OPEN ACCESS

Severe immune-mediated hepatitis caused by sindilizumab combined with local radiotherapy: a case report

Guofei Ren ,[1] Hangping Chen,[1] Jing Fang[2]

[1]Pharmacy Department, Affiliated Xiaoshan Hospital, Hangzhou Normal University, Hangzhou, Zhejiang, China
[2]Department of Oncology, Affiliated Xiaoshan Hospital, Hangzhou Normal University, Hangzhou, Zhejiang, China

Correspondence to
Jing Fang, Department of Oncology, Zhejiang Xiaoshan Hospital, Hangzhou, Zhejiang, 311202, China; fj15268118263@outkook.com

HC and JF are joint first authors.

Received 23 May 2023
Accepted 11 July 2023
Published Online First 8 August 2023

SUMMARY

A man with diffuse large B-cell lymphoma in the nasal cavity was treated with sindilizumab, an immune checkpoint inhibitor, combined with local radiotherapy for multiple nodules of the left upper arm. After a single administration of sindilizumab and 10 radiotherapy treatments, the patient presented with liver dysfunction. Liver function tests showed that the levels of transaminases had increased abnormally and deteriorated though with intense treatment. His bilirubin level was also increased with obvious yellow staining of the skin and sclera. The patient was considered to have severe immune-mediated hepatitis (IMH) caused by sindilizumab combined with local radiotherapy. His liver function did not improve and he died of organ failure. This is a case of rare liver failure which was considered to be IMH induced by synergistic treatment with immune checkpoint therapy and radiotherapy.

BACKGROUND

Sindilizumab is a programmed death protein-1 (PD-1) inhibitor which is an immune checkpoint inhibitor (ICI) that can enhance the ability of T cell receptors to recognise antigens and promote T cell proliferation by blocking the PD-1/PD-L1 signalling pathway between T cells and tumour cells, thereby increasing the antitumour immune response. However, while enhancing the antitumour effect of T cells, it may also abnormally enhance the normal self-immune response, leading to an imbalance in immune tolerance and autoimmune inflammatory reactions when involved in normal tissues, known as immune-related adverse events.[1] An immune-related adverse event occurring in the liver is called immune-mediated hepatitis (IMH).

Acute liver injury refers to liver cell injury due to various causes in patients without chronic liver disease, and most patients can maintain normal operation of the liver. Clinically, mild cases are characterised by elevated serum transaminase and bilirubin, and severe cases may develop liver failure and coagulation dysfunction. Common causes of acute liver injury include viral infection, ischaemia, drugs, ingestion of toxic food by mistake, excessive alcohol intake, radiation damage and systemic infection. Of these, drugs are one of the most common causes of acute liver injury. IMH is a special type of drug-induced liver injury. The incidence of IMH caused by PD-1 inhibitors alone is 1–4%,[2] which often occurs 8–12 weeks after the first administration. PD-1 plays an important role in maintaining T cell activity in peripheral tissues, thereby maintaining immunologic tolerance.[3] PD-L1 is expressed on hepatocytes, hepatic stellate cells, liver sinusoidal endothelial cells and Kupffer cells, and PD-L2 is expressed on liver sinusoidal endothelial cells, Kupffer cells and intrahepatic leucocytes.[4 5] Liver toxicity associated with ICIs is usually mild to moderate. Most of the reported cases of severe liver dysfunction induced by ICIs are related to reactivation of hepatitis B virus. We describe a patient who died of IMH caused by a PD-1 inhibitor combined with local radiotherapy, without reactivation of hepatitis B virus. The presentation, treatment and outcome are detailed below. In this case, the immune regulatory effect caused by radiotherapy cannot be ignored.

