Misdiagnosis of severe and atypical oxaliplatin-related hypersensitivity reaction following chemotherapy combined with PD-1 inhibitor: A case report and literature review

MAOBEN SUN[1,2], GUIHUA XU[2], LIANGZHEN CAI[1] and SHAOZHONG HE[1]

[1]Department of Oncology, Binhaiwan Central Hospital of Dongguan, Dongguan, Guangdong 523000, P.R. China;
[2]Dongguan Key Laboratory of Precision Medicine, Binhaiwan Central Hospital of Dongguan, Dongguan, Guangdong 523000, P.R. China

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Abstract. Although the efficacy of treatment strategies for cancer have been improving steadily over the past decade, the adverse event profile following such treatments has also become increasingly complex. The present report described the case of a 67-year-old male patient with gastric stump carcinoma with liver invasion. The patient was treated with oxaliplatin and capecitabine (CAPEOX regimen) chemotherapy, combined with the programmed cell death protein-1 (PD-1) inhibitor tislelizumab. Following treatment, the patient suffered from chills, high fever and facial flushing, followed by shock. Relevant examination results revealed severe multiple organ damage, as well as a significant elevation in IL-6 and procalcitonin (PCT) levels. Initially, the patient was diagnosed with either immune-related adverse events (irAEs) associated with cytokine release syndrome caused by tislelizumab or severe bacterial infection. However, when tislelizumab treatment was stopped and the CAPEOX chemotherapy regimen was reapplied, similar symptoms recurred. Following screening, it was finally determined that severe hypersensitivity reaction (HSR) caused by oxaliplatin was the cause underlying these symptoms. A literature review was then performed, which found that severe oxaliplatin-related HSR is rare, rendering the present case atypical. The present case exhibited no common HSR symptoms, such as cutaneous and respiratory symptoms. However, the patient suffered from serious multiple organ damage, which was misdiagnosed as irAE when oxaliplatin chemotherapy combined with the PD-1 inhibitor was administered. In addition, this apparent severe oxaliplatin-related HSR caused a significant increase in PCT levels, which was misdiagnosed as severe bacterial infection and prevented the use of glucocorticoids. This, in turn, aggravated the damage in this patient.

Correspondence to: Dr Shaozhong He, Department of Oncology, Binhaiwan Central Hospital of Dongguan, 111 Humen Avenue, Dongguan, Guangdong 523000, P.R. China
E-mail: heshaozhong8@126.com

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Introduction

Despite the importance of adverse events associated with cancer treatments and the broad range of mitigating interventions, limited systematic efforts have been made to identify, appraise and summarize the totality of evidence on the effectiveness of such interventions. In particular, the burden of these adverse events remains high, which is associated with considerable rates of morbidity and mortality, in addition to the high cost involved for the patient. All the aforementioned factors contribute to a negative effect on the physical, emotional and social wellbeing of the patient (1,2). However, the trajectory of adverse toxicities associated with cancer treatments is unique to each cancer type, and dependent on the physiology of each individual patient. Therefore, particular attention must be paid to the management of adverse events during anti-tumour treatment. Chemotherapy is one of the most common cancer treatment options, and immune checkpoint inhibitors (ICIs) have transformed the treatment of cancer in recent years.

ICI treatment combined with chemotherapy has been widely used for various types of cancer in clinical practice. However, this type of combined therapy increases the difficulty of identifying adverse events, especially when they are rare or atypical. Oxaliplatin is a third-generation platinum agent approved for the treatment of gastric, colorectal and other types of cancer. Among known oxaliplatin-induced dose-limiting toxicities are common neurological (paraesthesia and dysaesthesia of the hands, feet and perioral region), haematopoietic and gastrointestinal toxicities, and more rarely, hypersensitivity reactions (HSRs) (3). These HSRs are often mild or moderate, but occasionally can be serious and lead to patient mortalities. In the present report, a male patient who was misdiagnosed with severe and atypical oxaliplatin-related HSR following chemotherapy combined with programmed cell death protein-1 (PD-1) inhibitor immunotherapy was documented.

