REVIEW

3321 Encouraging specific biomarkers-based therapeutic strategies for hepatocellular carcinoma

ORIGINAL ARTICLE

Clinical and Translational Research

3334 Autophagy-related long non-coding RNA prognostic model predicts prognosis and survival of melanoma patients

3352 Identification of circ_0000375 and circ_0011536 as novel diagnostic biomarkers of colorectal cancer
Yin T, Du SY, Zhao DY, Sun XZ, Zhou YC, Wang QQ, Zhou GYJ, Yao SK

Retrospective Study

3369 Echocardiography in the diagnosis of Shone’s complex and analysis of the causes for missed diagnosis and misdiagnosis
Li YD, Meng H, Pang KJ, Li MZ, Xu N, Wang H, Li SJ, Yan J

3379 Predictors and prognostic impact of post-operative atrial fibrillation in patients with hip fracture surgery
Bae SJ, Kwon CH, Kim TY, Chang H, Kim BS, Kim SH, Kim HJ

3389 Added value of systemic inflammation markers for monitoring response to neoadjuvant chemotherapy in breast cancer patients
Ke ZR, Chen W, Li MX, Wu S, Jin LT, Wang TJ

3401 Washed microbiota transplantation reduces serum uric acid levels in patients with hyperuricaemia
Cai JR, Chen XW, He YJ, Wu B, Zhang M, Wu LH

Clinical Trials Study

3414 Concurrent chemoradiotherapy using gemcitabine and nedaplatin in recurrent or locally advanced head and neck squamous cell carcinoma

META-ANALYSIS

3426 Effect of enhanced recovery after surgery on inflammatory bowel disease surgery: A meta-analysis
Peng D, Cheng XY, Tao W, Tang H, Ji GY

3436 Accuracy of ultrasound elastography for predicting breast cancer response to neoadjuvant chemotherapy: A systematic review and meta-analysis
Chen W, Fang LX, Chen HL, Zheng JH
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3449</td>
<td>Association of chronic obstructive pulmonary disease with mild cognitive impairment and dementia risk: A systematic review and meta-analysis</td>
<td>Zhao LY, Zhou XL</td>
</tr>
<tr>
<td>3472</td>
<td>Difference and similarity between type A interrupted aortic arch and aortic coarctation in adults: Two case reports</td>
<td>Ren SX, Zhang Q, Li PP, Wang XD</td>
</tr>
<tr>
<td>3478</td>
<td>Combination therapy (toripalimab and lenvatinib)-associated toxic epidermal necrolysis in a patient with metastatic liver cancer: A case report</td>
<td>Huang KK, Han SS, He LY, Yang LL, Liang BY, Zhen QY, Zhu ZB, Zhang CY, Li HY, Lin Y</td>
</tr>
<tr>
<td>3485</td>
<td>Unusual glomus tumor of the lower leg: A case report</td>
<td>Wang HY, Duan P, Chen H, Pan ZY</td>
</tr>
<tr>
<td>3490</td>
<td>Pulmonary <em>Cladosporium</em> infection coexisting with subcutaneous Corynespora cassiicola infection in a patient: A case report</td>
<td>Wang WY, Luo HB, Hu JQ, Hong HH</td>
</tr>
<tr>
<td>3496</td>
<td>Preoperative diagnosis and management of breast ductal carcinoma in situ arising within fibroadenoma: Two case reports</td>
<td>Wu J, Sun KW, Mo QP, Yang ZR, Chen Y, Zhong MC</td>
</tr>
<tr>
<td>3505</td>
<td>Reconstruction of complex chest wall defects: A case report</td>
<td>Huang SC, Chen CY, Qiu P, Yan ZM, Chen WZ, Liang ZZ, Luo KW, Li JW, Zhang YQ, Huang BY</td>
</tr>
<tr>
<td>3511</td>
<td>Young children with multidrug-resistant epilepsy and vagus nerve stimulation responding to perampanel: A case report</td>
<td>Yang H, Yu D</td>
</tr>
<tr>
<td>3541</td>
<td>Severe gastric insufflation and consequent atelectasis caused by gas leakage using AIR-Q laryngeal mask airway: A case report</td>
<td>Zhao Y, Li P, Li DW, Zhao GF, Li XY</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>3547</td>
<td>Hypereosinophilic syndrome presenting as acute ischemic stroke, myocardial infarction, and arterial involvement: A case report</td>
<td>Sun RR, Chen TZ, Meng M</td>
</tr>
<tr>
<td>3553</td>
<td>Cytochrome P450 family 17 subfamily A member 1 mutation causes severe pseudohermaphroditism: A case report</td>
<td>Gong Y, Qin F, Li WJ, Li LY, He P, Zhou XJ</td>
</tr>
<tr>
<td>3573</td>
<td>Qingchang decoction retention enema may induce clinical and mucosal remission in left-sided ulcerative colitis: A case report</td>
<td>Li PH, Tang Y, Wen HZ</td>
</tr>
<tr>
<td>3587</td>
<td>Ultrasound-guided local ethanol injection for fertility-preserving cervical pregnancy accompanied by fetal heartbeat: Two case reports</td>
<td>Kakinuma T, Kakinuma K, Matsuda Y, Ohwada M, Yanagida K, Kajiima H</td>
</tr>
<tr>
<td>3593</td>
<td>Successful apatinib treatment for advanced clear cell renal carcinoma as a first-line palliative treatment: A case report</td>
<td>Wei HP, Mao J, Hu ZL</td>
</tr>
<tr>
<td>3601</td>
<td>Del(5q) and inv(3) in myelodysplastic syndrome: A rare case report</td>
<td>Liang HP, Luo XC, Zhang YL, Liu B</td>
</tr>
<tr>
<td>3609</td>
<td>Papillary thyroid microcarcinoma with contralateral lymphatic skip metastasis and breast cancer: A case report</td>
<td>Ding M, Kong YH, Gu JH, Xie RL, Fei J</td>
</tr>
<tr>
<td>3615</td>
<td>Contrast-enhanced ultrasound manifestations of synchronous combined hepatocellular-cholangiocarcinoma and hepatocellular carcinoma: A case report</td>
<td>Gao L, Huang JY, Lu ZJ, Lu Q</td>
</tr>
<tr>
<td>3624</td>
<td>Thyrotoxicosis after a massive levothyroxine ingestion: A case report</td>
<td>Du F, Liu SW, Yang H, Duan RX, Ren WX</td>
</tr>
<tr>
<td>3630</td>
<td>Pleomorphic adenoma of the left lacrimal gland recurred and transformed into myoepithelial carcinoma after multiple operations: A case report</td>
<td>Huang WP, Li LM, Gao JB</td>
</tr>
</tbody>
</table>
ABOUT COVER
Editorial Board Member of World Journal of Clinical Cases, Chi-Yuan Yeh, MD, PhD, Assistant Professor, Chief Doctor, radiation oncology, Tungs' Taichung MetroHarbor Hospital, Taichung 43503, Taiwan.
peteryeh46@gmail.com

