Hypersensitivity Reaction after Transarterial Chemoembolization

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Transarterial chemoembolization (TACE) is commonly employed in the locoregional therapy (LRT) of patients with hepatocellular carcinoma (HCC). This procedure is generally well tolerated and carries a low overall risk of morbidity, with major adverse events occurring in approximately 2 to 5% of cases.^{1,2} Recognized complications include technical events (e.g., vessel injury), hepatic events (e.g., liver failure, infarction, abscess), extrahepatic events (e.g., cholecystitis, hematologic suppression, gastrointestinal ulceration, contrast-induced nephropathy), and other side effects (e.g., postembolization syndrome).³ Chemotherapy hypersensitivity reaction is a rare potential adverse event of TACE that may result in acute clinical deterioration, and as such warrants awareness and recognition by interventional radiologists (IRs) performing TACE. This report presents the case of a patient who developed a hypersensitivity reaction after TACE, and provides an overview of the clinical manifestations, diagnostic considerations, and management strategies for this uncommon complication.

Case Presentation

A 77-year-old man with a history of treated hepatitis C with sustained virologic response and no overt evidence of liver cirrhosis presented to medical attention with a chief complaint of intermittent mild fatigue and weakness. An abdominal magnetic resonance imaging (MRI) scan revealed multiple liver masses with imaging features diagnostic of HCC (►Fig. 1). Laboratory analysis and physical examination revealed compensated liver function (Child–Pugh class A) and normal functional status (Eastern Cooperative Oncology Group performance status 0). As the patient demonstrated Barcelona Clinic Liver Cancer (BCLC) stage B disease, he was deemed to be a suitable candidate for LRT with intent for tumor cytorreduction and lifespan prolongation. TACE was prescribed, and the patient elected to pursue this treatment option. Due to the multifocal nature of his disease, the patient was advised that multiple consecutive scheduled

TACE sessions would be required. Of note, the patient had no prior cancer history and was chemotherapy naive.

The patient returned 1 week later for the first TACE session, with intent to treat the 14-cm right hepatic lobe index tumor. He was pretreated with cefazolin 2 g IV, metronidazole 500 mg IV, diphenhydramine 50 mg IV, and dexamethasone-ondansetron 10 mg/16 mg IV within 1 hour of TACE. Standard ultrasound-guided access was gained into the right common femoral artery, with placement of a 5-Fr vascular sheath (Pinnacle; Terumo, Somerset, NJ). A reverse curve catheter (Sos Omni Selective 2; AngioDynamics, Latham, NY) was introduced into the abdominal aorta, and was used to select the celiac artery. Arteriography demonstrated multifocal hypervascular tumors within the liver. A 5-Fr angled catheter (GLIDECATH; Terumo, Somerset, NJ) was advanced into the right hepatic artery, and arteriography confirmed tumor vascular supply (►Fig. 2). Chemotherapy emulsion—consisting of a 2:1 mixture containing 20 mL ethiodized oil (Lipiodol Ultra-Fluide; Guerbet, Villepinte, France) and 10 mL aqueous chemotherapy solution comprising doxorubicin 50 mg and mitomycin C 10 mg—was injected, followed by administration of four vials of 100 to 300 µm microspheres (Embosphere; Merit Medical, South Jordan, UT) and two vials of 300 to 500 µm microspheres (Embosphere). Final postembolization arteriography demonstrated dense staining of the treated right hepatic lobe tumor (►Fig. 3). Though there was reduction of antegrade blood flow within the tumor neovasculature, some tumor vascular supply remained (►Fig. 4) and a second treatment of the mass was planned. All vascular devices were removed, access site hemostasis was obtained using a vascular closure device (StarClose SE Vascular Closure System; Abbott, Chicago, IL), and a sterile dressing was applied. The patient had a generally unremarkable postprocedural course, though he experienced transient low-grade fevers consistent with postembolization syndrome for 2 days after the procedure.

The patient returned 3 weeks later for a second TACE treatment, with intention to retreat the right hepatic lobe index

Fig. 1 Contrast-enhanced abdominal MRI scan displays multifocal liver masses with imaging features diagnostic of hepatocellular carcinoma; right hepatic lobe index tumor demarcated by arrows.