Case report

A 67-year-old man was diagnosed with gastric stump cancer with local liver invasion and underwent resection in the general surgery department of Binhaiwan Central Hospital of Dongguan (Dongguan, China) in February 2023. The postoperative pathology results were as follows: i) Poorly differentiated adenocarcinoma; ii) pT4b N3a M0; iii) stage IIIc; iv) microsatellite stable; and v) programmed death-ligand 1 (PD-L1) combined positive score (CPS) of 15 (IHC 22C3 pharmDx assay) (Fig. 1). The patient recovered well and came to the oncology department of the same hospital for further treatment. Historically, the patient had undergone Billroth II gastrectomy due to gastric bleeding in 2013.

An attraction-5 study showed that, although oxaliplatin and capecitabine (CAPEOX regimen) chemotherapy combined with PD-1 inhibitor could not reduce the 3-year rate of relapse-free survivals of postoperative stage III gastric/gastro-esophageal junction cancer compared with CAPEOX regimen chemotherapy alone, clinical benefits were observed in subgroups of patients with either stage IIIc or PD-L1 CPS >1 when chemotherapy was combined with PD-1 inhibitor (4). Following comprehensive discussions with the patient, he requested chemotherapy combined with PD-1 inhibitor immunotherapy and signed the informed consent.

In March 2023, the patient was treated with the CAPEOX chemotherapy regimen (oxaliplatin, 130 mg/m^2 on day 1; capecitabine, 1,000 mg/m^2 on days 1-14) combined with the PD-1 inhibitor (tislelizumab, 200 mg on day 1) for the first course. At 3 days after treatment, the liver function of the patient was slightly impaired but recovered spontaneously after 1 week. Other laboratory test results were near normal. In April 2023, the patient was treated with a second course of the same regimen. Chills and high fever occurred in the patient following treatment on day 1. The patient noted that several family members, with whom he maintained close interactions, had contracted influenza. Blood test results on days 4 and 7 from treatment were as follows: i) Common Terminology Criteria for Adverse Events (CTCAE) grade II neutropenia, thrombocytopenia and liver function impairment; ii) CTCAE grade I cardiac and renal function impairment; iii) elevation of inflammatory marker procalcitonin (PCT) levels; and iv) no microbial growth in blood culture. The aforementioned results led to the diagnosis of side effects of chemotherapy combined with influenza. The patient was therefore treated with anti-bacterial, anti-viral and organ-protective drugs, and recovered after 2 weeks.

In May 2023, the patient was treated with a third course of the same regimen. After treatment on day 1, the patient suffered from sudden chills, high fever (40.2˚C) and facial flushing. After anti-pyretic drug treatment, his fever was slightly alleviated (38-39˚C). However, 8 h later, the mental state of the patient deteriorated, exhibiting somnolence. His blood pressure and blood oxygen saturation were immediately measured, and were found to be 55/36 mmHg and 65% respectively; the patient was therefore diagnosed with shock. Rapid fluid infusion and dopamine were administered to raise his blood pressure, alongside high-flow oxygen inhalation. The shock was then rectified and his mental state improved, but dopamine was required to maintain his blood pressure. Blood test results were as follows: i) PCT, 52.48 ng/ml [normal range (NR), 0.00-0.05 ng/ml]; ii) IL-6, >2,500.00 pg/ml (NR, 0-7 pg/ml); iii) creatinine, 214.30 μmol/l (NR, 46-104 μmol/l); iv) alanine transaminase, 234.40 U/l (NR, 10-40 U/l); v) aspartate transaminase, 383.00 U/l (NR, 10-40 U/l); vi) pro-brain natriuretic peptide (pro-BNP), 7,732 pg/ml (NR, 0-125 pg/ml); vii) troponin T, 23.4 pg/ml (NR, 0-14 pg/ml); viii) triiodothyronine, 0.619 nmol/l (NR, 1.2-3.1 nmol/l); and ix) thyroxine, 42.9 nmol/l (NR, 66-181 nmol/l). Electrocardiogram and cardiac ultrasound results did not reveal abnormalities. Computed tomography scans revealed the following findings: i) No abnormalities in the brain; ii) diffuse exudative changes in the neck; iii) patchy shadows in both sides of the lungs, most likely inflammation; iv) small amount of pleural effusion in both sides; and v) a small amount of ascites (Fig. 2).