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CASE REPORT

Combination therapy (toripalimab and lenvatinib)-associated toxic epidermal necrolysis in a patient with metastatic liver cancer: A case report

Kai-Kai Huang, Shan-Shan Han, Li-Ya He, Lin-Lin Yang, Bao-Ying Liang, Qing-Yu Zhen, Zi-Bo Zhu, Cai-Yun Zhang, Hong-Yi Li, Ying Lin

BACKGROUND
Both programmed cell death-1 (PD-1) inhibitors and lenvatinib, which have a synergistic effect, are promising drugs for tumor treatment. It is generally believed that combination therapy with a PD-1 inhibitor and lenvatinib is safe and effective. However, we report a case of toxic epidermal necrolysis (TEN), a grade 4 toxicity, after this combination therapy.

CASE SUMMARY
A 39-year-old male presented with erythema, blisters and erosions on the face, neck, trunk and limbs 1 wk after receiving combination therapy with lenvatinib and toripalimab, a PD-1 inhibitor. The skin injury covered more than 70% of the body surface area. He was previously diagnosed with liver cancer with cervical vertebra metastasis. Histologically, prominent necrotic keratinocytes, hyperkeratosis, liquefaction of basal cells and acantholytic bullae were observed in the epidermis. Blood vessels in the dermis were infiltrated by lymphocytes and eosinophils. Direct immunofluorescence staining was negative. Thus, the diagnosis was confirmed to be TEN (associated with combination therapy with toripalimab and lenvatinib). Full-dose and long-term corticosteroids, high-dose intravenous immunoglobulin and targeted antibiotic drugs were administered. The rashes gradually faded; however, as expected, the tumor progressed.
Therefore, sorafenib and regorafenib were given in succession, and the patient was still alive at the 10-mo follow-up.

**CONCLUSION**
Cautious attention should be given to rashes that develop after combination therapy with PD-1 inhibitors and lenvatinib. Large-dose and long-course glucocorticoids may be crucial for the treatment of TEN associated with this combination treatment.

