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Contents

Thrice Monthly Volume 9 Number 16 June 6, 2021

REVIEW

- 3796 COVID-19 and the digestive system: A comprehensive review
Wang MK, Yue HY, Cai J, Zhai YJ, Peng JH, Hui JF, Hou DY, Li WP, Yang JS

MINIREVIEWS

- 3814 COVID-19 impact on the liver
Baroiu L, Dumitru C, Iancu A, Leșe AC, Drăgănescu M, Baroiu N, Anghel L
- 3826 Xenogeneic stem cell transplantation: Research progress and clinical prospects
Jiang LL, Li H, Liu L

ORIGINAL ARTICLE

Case Control Study

- 3838 Histopathological classification and follow-up analysis of chronic atrophic gastritis
Wang YK, Shen L, Yun T, Yang BF, Zhu CY, Wang SN

Retrospective Study

- 3848 Effectiveness of sharp recanalization of superior vena cava-right atrium junction occlusion
Wu XW, Zhao XY, Li X, Li JX, Liu ZY, Huang Z, Zhang L, Sima CY, Huang Y, Chen L, Zhou S
- 3858 Management and outcomes of surgical patients with intestinal Behçet's disease and Crohn's disease in southwest China
Zeng L, Meng WJ, Wen ZH, Chen YL, Wang YF, Tang CW
- 3869 Clinical and radiological outcomes of dynamic cervical implant arthroplasty: A 5-year follow-up
Zou L, Rong X, Liu XJ, Liu H

Observational Study

- 3880 Differential analysis revealing APOC1 to be a diagnostic and prognostic marker for liver metastases of colorectal cancer
Shen HY, Wei FZ, Liu Q

Randomized Clinical Trial

- 3895 Comparison of white-light endoscopy, optical-enhanced and acetic-acid magnifying endoscopy for detecting gastric intestinal metaplasia: A randomized trial
Song YH, Xu LD, Xing MX, Li KK, Xiao XG, Zhang Y, Li L, Xiao YJ, Qu YL, Wu HL

CASE REPORT

- 3908** Snapping wrist due to bony prominence and tenosynovitis of the first extensor compartment: A case report
Hu CJ, Chow PC, Tzeng IS
- 3914** Massive retroperitoneal hematoma as an acute complication of retrograde intrarenal surgery: A case report
Choi T, Choi J, Min GE, Lee DG
- 3919** Internal fixation and unicompartmental knee arthroplasty for an elderly patient with patellar fracture and anteromedial osteoarthritis: A case report
Nan SK, Li HF, Zhang D, Lin JN, Hou LS
- 3927** Haemangiomas in the urinary bladder: Two case reports
Zhao GC, Ke CX
- 3936** Endoscopic diagnosis and treatment of an appendiceal mucocele: A case report
Wang TT, He JJ, Zhou PH, Chen WW, Chen CW, Liu J
- 3943** Diagnosis and spontaneous healing of asymptomatic renal allograft extra-renal pseudo-aneurysm: A case report
Xu RF, He EH, Yi ZX, Li L, Lin J, Qian LX
- 3951** Rehabilitation and pharmacotherapy of neuromyelitis optica spectrum disorder: A case report
Wang XJ, Xia P, Yang T, Cheng K, Chen AL, Li XP
- 3960** Undifferentiated intimal sarcoma of the pulmonary artery: A case report
Li X, Hong L, Huo XY
- 3966** Chest pain in a heart transplant recipient: A case report
Chen YJ, Tsai CS, Huang TW
- 3971** Successful management of therapy-refractory pseudoachalasia after Ivor Lewis esophagectomy by bypassing colonic pull-up: A case report
Flemming S, Lock JF, Hankir M, Reimer S, Petritsch B, Germer CT, Seyfried F
- 3979** Old unreduced obturator dislocation of the hip: A case report
Li WZ, Wang JJ, Ni JD, Song DY, Ding ML, Huang J, He GX
- 3988** Laterally spreading tumor-like primary rectal mucosa-associated lymphoid tissue lymphoma: A case report
Wei YL, Min CC, Ren LL, Xu S, Chen YQ, Zhang Q, Zhao WJ, Zhang CP, Yin XY
- 3996** Coronary artery aneurysm combined with myocardial bridge: A case report
Ye Z, Dong XF, Yan YM, Luo YK
- 4001** Thoracoscopic diagnosis of traumatic pericardial rupture with cardiac hernia: A case report
Wu YY, He ZL, Lu ZY