CASE PRESENTATION

A man aged >70 years with stage IIA diffuse large B-cell lymphoma of the nasal cavity was admitted to hospital on 23 July 2021 with multiple nodules on the left upper arm and right chest wall. The patient had received eight cycles of the R-CHOP regimen (cyclophosphamide, doxorubicin, prednisone, rituximab and vincristine) from February 2019 to August 2019 after diagnosis, followed by radiotherapy for local residual and recurring sites such as the nasal cavity from September 2019 to October 2019. The efficacy was evaluated as complete response (CR) by positron emission tomography/CT in December 2019. In August 2020, nodules appeared on the left upper arm and right chest wall, which gradually increased and enlarged. Pathological analysis confirmed diffuse large B-cell lymphoma. The nodules completely subsided after palliative radiotherapy with DT 36 Gy/18 fx. However, in May 2021 multiple new nodules appeared in different parts of the left upper arm and right chest wall, with the nodule size progressively enlarging (maximum diameter 4-5 cm). The patient had no history of cardiovascular disease, kidney disease, viral hepatitis, endocrine system disease or major surgery.

INVESTIGATIONS

After admission, laboratory tests showed normal liver and kidney function, normal urine routine examination, coagulation function, B-type natriuretic peptide and troponin I.

TREATMENT

On 28 July 2021 a treatment regimen with intravenous sindilizumab 200 mg/day every 3 weeks and local radiotherapy (6 MV-X, IMRT: 36 Gy/18 fx) for multiple nodules on the left upper arm starting

To cite: Ren G, Chen H, Fang J. *Eur J Hosp Pharm* 2024;**31**:381–383.

Table 1 Results of routine blood tests and CRP levels during hospitalisation

Date	White blood cells ($\times 10^9$/L)	Neutrophils ($\times 10^9$/L)	Haemoglobin (g/L)	Thrombocytes ($\times 10^9$/L)	CRP (mg/L)
23 July	6.21	4.72	122	126	10.34
31 July	2.8	2.02	122	21	114.49
2 August	5.22	4.5	117	39	142.84
6 August	3.08	1.74	109	66	145.76
12 August	2.94	2.35	102	107	87.88
16 August	3.16	2.36	124	63	95.76
18 August	4.07	3.52	129	95	58.11
20 August	6.21	5.8	129	150	54.99
22 August	10.25	9.12	117	260	141.35

CRP, C-reactive protein.

on 29 July 29 2021 was undertaken. Sindilizumab was administered as a single dose on 28 July. Three days after the initial treatment, the patient presented with fever, hypoleukaemia, thrombocytopenia and elevated C-reactive protein (CRP). Moxifloxacin tablets, recombinant human granulocyte stimulating factor injection and interleukin-11 for injection were given, and radiotherapy was stopped. The results of routine blood tests and CRP levels are shown in table 1. Radiotherapy was restarted on 4 August 2021. Methylprednisolone sodium succinate was given via intravenous injection at a dose of 30 mg twice daily for 1 week later owing to persistent high fever and CRP. The patient had fatigue and a poor appetite. Blood biochemical tests revealed an obvious increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) and a decrease in albumin. Compound glycyrrhizin injection and bicyclol tablets were used to improve liver function. On 13 August the patient began to develop oedema of both lower limbs, which gradually extended to the head. Radiotherapy was once again stopped. Liver function tests showed no improvement with elevated bilirubin and decreased albumin levels. A spiral CT plain scan of the upper and lower abdomen on 14 August showed no significant abnormality of the liver. Serologic markers of hepatitis B showed positive HBsAb and negative HBsAg, HBeAg, HBeAb and HBcAb. On 16 August the methylprednisolone dosage was adjusted to 80 mg once daily, and acetyl cysteine injections 8 g once daily and human albumin 10 g once daily were also used. However, the patient's liver function continued to deteriorate (table 2). On 19 August his skin and sclera had obvious yellow staining. The results of hepatitis B virus DNA testing on 14 August were below the detection limit, indicating no obvious activation of hepatitis B virus. After multidisciplinary consultation, methylprednisolone was adjusted to 80 mg every 8 hours, magnesium isoglycyrrhizin injection of 200 mg once daily, adenosine methionine injection of 1 g once daily and diuretic treatment were given.

OUTCOME AND FOLLOW-UP

The patient's liver function did not improve and on 22 August he was discharged at the request of his guardian. The patient died of liver failure at home.