Since similar symptoms had occurred in this patient on treatment day 1 of the two previous courses, and the symptoms during the third course were notably more severe compared with those during the second course, the symptoms of both courses were suspected to be immune-related adverse events (irAEs) induced by tislelizumab, causing multiple organ damage. The adverse events of the third course involved the heart, lungs, liver, kidneys and the thyroid gland, which were classified into CTCAE grades IV, I, III, II and I, respectively. In addition, cytokine release syndrome (CRS) was also suspected, since this patient had high fever with markedly increased IL-6 levels. However, since the PCT level was also markedly elevated in this patient, the possibility of severe bacterial infection could not be ruled out. The patient was then treated with methylprednisolone (200 mg on days 1-7) and immunoglobulin (20 g on days 1-7) plus tocilizumab (160 mg on days 1-2), to suppress the immune response, combined with plasma exchange and anti-bacterial and organ-protective drugs. The high fever in the patient subsequently dissipated and the patient no longer needed dopamine to maintain blood pressure.

A review of the various indicators revealed significant improvements, with no microbial growth observed in the blood culture. However, during treatment the patient developed atrial fibrillation and his cardiac function deteriorated [pro-BNP, 12,334 pg/ml (NR, 0-125 pg/ml); left ventricular ejection fraction, 48% (NR, 50-70%)], which were rectified by cedilanid treatment. The aforementioned events were then verified as irAEs associated with CRS, instead of bacterial infection. The patient therefore continued with the methylprednisolone treatment (dosage was reduced step by step for 6 weeks) regimen, and his condition was stable during follow-up. The results of the computed tomography (CT) scan showed that the cervical exudation, patchy shadows of the lung and pleural effusion had been absorbed (Fig. 2).

Due to the occurrence of severe adverse events induced by tislelizumab during the third course, tislelizumab was permanently discontinued for the patient. In June 2023, the patient underwent a fourth course of the CAPEOX regimen. Following treatment on day 1, the patients developed chills, high fever and facial flushing again. The patient was immediately treated with methylprednisolone (200 mg) plus immunoglobulin (15 g), which relieved the symptoms. However, 2 h later, shock re-occurred and had to be treated with rapid fluid infusion, dopamine and oxygen inhalation.

