LUF and EPI through the right hepatic artery. No adverse events related to TACE were recorded, during and immediately after the procedure. Twenty hours later, the patient presented with fever (38.0°C) and desaturation (SatO₂ 78%), in absence of pronounced dyspnea. Arterial blood gas analysis showed respiratory failure with pH 7.40, pO₂ 34, pCO₂ 49, SpO₂ 65%,

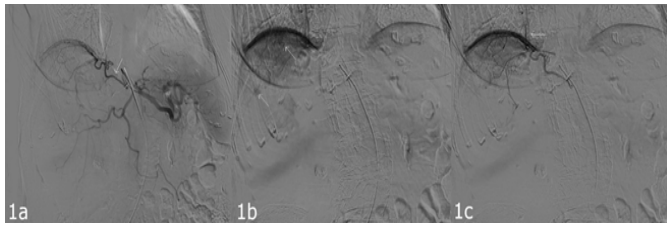


Figure 1: Angiographic study of the celiac trunk showing the hypertrophic right inferior phrenic artery (a), which appear to supply the upper liver segments on the selective study, and two lesions (b); note the pulmonary shunts after LUF injection (c).

lactates 1.2, P/F 161. Differential diagnosis was made. Acute Respiratory Failure should prompt a rapid evaluation and physicians are required to quickly rule out the most common acute pulmonary pathologies. Acquired infectious pneumonia is quite a common cause of rapid deteriorating respiratory function and acute respiratory distress syndrome. Among infectious pneumonia, due to current high incidence scenario with rapidly spreading intra-hospital potential outbreaks, COVID-19 should be the first pathology to be excluded in order to keep infected patients out of SARS-CoV-2 free departments and, on the other hand, to prevent SARS-CoV-2 negative patients to become ill. Although our patient had been tested for COVID-19 before hospital admission, high rates of false negative RT-PCR tests should suggest to keep a low threshold for re-testing, especially if we take into consideration our subject's clinical presentation with fever, acute respiratory failure and the absence of frank dyspnea which are all clinical characteristics of acute SARS-CoV-2 infection. Also, in this specific case, pulmonary venous thromboembolism should be suspected given the sudden desaturation and considering the hypercoagulable state due to active cancer, the post-procedural bed confinement and the recent vascular maneuvers.

Furthermore, the accidental injection of LUF + EPI into not previously known pulmonary shunt should raise the suspicion of possible adverse events related to the injection of relatively high doses of iodinated contrast agents into pulmonary parenchyma thus provoking chemical pneumonia. Oxygen support was then delivered (VM 50% 12 l/min), with benefit. Blood tests were repeated and they revealed unchanged white blood cells count (3,780/mm³), with relatively low lymphocytes (10%); hemoglobin, C-Reactive Protein, D-Dimer and ferritin were normal.

Chest X-ray showed an interstitial lung reinforcement and a possible basal right pneumonia. Due to parallel high incidence clinical scenario and the radiologic findings, a third SARS-CoV-2 nasopharyngeal swab was obtained, which still tested negative. To rule out the other possible complications, the patient underwent chest CT-scan which revealed the presence of radio-opaque material within the apical and posterior segment of the lower right lobe, that was suggestive for lipiodol ac-

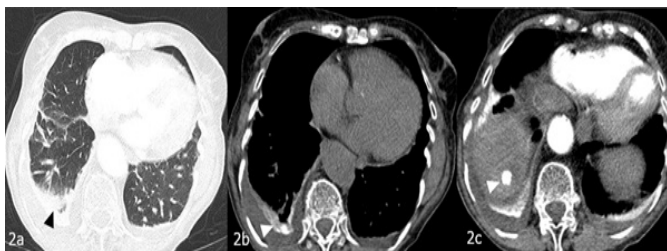


Figure 2: Chest CT-scan showing the presence of parenchymal dystelectasia (a) and radio-opaque material within the apical and posterior segment of the lower right lobe (b), as well as liver accumulation (c).

cumulation (Figures 2a,2b). Liver accumulation were as well noted (Figure 2c). Right basal pneumonia was not confirmed, despite the presence of mild pleural effusion and lobar dystelectasia. Both antibiotics and low-molecular-weight heparin prophylaxis were started, and patient's respiratory function was closely monitored. The patient experienced a progressive improvement in respiratory function with oxygen weaning after 7 days, and was discharged without sequelae.

Discussion

Here, we described a case of chemical pneumonia in a patient affected by HCC undergoing loco-regional treatment with TACE. Due to her high motivation, the absence of major comorbidities, as well as the decrease in AFP values following previous HCC treatments, the patient was hospitalized despite several difficulties related to the concomitant peak of SARS-CoV-2 spread in Milan, Italy [1]. In order to minimize the risk of nosocomial infection, she had previously undergone two SARS-CoV-2 nasopharyngeal swabs, which tested negative. However, the onset of desaturation in absence of respiratory symptoms led physicians to reconsider COVID-19, due to the current high-risk clinical scenario. In fact, it has been recognized that several factors may limit molecular assays accuracy [2], with false negative rates of nearly 30%. Moreover, SARS-CoV-2 incubation period is crucial when interpreting swab results, thus making patient history collection essential, especially in the current "COVID-19 era" [3]. Also, the presence of liver diseases may increase the risk of unfavorable SARS-CoV-2 infection [4].

Our patient reported a rare complication of TACE, ranging between 0.05%-4.5% [5]. In fact, patients undergoing multiple TACE can develop collateral vessels, arising from non-hepatic arteries. Interestingly, S7 and S8 can be supplied by the right inferior phrenic artery, which accounts for 62-83% of extrahepatic collaterals. Moreover, naturally present pulmonary shunts could significantly increase. Although demonstrated that in these cases TACE remains a safe procedure, infused ethiodized oils or chemotherapeutic agents could shunt into lung vessels, with chemical injury being further worsened by the consequent inflammatory response. Despite both LUF and EPI had been injected at lower than standard doses following the identification of previously unrecognized pulmonary shunts, their quantity was probably enough to cause subsequent pulmonary inflammation and respiratory failure.

Although is strongly advisable to "think of horses not zebras, when you hear hoof beats", this case reminds us to keep an open-minded approach even in specific pandemic high incidence scenarios.

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Ethical Approval

Approval was obtained from the local ethics committee.

Consent for Publication

The Author transfers to Springer the non-exclusive publication rights and he/she warrants that his/her contribution is original and that he/she has full power to make this grant. The author signs for and accepts responsibility for releasing this material on behalf of any and all co-authors.

Contributors

We were all involved in caring, treating, diagnosing and providing follow-up for the patient. RDA and AR wrote the manuscript; AR, IB and MI collected data; SC was responsible for Radiology; PL revised the paper. Written consent for publication was obtained from the patient.

References

1. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1,591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020.
2. Lowe CF, Matic N, Ritchie G, Lawson T, Stefanovic A, Champagne S, et al. Detection of low levels of SARS-CoV-2 RNA from nasopharyngeal swabs using three commercial molecular assays. *J Clin Virol*. 2020.
3. Nandini S, Sundararaj SJ, Akihida R. Interpreting Diagnostic Tests for SARS-CoV-2. *JAMA*. 2020.
4. Iavarone M, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, et al. High Rates of 30-Day Mortality in Patients with Cirrhosis and COVID-19. 2020.
5. Nhu Q, Knowles H, Pockros PJ, Frenette CT. Pulmonary complications of transcatheter arterial chemoembolization for hepatocellular carcinoma *World J Respirol*. 2016;6:69-75.