- 4007** Delayed diagnosis and comprehensive treatment of cutaneous tuberculosis: A case report
Gao LJ, Huang ZH, Jin QY, Zhang GY, Gao MX, Qian JY, Zhu SX, Yu Y
- 4016** Rapidly progressing primary pulmonary lymphoma masquerading as lung infectious disease: A case report and review of the literature
Jiang JH, Zhang CL, Wu QL, Liu YH, Wang XQ, Wang XL, Fang BM
- 4024** Asymptomatic carbon dioxide embolism during transoral vestibular thyroidectomy: A case report
Tang JX, Wang L, Nian WQ, Tang WY, Xiao JY, Tang XX, Liu HL
- 4032** Transient immune hepatitis as post-coronavirus disease complication: A case report
Drăgănescu AC, Săndulescu O, Bilașco A, Kouris C, Streinu-Cercel A, Luminos M, Streinu-Cercel A
- 4040** Acute inferior myocardial infarction in a young man with testicular seminoma: A case report
Scafa-Udriste A, Popa-Fotea NM, Bataila V, Calmac L, Dorobantu M
- 4046** Asymptomatic traumatic rupture of an intracranial dermoid cyst: A case report
Zhang MH, Feng Q, Zhu HL, Lu H, Ding ZX, Feng B
- 4052** Parotid mammary analogue secretory carcinoma: A case report and review of literature
Min FH, Li J, Tao BQ, Liu HM, Yang ZJ, Chang L, Li YY, Liu YK, Qin YW, Liu WW
- 4062** Liver injury associated with the use of selective androgen receptor modulators and post-cycle therapy: Two case reports and literature review
Koller T, Vrbova P, Meciarova I, Molcan P, Smitka M, Adamcova Selcanova S, Skladany L
- 4072** Spinal epidural abscess due to coinfection of bacteria and tuberculosis: A case report
Kim C, Lee S, Kim J
- 4081** Rare complication of inflammatory bowel disease-like colitis from glycogen storage disease type 1b and its surgical management: A case report
Lui FCW, Lo OSH
- 4090** Thymosin as a possible therapeutic drug for COVID-19: A case report
Zheng QN, Xu MY, Gan FM, Ye SS, Zhao H
- 4095** Arrhythmogenic right ventricular cardiomyopathy characterized by recurrent syncope during exercise: A case report
Wu HY, Cao YW, Gao TJ, Fu JL, Liang L
- 4104** Delayed pseudoaneurysm formation of the carotid artery following the oral cavity injury in a child: A case report
Chung BH, Lee MR, Yang JD, Yu HC, Hong YT, Hwang HP
- 4110** Atezolizumab-induced anaphylactic shock in a patient with hepatocellular carcinoma undergoing immunotherapy: A case report
Bian LF, Zheng C, Shi XL

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Atezolizumab-induced anaphylactic shock in a patient with hepatocellular carcinoma undergoing immunotherapy: A case report

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Abstract

BACKGROUND

Atezolizumab is a programmed death ligand 1 (PD-L1) inhibitor, and its combination with bevacizumab has been proven an effective immunotherapy for unresectable hepatocellular carcinoma (HCC). Treatment with immune checkpoint inhibitors (ICIs) can lead to hypersensitivity reactions; however, anaphylactic shock is rare. We present a case of life-threatening anaphylactic shock during atezolizumab infusion and performed a relevant literature review.

CASE SUMMARY

A 75-year-old man was diagnosed with HCC recurrence after hepatectomy. He was administered immunotherapy with atezolizumab plus bevacizumab after an allergy to a programmed death-1 (PD-1) inhibitor. The patient showed a sudden onset of dizziness, numbness, and lack of consciousness with severe hypotension during atezolizumab infusion. The treatment was stopped immediately. The patient's symptoms resolved after 5 mg dexamethasone was administered. Because of repeated hypersensitivity reactions to ICIs, treatment was changed to oral targeted regorafenib therapy.

CONCLUSION

Further research is necessary for elucidating the hypersensitivity mechanisms and establishing standardized skin test and desensitization protocols associated with PD-1 and PD-L1 to ensure effective treatment with ICIs.