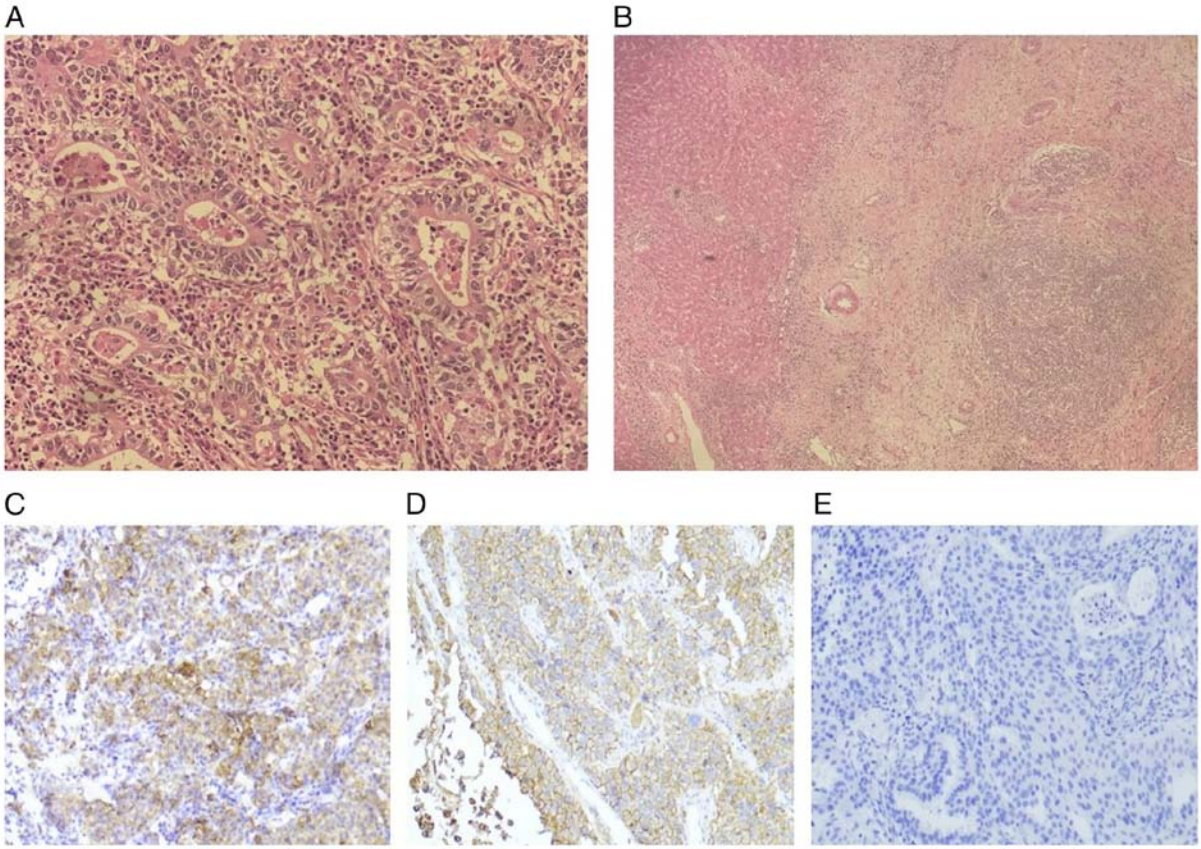

Figure 1. Pathological features. (A) Gastric lesions: Poorly differentiated adenocarcinoma (haematoxylin and eosin; magnification, x200). (B) Gastric cancer with local liver invasion: Hepatocytes (the left side) and gastric cancer cells (the right side) (haematoxylin and eosin; magnification, x50). (C-E) PD-L1 expression in tumour sample (IHC 22C3 pharmDx assay) (magnification, x100): (C) PD-L1 CPS=15, (D) positive quality control and (E) negative quality control. PD-L1, programmed death-ligand 1; IHC, immunohistochemistry; CPS, combined positive score.

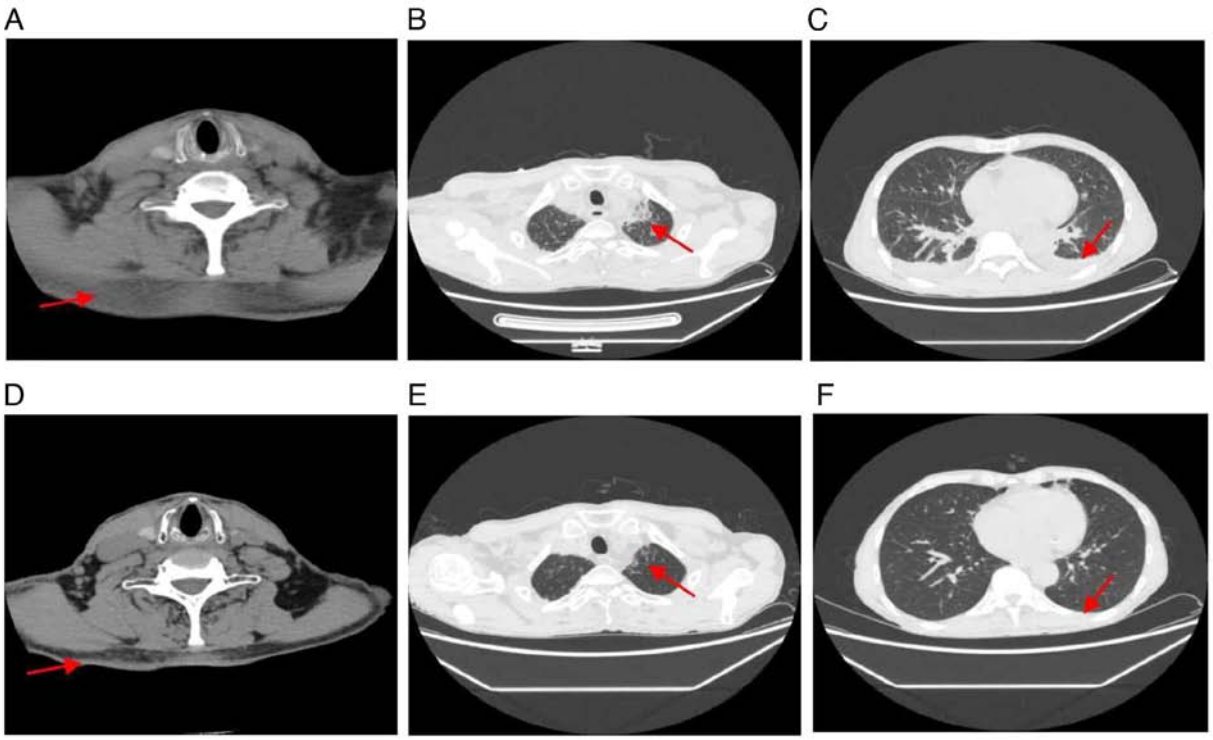

Figure 2. CT scan results before and after adverse events were controlled during the third course. (A) Cervical exudation when the adverse events occurred (arrow). (B) Patchy shadows of the lung when adverse events occurred (arrow). (C) Pleural effusion when the adverse events occurred (arrow). (D) Cervical exudation was absorbed when the adverse events were controlled (arrow). (E) Patchy shadows of the lung were absorbed when the adverse events were controlled (arrow). (F) Pleural effusion was absorbed when the adverse events were controlled (arrow). CT, computed tomography.