Fig. 2 Pre-transarterial chemoembolization digital subtraction arteriography reveals mild hypervascularity of the right hepatic lobe liver tumor (arrows).

tumor. He underwent the same pretreatment regimen as the first TACE session. Using the same approach, a 5-Fr angled catheter (GLIDECATH; Terumo) was advanced into the right hepatic artery. Arteriography confirmed persistent tumor vascular supply (→**Fig. 5**). Chemotherapy emulsion—again comprising a 2:1 mixture containing 20 mL ethiodized oil (Lipiodol Ultra Fluide) and 10 mL aqueous chemotherapy solution comprising doxorubicin 50 mg and mitomycin C 10 mg—was injected. Immediately after completion of chemotherapy emulsion administration, the patient acutely developed a constellation of symptoms and signs including dyspnea, tachypnea with a capnography measured partial pressure of carbon dioxide decreased to 13 mm Hg, hypoxia (oxygen saturation: 86%), rigors, hypertension to approximately 200 mm Hg systolic blood pressure, and fever (temperature: 38.2°C). The procedure was

Fig. 3 Fluoroscopic spot image obtained after conventional transarterial chemoembolization shows deposition of high attenuation chemotherapy emulsion within right liver lobe tumor (arrows).

Fig. 4 Postembolization digital subtraction arteriography demonstrates residual right hepatic lobe vascular supply to tumor (arrows).

quickly completed, with removal of all devices and hemostasis at the vascular access site using a vascular closure device (MYNXGRIP Vascular Closure Device; Cordis, Hialeah, FL). A portable chest radiograph was unremarkable, and showed no evidence of pulmonary deposition of chemotherapy emulsion. An electrocardiography (ECG) showed no acute abnormality; no myocardial infarction was evident. The patient's symptoms were managed with a bronchodilator medication (albuterol nebulizer treatment), antihypertensive medication (hydralazine 10 mg), and antipyretic medication (acetaminophen 650 mg). This treatment regimen resulted in improvement

Fig. 5 Digital subtraction arteriography depicts persistent right hepatic lobe tumor enhancement (arrows).

and then resolution of the described symptoms over the course of 15 to 20 minutes. The constellation of symptoms and signs as well as the treatment response was felt to be most consistent with a diagnosis of a hypersensitivity reaction to the administered chemotherapeutic agents.

After the procedure, the patient was admitted to the hospital for overnight observation. During this time, he received the standard post-TACE care, including antibiotics, fluid management, as needed medication for pain control, serial abdominal examinations, and monitoring of the puncture site. The patient's remaining postprocedure course was otherwise unremarkable, and he experienced no recurrent respiratory difficulty, chills, hypertension, or fever. The patient was discharged home on postprocedure day 1. The patient subsequently underwent three transarterial embolization (TAE) procedures using bland microspheres—omitting the use of chemotherapy to avoid recurrent untoward reactions—all of which were well tolerated with no adverse events. However, he experienced marked disease progression 6 months after the initial presentation, which prompted transition to systemic therapy with lenvatinib.

Discussion

Hypersensitivity reaction is an uncommon adverse response to chemotherapy. A 2010 study conducted by Kawaoka et al reported on the incidence and clinical features of hypersensitivity reactions in a cohort of 434 patients receiving a total of 847 TACE procedures for the treatment of HCC.⁴ These patients were treated with locoregional delivery of cisplatin in ethiodized oil suspension. Of the 434 patients receiving TACE, 14 patients (1.7%) developed some form of hypersensitivity reaction.⁴ The authors examined whether a dosage effect may exist, and found that delivery of a higher dose of cisplatin did not correlate with a higher rate of hypersensi-

tivity reaction occurrence. On multivariate analysis, the performance of three or more rounds of TACE was independently associated with a higher risk of hypersensitivity reaction.⁴

Chemotherapy-hypersensitivity reaction is recognized to be a systemic process, and, as such, is generally associated with the systemic delivery of chemotherapeutic agents. However, as the current case and published literature⁴ have demonstrated, it may be possible for these reactions to occur even with locoregional delivery of chemotherapeutic agents. The mechanism underlying hypersensitivity reaction is not well understood, though IgE-mediated and nonallergic mechanisms have been described.⁵ Given that these reactions present after several courses of chemotherapy, it is very likely that there is a sensitization process that the patient may undergo before developing a hypersensitivity reaction.⁵ In the case described herein, the patient developed a hypersensitivity reaction during his second round of TACE, suggesting that he might have been sensitized after the initial administration of doxorubicin and mitomycin C during the first TACE session.