**Key Words:** Toxic epidermal necrolysis; Toripalimab; Lenvatinib; Programmed cell death-1 inhibitor; Liver cancer; Case report

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**INTRODUCTION**
Toripalimab, also known as JS001 or TAB001, is a humanized immunoglobulin G4 monoclonal antibody against programmed cell death-1 (PD-1)[1,2]. PD-1 inhibitors help to enhance the ability of the immune system to defeat tumor cells, but immune-related adverse events (irAEs) occur in many cases[3]. Toxic epidermal necrolysis (TEN) is a rare type of irAE caused by PD-1 inhibitors, with a mortality rate of up to 60%[4]. Lenvatinib is an antiangiogenic tyrosine kinase inhibitor (TKI) and shows synergism with PD-1 inhibitors in solid tumors[5,6]. There have been no case reports on TEN associated with toripalimab or lenvatinib[7]. However, we encountered a patient with metastatic liver cancer who developed TEN after combination therapy with toripalimab and lenvatinib. We are the first group to report this severe cutaneous adverse event following combination therapy with a PD-1 inhibitor and lenvatinib. This case report demonstrates that cautious attention should be given to rashes that develop following this combination treatment. The successful treatment of our case also demonstrated the significance of large-dose and long-course glucocorticoid application for this special type of TEN.

**CASE PRESENTATION**

**Chief complaints**
Erythema, blisters and erosions appeared on the face, neck, trunk and limbs 1 wk after combination therapy with toripalimab and lenvatinib.

**History of present illness**
Four weeks prior to presentation, a 39-year-old male began to receive combination therapy with toripalimab and lenvatinib, as well as radiotherapy, after being diagnosed with liver cancer with cervical vertebra metastasis. The oral administration dose of lenvatinib was 12 mg once daily. Toripalimab (240 mg) was administered intravenously every two weeks. One week prior to presentation, erythema, blisters and erosions began to appear on the face and neck, along with pain and fever. Rashes soon spread to the trunk and limbs, as well as the scrotum and oral mucosa. Therefore, the patient was admitted to the Dermatology Department of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine.
History of past illness
The patient experienced neck pain 2 mo prior to presentation at our clinic. The diagnosis of liver cancer with cervical vertebral metastasis was ultimately confirmed by PET-CT. Hepatitis B virus (HBV) infection was diagnosed at the same time, and the patient was then treated with entecavir. The patient had no other medical history, such as diabetes or hypertension.

Personal and family history
The patient had no history of exposure to industrial poisonous substances and reported no habit of smoking or drinking alcohol. The family history was unremarkable.

Physical examination
The patient presented with typical erythema multiforme, slack bullae and epidermal peeling on the face, neck, trunk and limbs. Nikolsky’s sign was positive. Scrotal and oral mucosal erosion was observed. Skin injury covered more than 70% of the body surface area (BSA) (Figure 1A and B). The patient weighed 71 kg.

Laboratory examinations
Skin biopsy was performed. Prominent necrotic keratinocytes, hyperkeratosis, liquefaction of basal cells and acantholytic bullae were observed in the epidermis. Blood vessels in the dermis were infiltrated by lymphocytes and eosinophils (Figure 2A-C). Direct immunofluorescence (DIF) staining was negative. Serum albumin decreased to 33.6 g/L. CRP and procalcitonin slightly increased to 20.9 mg/L and 0.09 ng/mL, respectively. Random blood glucose was 11.23 mmol/L. Quantitative analysis of HBV DNA yielded a value of $3.57 \times 10^3$ IU/mL. The AFP value was 1497 ng/mL. The results of routine blood, blood coagulation function, liver and kidney function, routine stool, and routine urine tests, as well as of electrocardiography and chest radiography, were normal. Staphylococcus aureus, Escherichia coli, and Klebsiella aerogenes were cultured from the sites of skin erosion.

FINAL DIAGNOSIS
The diagnosis was confirmed to be TEN (associated with combination therapy with toripalimab and lenvatinib) according to the patient’s medical history, typical lesion morphologies, and typical pathological findings.

TREATMENT
The patient ceased treatment with toripalimab and lenvatinib. Methylprednisolone was administered at an initial dose of 80 mg/d. The rashes continued to worsen; thus, 3 days later, the dosage of methylprednisolone was increased to 120 mg/d. Blood pressure and blood glucose were monitored, and insulin was used to control secondary hyperglycemia. The patient received high-dose intravenous immunoglobulin (IVIG) at 0.4 g/kg/d for 5 days. Targeted antibiotic drugs, such as piperacillin-tazobactam and cefuroxime, were chosen in succession based on the drug sensitivity tests in pathogenic bacteria. A potassium permanganate solution bath and compound polymyxin B ointment were administered for external use. The ocular, scrotal and oral mucosa were also carefully treated with topical medication. Oxycontin was administered to relieve the cancer-related pain.