Key Words: Atezolizumab; Immune checkpoint inhibitors; Anaphylactic shock; Hypersensitivity reaction; Infusion reaction; Hepatocellular carcinoma; Case report

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Core Tip: Treatment with immune checkpoint inhibitors (ICIs) can lead to hypersensitivity reactions; however, anaphylactic shock is rare. We present a case of life-threatening anaphylactic shock during atezolizumab infusion and performed a relevant literature review. Patients may be allergic to drugs targeting both programmed death-1 (PD-1) and programmed death ligand 1 (PD-L1). Adequate attention should be paid to the related complications in the use of immune checkpoint inhibitors. Nevertheless, further studies are needed to understand the underlying mechanisms of hypersensitivity reactions and establish standardized skin test and desensitization protocols associated with PD-1 and PD-L1 to ensure effective treatment with ICIs.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a common carcinoma worldwide and a leading cause of cancer-related death[1]. Although early-stage disease may be curable by resection, most patients present with an advanced and unresectable disease[2]. The multikinase inhibitors sorafenib and lenvatinib are the approved first-line systemic treatments for unresectable HCC. Both are associated with considerable side effects that impair patients' quality of life. Programmed death-1 (PD-1) inhibitors and anti-programmed death ligand 1 (PD-L1) have shown promising clinical activity as second-line treatments for HCC. A 2020 global phase 3 trial showed that in patients with unresectable HCC, atezolizumab combined with bevacizumab resulted in better overall and progression-free survival outcomes than sorafenib[3].

Although immune checkpoint inhibitors induce immune activation with strong antitumor effects, they can lead to hypersensitivity reactions (HSRs) and infusion reactions (IRs). These reactions range from mild cutaneous manifestations to life-threatening anaphylaxis with hypotension, oxygen desaturation, cardiovascular collapse, and death[4]. Atezolizumab is a humanized immunoglobulin (Ig)G-1 class antibody that binds to PD-L1 approved by the Food and Drug Administration (FDA) for the treatment of cancer[5]. The FDA reported severe IRs in 1.3%-1.7% and HSRs in ≤ 1% of cases in which atezolizumab was used[6]. However, cases of atezolizumab-associated anaphylactic shock are rare. Herein, we present the case of a patient who developed life-threatening anaphylactic shock during atezolizumab infusion.

CASE PRESENTATION

Chief complaints

Fatigue, back pain, and loss of appetite for 1 mo.

History of present illness

A 75-year-old man with liver cancer recurrence after right radical hepatectomy in April 2019 was diagnosed with HCC. After a multidisciplinary discussion, the patient received a combination treatment of lenvatinib and a PD-1 inhibitor (camrelizumab, 200 mg/bottle; Heng Rui Pharmaceuticals Inc., China). Because the patient developed hypotension and rash on the second use of camrelizumab, it was discontinued. Moreover, the patient showed significant side effects of oral administration of lenvatinib, including diarrhea, fatigue, and loss of appetite, the drug was discontinued. In November 2020, the patient was hospitalized for immunotherapy. The regimen was changed to a PD-L1 inhibitor (atezolizumab, 1200 mg/bottle; Genentech, Inc., United States) combined with bevacizumab therapy. The first 1200 mg infusion was administered on November 10, 2020. Ten minutes into the atezolizumab infusion,

the patient reported dyspnea, sudden dizziness, and numbness in his feet and was soon unconscious, with hypotension (56/38 mmHg), a heart rate of 85 bpm, temporal temperature of 36.7 °C, respiration rate of 25 breaths per minute, and oxygen saturation of 92%.

History of past illness

The patient has a medical history of hypertension, diabetes, and coronary heart disease for many years, cerebral infarction for more than 4 years without obvious sequelae, and hepatitis B for more than 50 years, for which he was taking “entecavir”. He had an allergy history of PD-1.

Personal and family history

There was no family history of malignant tumors.

Physical examination

Abdominal distension, back pain, concave edema of lower limbs, and no jaundice or palpable masses were observed.

Laboratory examinations

Blood analysis revealed high levels of alpha-fetoprotein (66 ng/mL; normal, < 25 ng/mL), carcinoembryonic antigen (4.8 ng/mL; normal, < 5 ng/mL), and ferritin (355.7 ng/mL; normal, female < 150 U/mL, male < 200 U/mL). Routine blood test showed leukopenia ($1.9 \times 10^9/L$; normal, $4-10 \times 10^9/L$) with predominant neutrophils (62.9%) with normal hematocrit and platelet count. Prothrombin and partial thromboplastin times were normal.

Imaging examinations

Contrast-enhanced computed tomography and magnetic resonance imaging of the chest and abdomen performed in September 2020 showed multiple intrahepatic tumors invading the inferior vena cava and right branch of the portal vein and tumor thrombus formation in the inferior vena cava and left atrium (Figure 1).

FINAL DIAGNOSIS

Hepatocellular carcinoma recurrence and atezolizumab-induced anaphylactic shock.

TREATMENT

A nurse immediately stopped atezolizumab infusion, made the patient lie in the supine position, and reported to the physician. The patient was administered 5 mg dexamethasone intravenously, 500 mL of Ringers solution intravenous drip quickly, and oxygen at a flow rate of 3 L/min.