It is possible for a hypersensitivity reaction to occur with the use of almost any chemotherapeutic agent.⁶ These reactions most commonly occur with the use of platinum compounds, L-asparaginase, taxanes, procarbazine, and epipodophyllotoxins,^{6,7} but hypersensitivity to doxorubicin⁸ and mitomycin-C⁹—as used in TACE—have been reported. The clinical features of hypersensitivity reactions may include symptoms such as anxiety, fever, tachycardia, hypertension, hypotension, chest tightness, bronchospasm, facial swelling, dyspnea, pruritus, cough, and diffuse erythroderma.⁶ If a constellation of these symptoms occurs within minutes of treatment, it may be classified as a hypersensitivity reaction to the administered chemotherapeutic agent.⁴ Before a definitive diagnosis may be made, other conditions must be considered in the differential diagnosis. First, it is possible for pulmonary deposition of embolic material to occur with the manifestation of acute hypoxia.¹⁰ In the current case, we excluded this diagnosis, as there was no evidence of ethiodized oil deposition in the lungs on chest radiograph. Second, several hypersensitivity reaction symptoms, including anxiety, chest tightness, diaphoresis, hypertension, hypotension, dyspnea, and tachycardia, may be indications of myocardial infarction.¹¹ It may therefore be prudent to obtain an ECG to assess for electrophysiologic evidence of ischemic cardiac injury. In the case described herein, no ECG abnormality was evident. Third, venous thromboembolism is another potentially deadly condition that may emulate features of hypersensitivity reaction, and, as such, must be ruled out promptly.

Chemotherapy hypersensitivity reactions may be potentially life threatening, and, as such, it is critically important that providers of cytotoxic agents are well prepared to treat this condition.⁷ Discontinuation of the offending drug is the first step in the management of a hypersensitivity reaction.⁷ Kawaoka et al described switching from cisplatin to epirubicin TACE, without any recurrent reactions.⁴ Similar to anaphylactic reaction, it is possible that airway and breathing may become compromised, and, therefore, oxygen supplementation, maintenance of a patent airway, and treatment of bronchospasm are

top priorities.⁷ As hemodynamic instability may occur, providers should be prepared to rapidly administer intravenous fluid resuscitation, vasopressor medications, or antihypertensive medication.⁷ Antihistamines may offer symptomatic relief, but have not been demonstrated to be a lifesaving intervention.¹² The role of steroids has not been clearly delineated in the treatment of hypersensitivity reaction; however, in the case of systemic chemotherapy, studies have demonstrated that many patients tolerate reexposure to the offending cytotoxic drug if it is administered slowly after pretreatment with corticosteroids and antihistamine therapy.¹³ To this end, the TACE procedures in the presented case were accompanied by pretreatment with both corticosteroids and antihistamines as per institutional protocol. Unfortunately, the patient developed a hypersensitivity reaction despite these measures.

The timing of TACE-related chemotherapy-hypersensitivity reaction tends to follow the timing of chemoembolic infusion, with all reactions occurring at the time of chemoemulsion administration in the series reported by Kawaoka et al.⁴ This likely correlates with the early peak systemic drug concentrations observed within minutes after TACE.¹⁴ Interestingly, the prolonged exposure to chemotherapy over time as it elutes systemically from the liver tumor and liver parenchyma over several days after TACE raises a theoretical concern about repeated exposure to the drug over time, and the hypothetical risk that a patient may develop recurrence of a hypersensitivity reaction beyond the procedural setting. Kawaoka et al reported no delayed reactions,⁴ suggesting this concern may be overstated, but as there are few other data to further quantify this theoretical risk, close monitoring of the patient in the post-procedural period for the recurrence of hypersensitivity reaction may be wise. Alternatively, a different LRT—such as TAE and yttrium-90 radioembolization—may be prescribed to avoid the risk associated with chemotherapy. Given the similar effectiveness of bland TAE for HCC therapy,¹⁵ the patient in the reported case underwent subsequent TAE procedures using bland microspheres.

Conclusion

Hypersensitivity reaction is a rare potential adverse event of TACE that may result in acute clinical deterioration and, as such, must be anticipated by IRs performing TACE as a potential complication that may occur within the procedural setting. Vigilance is required, especially after multiple TACE sessions, as the patient very likely undergoes a sensitization process to the chemotherapeutic agent. If this reaction occurs, delivery of the offending agent must first be discontinued. Providers must be diligent to protect the airway, maintain oxygenation and ventilation, and be prepared to provide hemodynamic resuscitation. Pretreatment with corticosteroids and antihistamines may prevent the development of this condition; however, swapping to a different LRT modality may be prudent after

the development of a hypersensitivity reaction to a cytotoxic agent.

Conflict of Interest

Disclosures not related to this work: Ron C. Gaba receives research support from Guerbet USA LLC, Janssen Research & Development LLC, the United States Department of Defense, and the United States National Institutes of Health. He serves as a consultant for Sus Clinicals, Inc.

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