OUTCOME AND FOLLOW-UP
Interestingly, the rashes began to improve on the face and neck and progressed on the trunk and edge of the limbs at a much lower speed when the methylprednisolone dose was adjusted to 120 mg/d. This course lasted for 2 wk, and we did not reduce the dosage of methylprednisolone until we observed remarkable improvements in erythema, blisters and erosions (Figure 1C and D).

At the 2-mo follow-up for glucocorticoid therapy, the dosage of methylprednisolone was gradually reduced to 8 mg/d, and the rashes did not recur. Enhanced computed tomography (CT) scans showed that the size of the primary liver cancer focus increased, and rib metastasis and portal vein tumor thrombosis were noticed. The patient was then treated by transcatheter arterial chemoembolization (TACE).

At the 4-mo follow-up, enhanced CT scans showed that portal vein tumor thrombosis improved, while rib metastasis progressed. Thus, ultrasound-guided microwave ablation and radiotherapy were conducted in succession. Oral sorafenib was also administered, and no cutaneous adverse drug reactions were observed.
Figure 1 Clinical images before and after treatment. A: Erythema, blisters and erosions appeared on the face and neck, as well as the oral mucosa; B: Typical erythema multiforme, slack bullae and epidermal peeling could be seen and covered more than 70% of the body surface area; C and D: The rashes gradually faded after 3 wk of treatment.

Figure 2 Pathological biopsy of the lesion. A: Acantholytic bullae were observed in the epidermis (hematoxylin-eosin staining (HE) × 40); B: Hyperkeratosis and liquefaction of basal cells could be seen in the epidermis. Blood vessels in the dermis were infiltrated by lymphocytes and eosinophils (HE × 100); C: Prominent necrotic keratinocytes were identified in the epidermis (HE × 400).

At the 6-mo follow-up, the patient reported paraplegia, which was possibly due to the intraspinal metastatic tumors revealed on the contrast-enhanced magnetic resonance imaging scan. Emission computed tomography (ECT) revealed metastasis of the occipital bone, cervical vertebra, ribs and femur. The patient was experiencing severe pain and agreed to take the risk of the rash recurring to receive additional combination treatment with immunotherapy and targeted therapy. Due to the poor therapeutic effect of sorafenib, the therapeutic regimen was adjusted to 120 mg regorafenib once daily in combination with sintilimab, another PD-1 inhibitor, in addition to toripalimab[8]. A maculopapular rash developed on the trunk 2 wk later; thus, sintilimab was stopped. The rashes were not as severe as the initial rashes and vanished after a small dose of methylprednisolone was administered. The patient continued taking regorafenib, and disease progression seemed to decrease. At the 10-mo follow-up, the patient was still alive.

**DISCUSSION**

TEN and Stevens Johnson syndrome (SJS) are two ends of a spectrum of rare severe adverse cutaneous drug reactions, typically with a clinical presentation of erythema multiforme, slack bullae and epidermal peeling[9]. They are distinguished only by their extent of skin detachment (< 10% BSA: SJS,
In conclusion, we are the first group to report TEN following combination therapy with a PD-1 inhibitor.
and lenvatinib. Cautious attention should be given to rashes that develop after this combination treatment. Large-dose and long-course glucocorticoid application may be crucial for the treatment of this special type of TEN.

**FOOTNOTES**

**Author contributions:** Huang KK, Han SS, and Zhang CY contributed to the treatment, literature search; Huang KK, He LY and Zhen QY contributed to manuscript writing; Lin Y, Yang LL, and Liang BY contributed to the treatment and manuscript revision; Zhu ZB and Li HY provided comments to this literature; informed consent was conducted by Huang KK; all authors have read the final manuscript and approved the final manuscript.

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**Country/Territory of origin:** China

**ORCID number:** Kai-Kai Huang 0000-0001-8010-7737; Shan-Shan Han 0000-0001-5779-8701; Li-Ya He 0000-0002-7477-5189; Lin-Lin Yang 0000-0002-7963-2777; Bao-Ying Liang 0000-0003-2824-4448; Qing-Yu Zhen 0000-0003-2866-7897; Zibo Zhu 0000-0002-3295-0989; Cai-Yun Zhang 0000-0003-1841-3674; Hong-Yi Li 0000-0003-0099-5776; Ying Lin 0000-0003-2473-7851.

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