OUTCOME AND FOLLOW-UP

Ten minutes later, the patient regained consciousness. Thirty minutes later, the symptoms resolved: Blood pressure rose to 112/66 mmHg and heart rate to 75 bpm, the respiration rate was 20 breaths per minute, and oxygen saturation was 95%. Because of repeated hypersensitivity reactions, the medical team decided that the patient would not be rechallenged with immunotherapy and administered oral targeted regorafenib therapy instead. After 1 d, the patient's condition stabilized and he was discharged. The patient was in a stable condition 2 mo after discharge.

DISCUSSION

In recent years, immune checkpoint inhibitors have been widely used for patients with malignancies. Several cancer immunotherapies that target the PD-L1-PD-1 pathway is currently being evaluated in patients with HCC. The PD-1 drugs nivolumab, pembrolizumab, and camrelizumab are second-line drugs that have been approved by the

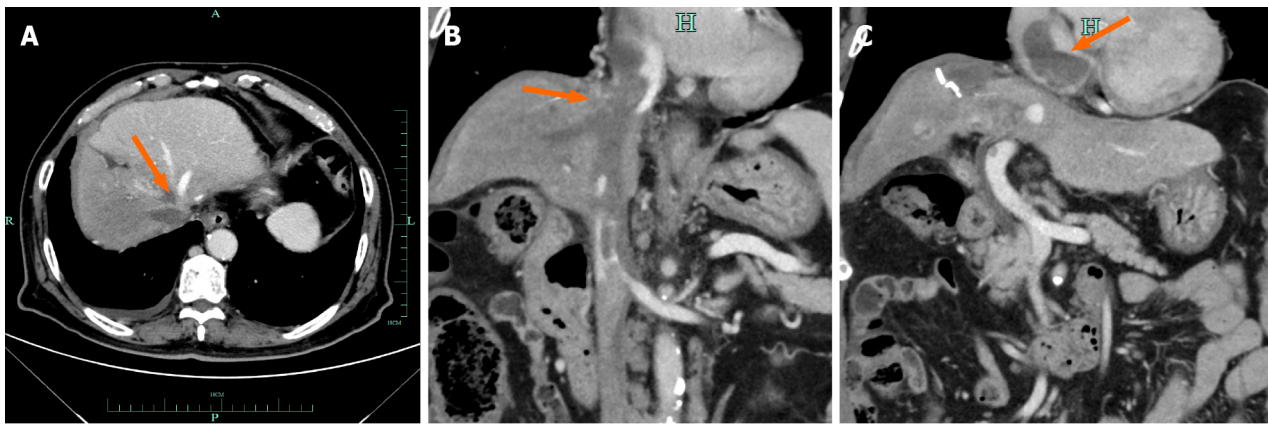


Figure 1 Abdominal contrast-enhanced computed tomography at 1.5 years after right radical hepatectomy. A: Computed tomography showed multiple recurrences of intrahepatic tumors; B: Computed tomography showed invasion of the inferior vena cava and the right branch of the portal vein; C: Computed tomography showed tumor thrombus formation in the inferior vena cava and left atrium.

FDA for the treatment of HCC. Atezolizumab selectively targets PD-L1 to prevent interaction with the receptors PD-1 and B7-1, thus reversing T-cell suppression[7]. Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor, inhibits angiogenesis and tumor growth, and showed response in patients with advanced liver cancer[8,9]. This patient, who had a recurrent tumor after liver cancer surgery, was advised to try immunotherapy with atezolizumab plus bevacizumab after an allergy to camrelizumab. Unfortunately, the patient had a severe allergic reaction at the first use of atezolizumab and immunotherapy was stopped after discussion between the medical group and the patient's family. The patient then received lenvatinib targeted treatment instead.

According to the FDA 2016 label, severe IRs of atezolizumab were observed in 1.3%-1.7% of patients[10]. These reactions include the following symptoms: Back or neck pain, dizziness, chills, feeling like passing out, dyspnea or wheezing, fever, flushing, itching or rash, and swelling of face or lips. Moreover, immune-related adverse reactions (such as pneumonitis, colitis, hypophysitis, encephalitis, hepatitis, and pancreatitis) have been reported to affect various organs. In the European Medicines Agency 2019 assessment report, HSRs of atezolizumab were reported in up to 10% of patients[11]. In addition, pruritis and rash were reported in more than 10% of patients[6]. According to the recent BC Cancer Agency Drug Manual, HSRs including anaphylaxis can be severe in < 1% of the patients, and immune-mediated rash may appear in 8%-18% (severe, 1%) of patients[10]. Prompt recognition and attention to immunotherapy infusion-related reactions could potentially prevent the fatal complications of anaphylaxis with immune checkpoint inhibitors.