Table I. Laboratory test results between the first and fourth courses.

Parameter	First course highest/ lowest value	Second course highest/ lowest value	Third course highest/ lowest value	Fourth course highest/ lowest value	Range of normal values
Pro-brain natriuretic peptide, pg/ml	532	2,875	12,334	3,800	0-125
Cardiac troponin T, pg/ml	9.49	17.92	23.40	12.50	0-14
Left ventricle ejection fraction	70%	-	48%	60%	50-70%
Alanine transaminase, U/l	47.3	146.9	234.2	78.0	10-40
Aspartate transaminase, U/l	45.0	186.0	383.0	81.0	10-40
Creatinine, μmol/l	82.7	147.2	214.3	104.1	46-104
Triiodothyronine, nmol/l	1.33	-	0.42	0.69	1.2-3.1
Thyroxine, nmol/l	66.59	-	36.40	44.25	66-181
Procalcitonin, ng/ml	<0.05	9.28	52.48	26.30	0.00-0.05
IL-6, pg/ml	-	-	>2,500	>2,500	0-7

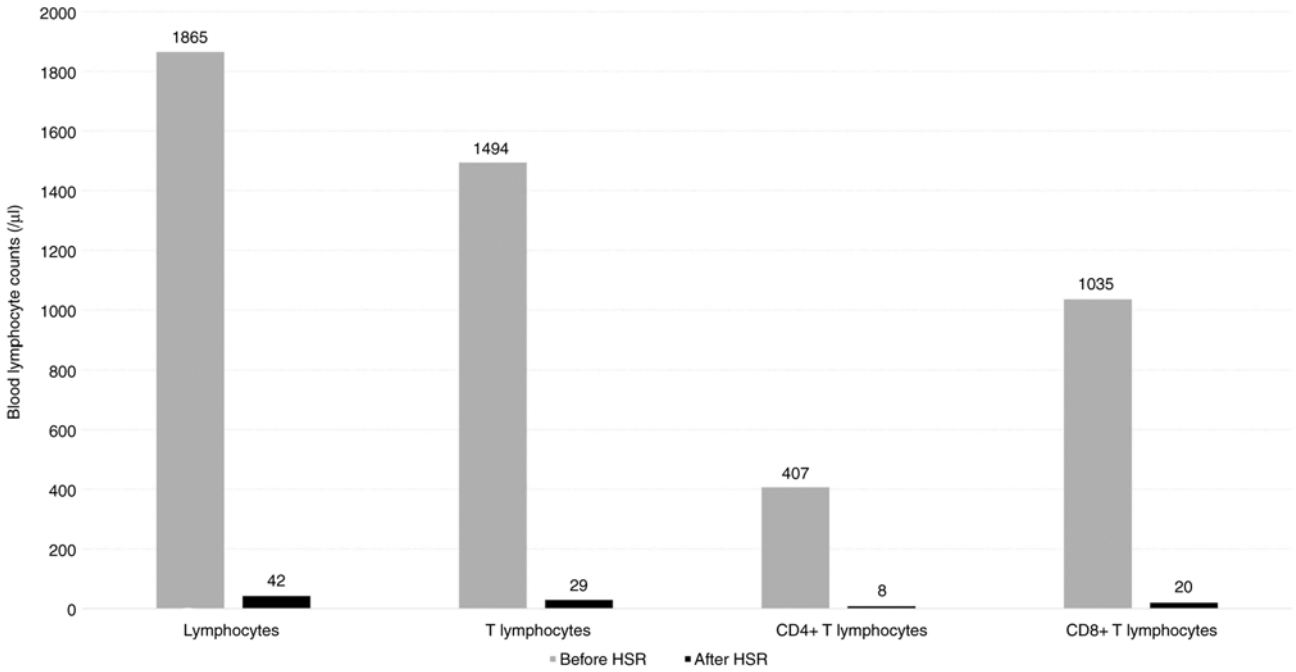

Figure 3. Blood lymphocyte counts before and after HSR in the third course. HSR, hypersensitivity reaction.