DISCUSSION

IMH is a special type of drug-induced liver injury, the diagnosis of which is exclusive. The patient's liver function deteriorated sharply within 1 week. He had no history of liver disease in the past. Before this treatment, no drugs causing definite liver injury were used and the patient had no history of drinking, no active bleeding and no obvious systemic infection. The lower value of hepatitis B virus DNA than the detection level ruled out the possibility of acute viral hepatitis. The radiotherapy site was the upper arm, which would not cause radiation liver injury. Excluding these pathogenic factors, drugs are considered the main cause of acute liver injury. According to the patient's medication records, the PD-1 inhibitor and local radiotherapy were added in the time window of liver function deterioration. Therefore, we consider that there was a significant relationship between abnormal liver function and the combined treatment. The patient's raised blood cytokine analysis (T cells (CD3+, CD8+) 30.0%) suggested an increased CD8+ T cell count. Increased T cell infiltration was identified as a common feature of immune-related adverse events related to ICIs.[6] There are reports in the literature that focal necrosis of the liver parenchyma with CD8+ T cell infiltration is also commonly observed in patients treated with ICIs.[7] Regrettably, no pathological examination of the liver was performed due to the patient's refusal.

Table 2 Results of liver function analysis during hospitalisation

Date	Albumin (g/L)	T-BIL (μmol/L)	D-BIL (μmol/L)	IBIL (μmol/L)	ALT (U/L)	AST (U/L)	LDH (U/L)
23 July	37.1	10.1	2.2	7.9	16.9	16.1	236.9
31 July	32.05	15.3	3.8	11.5	29.6	32	471.5
12 August	25.05	26.4	15.8	10.6	137.3	192.5	669.1
16 August	22.84	176.4	117.3	59.1	213.5	831.7	3397.5
18 August	22.83	268.5	210.4	58.1	312.1	1414.6	5975.7
20 August	23.04	329.7	267.1	62.6	319.7	1989.7	9166.3
22 August	23.05	395.8	201.9	193.9	205.2	1948.7	12179.3

ALT, alanine aminotransferase; AST, aspartate aminotransferase; D-BIL, direct bilirubin; IBIL, indirect bilirubin; LDH, lactate dehydrogenase; T-BIL, total bilirubin.

The abscopal effect introduced by Mole in the 1950s referred to the withdrawal of metastases outside the irradiation area during the course of primary radiotherapy. This phenomenon was not found in patients who received radiotherapy alone but in those with combined therapy with immunomodulators.[8] The immunomodulatory effect of radiotherapy on both the tumour microenvironment and surrounding normal tissues has been increasingly recognised.[9] The effect of radiotherapy on the immune system within the irradiated tumour can be either immunostimulatory or immunosuppressive, which is likely to be influenced by the immune contexture, the dose and the fractionation of the radiotherapy.[10] The abscopal effect caused by radiotherapy combined with immunotherapy is mainly based on the synergistic effect induced by the enhanced immune response. After local radiotherapy, DNA/RNA fragments are released from necrotic tumour cells to activate macrophages, promoting the activation of monocytes and natural killer cells to cause a natural immune response. Meanwhile, antigens are released after tumour necrosis to form neoantigen peptides, stimulating the proliferation and activation of dendritic cells and presenting antigens to induce T cell activation. As the blood circulates, activated T cells and cytokines are released to the distant tumour site to produce the immune response.[11 12]

The patient received one dose of sindilizumab (200 mg on the first day of treatment) and 10 doses of radiation, after which the focus in the local radiotherapy area subsided, while the focus on the right chest wall of the non-radiation area basically subsided, suggesting the existence of an abscopal effect of the radiotherapy. According to clinical data, immunotherapy treatment usually has effects after at least 2 weeks. PD-1 inhibitors may induce IMH, but there is a small possibility of hepatocyte necrosis when using PD-1 inhibitors alone. Thus, we inferred that T cell infiltration in the middle part and the perihilar area of the liver increased after sindilizumab treatment and, then, under the influence of the abscopal effect of the radiotherapy, the release of multiple proinflammatory factors further activated T lymphocytes. With blood circulation, activated T cells and cytokines enter the body's lymphoid tissue and the altered liver tissue to stimulate the immune response. Radiotherapy combined with immunotherapy increased the proportion of T cell infiltration, reduced immune tolerance, and finally led to liver cell damage. The severe abnormal liver function of the patient was considered to be the result of the abscopal effect of radiotherapy and sindilizumab.