HSRs are classified according to the time of onset as immediate (< 1 h of drug administration) or delayed (1 h to 1 wk after drug administration). Immediate-onset HSRs include IgE-mediated hypersensitivity reactions, acute infusion-related reactions, and cytokine release syndrome. However, these reactions may be clinically indistinguishable from each other, and patients may show mixed-type reactions[12,13]. An increase of serum tryptase indicates mast cell/basophil degranulation and suggests the possibility of an IgE-mediated reaction. There are two characteristics of anaphylactic shock: One set of characteristics appears before the shock or at the same time, and manifests as some allergy-related symptoms; the other set of characteristics include the appearance of shock, such as pale face, rapid and weak pulse, wet and cold limbs, unclear consciousness, or complete loss of consciousness. In such cases, shock should be identified, and the patients should be assessed for low blood pressure, which is characterized by systolic blood pressure < 90 mmHg or > 30% lower from baseline in adults. The patient may feel faint, dizzy, light-headed, floating, woozy, giddy, confused, helpless, or fuzzy, and may even collapse[14]. Emergency management of anaphylactic reactions to immune checkpoint inhibitors is the same as that for anaphylaxis from other causes. After the assessment of respiration and circulation and removal of allergens, the infusion is stopped immediately, and the first-line treatment is intramuscular injection of epinephrine. If the patient shows no response to adrenaline within 5-10 min, epinephrine administration should be repeated. Second-line and third-line treatments include adequate positioning, oxygen, nebulized adrenaline, nebulized beta-2-agonist, intravenous normal saline, corticosteroid, and

antihistamine administration depending on the clinical presentations of the patient[13,15]. The target oxygen saturation is > 94% to 96%. The latest evidence suggests that liberal use of supplemental oxygen (target SpO₂ > 96%) in acutely ill adults is associated with a higher mortality than more conservative oxygen therapy. Therefore, a reasonable approach in practice is to maintain a target oxygen saturation of 94% to 96% in acutely ill patients who are not at risk of hypercapnia[16,17]. The patient in the present case improved, so no adrenaline was administered. If the patient has life-threatening airway, breathing, or circulatory problems, adrenaline should be administered. Establishment of the airway should follow basic or advanced life support principles.

If the patient experiences suspected anaphylaxis to immune checkpoint inhibitors, a skin test with a nonirritating concentration of the culprit agent should be performed 4–6 wk after the reaction. A positive skin test strongly suggests an IgE-mediated mechanism. Timing is critical because mast cells are temporarily unresponsive to the allergen in skin tests for 4 wk. Although skin tests are the most specific and sensitive, there are no standardized protocols available for the definition of biological agents except omalizumab, adalimumab, infliximab, and etanercept[18]. Gonzalez-Diaz *et al* reported that they used concentrations of 60 mg/mL for atezolizumab and 25 mg/mL for bevacizumab in the skin prick test, and concentrations of 0.6 mg/mL and 0.25 mg/mL, respectively, in the intradermal skin tests[19]. Our patient did not undergo a skin test because of the severe allergic reaction.

If atezolizumab is the first-line treatment option or more effective than other drugs and the allergic reaction is not serious, desensitization can be performed under the supervision of an experienced allergist. A commonly used desensitization regimen for monoclonal antibodies (mAbs) is a 12-step/3 bag protocol previously for beta-lactam antibiotics[20]. Gonzalez-Diaz *et al*[19] reported that their 4-bag/16-step desensitization protocol for atezolizumab and bevacizumab was useful after severe anaphylaxis in the treatment of lung adenocarcinoma. The patient was premedicated with intravenous chlorpheniramine and methylprednisolone 1 h prior to the infusion of the mAbs. A total of 1200 mg of atezolizumab and 600 mg of bevacizumab were given on separate days with the 4-bag/16-step protocol (initial concentration, 1:1000 of the total dose), with an increasing rate and concentration every 15 min without manifestation of hypersensitivity reactions[19].

CONCLUSION

A case of anaphylactic shock associated with atezolizumab has been presented. With the evolution of cancer therapies, the likelihood of serious adverse events may increase. Patients may be allergic to drugs targeting both PD-1 and PD-L1. Adequate attention should be paid to the related complications in the use of immune checkpoint inhibitors. Nevertheless, further studies are needed to understand the underlying mechanisms of hypersensitivity reactions and establish standardized skin test and desensitization protocols to increase the safety and efficacy of immune checkpoint inhibitors.

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