Blood test results also showed multiple organ damage, coupled with the significant elevation of IL-6 and PCT levels, albeit the symptoms were less severe compared with those in the third course. The patient developed similar symptoms following the discontinuation of tislelizumab. Comprehensive analysis of clinical data during the three recent courses found that the symptom onset time was 1-7 h after oxaliplatin infusion (6 h and 34 min, 3 h and 52 min, and 1 h and 15 min, respectively) and the interval time was progressively shorter (Table I). Given that anti-allergic treatment was effective for these symptoms and no allergic reaction was observed following the administration of combined drugs in the past, it was adjudged that the aforementioned symptoms in the three recent courses were due to oxaliplatin-related HSRs (CTCAE grade II, IV and IV, respectively). The patient was therefore treated with gradually reducing doses of methylprednisolone (the duration was 2 weeks) and his condition was stable during follow-up. Between July 2023 and January 2024, tegafur/gimeracil/oteracil potassium capsule (S-1) chemotherapy was administered instead for the patient, and his condition was also stable. On last follow-up in February 2024, the patient's cancer remained stable without recurrence.

Discussion

The mechanism underlying oxaliplatin-related HSR remains unknown. Stahl *et al* (5) previously found that almost all examined patients experience oxaliplatin-related HSRs after multiple infusions, suggesting that sensitization to oxaliplatin is required during the initial courses. In addition,

Table II. Characteristics of oxaliplatin-related HSR in previous clinical studies.

Study	Patients	Patients with HSR, n (%)	Patients with grade III/IV HSR, n (%)	Median occurrence courses, range	Median onset time from start of infusion, min	Premedication	Main symptoms	Prognosis	(Refs.)
Brandi *et al*, 2003	124	17 (13.7)	N/A	9 (2-17)	10-20	N/A	Cutaneous and respiratory symptoms	Recovery	(7)
André *et al*, 2004	1,108	114 (10.3)	Grade III, 25 (2.3) Grade IV, 7 (0.6)	N/A	N/A	N/A	N/A	N/A	(8)
Siu *et al*, 2006	180	27 (15.0)	4 (2.2)	9 (1-18)	N/A	N/A	Cutaneous and respiratory symptoms	Recovery	(9)
Shao *et al*, 2010	383	47 (12.3)	N/A	10 (2-19)	40	Steroids Antihistamines	Cutaneous and respiratory symptoms	1 death	(10)
Parel *et al*, 2014	191	17 (8.9)	Grade III, 3 (1.6) Grade IV, 0 (0)	3 (1-13)	N/A	N/A	Cutaneous and respiratory symptoms	Recovery	(11)
Okayama *et al*, 2015	162	28 (17.2)	Grade III, 9 (5.5) Grade IV, 1 (0.6)	8 (5-17)	Grade III, 54 Grade IV, 18	N/A	N/A	Recovery	(12)
Shen *et al*, 2018	291	39 (13.4)	Grade III, 9 (3.1) Grade IV, 7 (1.0)	8 (4-15)	N/A	Steroids Antihistamines	N/A	Recovery	(13)
Sohn *et al*, 2018	679	103 (15.2)	Grade III, 8 (1.2) Grade IV, 2 (0.3)	4.72±2.73	N/A	N/A	N/A	Recovery	(14)
Barbin *et al*, 2022	153	17 (11.1)	Grade III, 12 (7.8) Grade IV, 1 (0.6)	2 (1-11)	N/A	Steroids Antihistamines	Cutaneous and respiratory symptoms	Recovery	(15)
Selcuk *et al*, 2023	57	11 (19.3)	N/A	4 (1-7)	N/A	Steroids Antihistamines	N/A	Recovery	(16)

HSR, hypersensitivity reaction; N/A, not applicable.