In this case, LDH increased significantly after 72 hours of immunotherapy and the CRP/albumin ratio increased significantly after 1 week of immunotherapy. Research results have shown that serum LDH levels and the CRP/albumin ratio may reflect increased inflammation and are associated with a poor prognosis. We therefore consider that the increase in LDH and the CRP/albumin ratio can indicate the beginning of liver injury, which is more sensitive than ALT and AST in judging liver injury. In addition, the neutrophil:lymphocytic ratio (NLR) is a powerful prognostic marker which is regarded as a predictor of disease severity and mortality. Patients with a higher NLR were found to have a poor prognosis after immunotherapy.[13] In our patient, the NLR increased to >3 during hospitalisation. We consider that a higher NLR has a predictive role in the treatment of the patient. However, more clinical research and literature evidence in this regard.

Learning points

⇒ Patients are at risk of serious immune-related adverse reactions when receiving a combination of immunotherapy and radiation therapy.
⇒ When such adverse reactions occur, close attention should be paid and timely identification should be made.
⇒ Raised lactate dehydrogenase and total bilirubin levels may help to evaluate the severity of drug-induced liver injury.

Contributors GR: the guarantor, conceptualisation, data curation, writing – original draft. HC: investigation, visualisation. JF: supervision, resources, writing – review and editing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained from next of kin.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

ORCID iD
Guofei Ren http://orcid.org/0000-0001-5295-0110

REFERENCES

1 Calabrese L, Mariette X. The evolving role of the rheumatologist in the management of immune-related adverse events (irAEs) caused by cancer Immunotherapy. *Ann Rheum Dis* 2018;77:162–4.
2 Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012;30:2691–7.
3 Keir ME, Liang SC, Guleria I, *et al*. Tissue expression of PD-L1 mediates peripheral T cell tolerance. *J Exp Med* 2006;203:883–95.
4 Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. *N Engl J Med* 2016;375:1767–78.
5 Makarova-Rusher OV, Medina-Echeverz J, Duffy AG, *et al*. The yin and yang of evasion and immune activation in HCC. *J Hepatol* 2015;62:1420–9.
6 Johnson DB, Balko JM, Compton ML, *et al*. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016;375:1749–55.
7 Koelzer VH, Rothschild SI, Zihler D, *et al*. Systemic inflammation in a melanoma patient treated with immune checkpoint inhibitors - an autopsy study. *J Immunother Cancer* 2016;4:13.
8 Weichselbaum RR, Liang H, Deng L, *et al*. Radiotherapy and immunotherapy: a beneficial liaison? *Nat Rev Clin Oncol* 2017;14:365–79.
9 Galluzzi L, Buqué A, Kepp O, *et al*. Immunogenic cell death in cancer and infectious disease. *Nat Rev Immunol* 2017;17:97–111.
10 Romano E, Honeychurch J, Illidge TM. Radiotherapy-immunotherapy combination: how will we bridge the gap between pre-clinical promise and effective clinical delivery. *Cancers (Basel)* 2021;13:457.
11 Demaria S, Golden EB, Formenti SC. Role of local radiation therapy in cancer immunotherapy. *JAMA Oncol* 2015;1:1325–32.
12 Cytlak UM, Dyer DP, Honeychurch J, *et al*. Immunomodulation by radiotherapy in tumour control and normal tissue toxicity. *Nat Rev Immunol* 2022;22:124–38.
13 Kim N, Yu JI, Lim DH, *et al*. Prognostic impact of sarcopenia and radiotherapy in patients with advanced gastric cancer treated with anti-PD-1 antibody. *Front Immunol* 2021;12:701668.