IgE-mediated type I HSRs were suspected (5). Another hypothesis of oxaliplatin-related HSR is that platinum-based drugs can act as 'superantigens' on peripheral blood mononuclear cells to induce the expansion of T lymphocytes, which in turn release large quantities of proinflammatory cytokines, such as IL-6, TNF-α and IFN-γ (6). Data from 10 oxaliplatin-related HSR studies over the past 20 years have subsequently been analysed and summarized. Briefly, the incidence has been revealed to be mostly 10-20%, with that of grade IV being <2%. However, pre-medication with steroids and anti-histamines seems ineffective for its prevention. The median occurrence time is within 1 h from the start of oxaliplatin infusion, with the main symptoms being cutaneous and respiratory symptoms. The treatment method for oxaliplatin-related HSR is anti-allergic treatment. The prognosis for the majority of patients was favourable, since deaths were rare (Table II) (7-16).

IrAEs are distinct types of toxicities that are caused by the non-specific activation of the immune system, which can damage almost any organ. The precise mechanism of irAE pathogenesis remains unclear, although several inflammatory cell types, such as Th_{17}, have been reported to be involved (17). However, CRS is not universally defined and is considered to be a phenomenon of immune hyperactivation, whereby lymphocytes (such as B cells, T cells and natural killer cells) and bone marrow cells (such as macrophages, dendritic cells and monocytes) are activated to release pro-inflammatory cytokines, including IL-6, IL-10 and IFN-γ (18). This effect has been commonly observed following various immunotherapies, such as chimeric antigen receptor-T cells and monoclonal antibodies. In addition, this phenomenon has been reported in the field of viral infection therapy, such as H1N1 and Coronavirus disease 2019 (18-20).

It is not common for oxaliplatin-related HSR to cause multiple organ damage unless it is particularly severe or not treated in a timely manner, due to the ensuing cytokine storm (19,21). The causes of misdiagnosis in the present patient were therefore investigated. The present patient had no common HSR symptoms, such as cutaneous and respiratory symptoms, while exhibiting serious multiple organ damage, which was misdiagnosed as irAEs. In addition, the occurrence time of the most severe symptoms was on day 52 of tislelizumab immunotherapy during the third course, which coincided with the high incidence time of fatal toxic effects associated with PD-1 inhibitor (22,23). PCT levels were markedly elevated in this patient with high fever, which was misdiagnosed as severe bacterial infection. PCT is a common biomarker of bacterial infection or sepsis. Although non-infectious diseases can also cause systemic inflammation and increase PCT, supporting data remain limited (24). The relationship between PCT and HSR was then assessed through a literature review, although no definitive reports could be found. The possibility of severe bacterial infection prevented the early use of glucocorticoid for this patient during the third course when oxaliplatin-related HSR occurred. There were 15 h between the onset of HSR and the use of glucocorticoid, which delayed the treatment and aggravated the damage to the patient. During the fourth course, glucocorticoid was applied early when HSR occurred, with the symptoms then becoming less severe.

Admittedly, irAEs caused by tislelizumab following HSR occurrence during the third course could not be completely ruled out. However, due to similar symptoms occurring during the third and fourth courses, coupled with cardiac toxicities manifesting as heart failure rather than myocardial damage, irAEs caused by tislelizumab became less likely in the third course. In addition, a significant decrease in the blood T lymphocyte counts following HSRs was observed in the patient during the third course (Fig. 3), further supporting this viewpoint. To date, several studies have reported that an increased T lymphocyte count is associated with irAEs (25-27). However, a previous study has found that patients with irAEs have lower levels of T and B lymphocyte subsets, and higher levels of IL-6, compared with those without irAEs (28); this requires further investigation. The lower severity and quicker control of the condition of the patient during the fourth course compared with that during the third course was attributed to the early intervention of glucocorticoid when HSR occurred.

In conclusion, severe oxaliplatin-related HSR is rare and at times atypical. It can cause serious multiple organ damage and significant increases in PCT levels, which often leads to misdiagnosis and a delay in treatment, particularly when oxaliplatin chemotherapy is combined with other treatments. Furthermore, given that combination therapy for cancer can increase therapeutic efficacy through multiple mechanisms (29) and become increasingly popular in clinical practice, we hypothesise that complex adverse events such as the ones that occurred in the present patient will increase, which is something that requires vigilance.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

MS and SH conceived and designed this study. MS, LC and GX contributed to the analysis and interpretation of data. MS wrote the manuscript. SH and LC supervised this study and critically reviewed the manuscript for important intellectual content. MS and SH confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Binhaiwan Central Hospital of Dongguan (approval no. 2023048) and was conducted in accordance with the Declaration of Helsinki.

Patient consent for publication

Written informed consent for publication was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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