

World Journal of *Gastroenterology*

World J Gastroenterol 2020 January 21; 26(3): 266-374



**MINIREVIEWS**

- 266 Abdominal compartment syndrome: Often overlooked conditions in medical intensive care units
Rajasurya V, Surani S
- 279 Fibroblast growth factor signaling in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: Paving the way to hepatocellular carcinoma
Ocker M

ORIGINAL ARTICLE**Basic Study**

- 291 *Bacteroides fragilis* enterotoxin upregulates heme oxygenase-1 in dendritic cells *via* reactive oxygen species-, mitogen-activated protein kinase-, and Nrf2-dependent pathway
Ko SH, Jeon JI, Woo HA, Kim JM

Case Control Study

- 307 Nucleotide excision repair pathway gene polymorphisms are associated with risk and prognosis of colorectal cancer
Li YK, Xu Q, Sun LP, Gong YH, Jing JJ, Xing CZ, Yuan Y

Retrospective Study

- 324 Idarubicin *vs* doxorubicin in transarterial chemoembolization of intermediate stage hepatocellular carcinoma
Roth GS, Teyssier Y, Abousalihac M, Seigneurin A, Ghelfi J, Sengel C, Decaens T

Observational Study

- 335 Metabolite profile comparisons between ascending and descending colon tissue in healthy adults
Baxter BA, Parker KD, Nosler MJ, Rao S, Craig R, Seiler C, Ryan EP

SYSTEMATIC REVIEWS

- 353 Programmed cell death-1 inhibitor-related sclerosing cholangitis: A systematic review
Onoyama T, Takeda Y, Yamashita T, Hamamoto W, Sakamoto Y, Koda H, Kawata S, Matsumoto K, Isomoto H

CASE REPORT

- 366 Unexpected metastasis of intraductal papillary neoplasm of the bile duct without an invasive component to the brain and lungs: A case report
Nam NH, Taura K, Kanai M, Fukuyama K, Uza N, Maeda H, Yutaka Y, Chen-Yoshikawa TF, Muto M, Uemoto S

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Rakesh Kumar Tandon, FRCP (Hon), MD, PhD, Doctor, Professor, Department of Gastroenterology, Pushpawati Singhania Hospital & Research Institute, Sheikh Sarai-Phase II, New Delhi 110017, Delhi, India

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2019 edition of Journal Citation Report® cites the 2018 impact factor for WJG as 3.411 (5-year impact factor: 3.579), ranking WJG as 35th among 84 journals in gastroenterology and hepatology (quartile in category Q2). CiteScore (2018): 3.43.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: Yu-Jie Ma

Proofing Production Department Director: Yun-Xiaojuan Wu

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Subrata Ghosh, Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE

Ze-Mao Gong, Director

PUBLICATION DATE

January 21, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Programmed cell death-1 inhibitor-related sclerosing cholangitis: A systematic review

Takumi Onoyama, Yohei Takeda, Taro Yamashita, Wataru Hamamoto, Yuri Sakamoto, Hiroki Koda, Soichiro Kawata, Kazuya Matsumoto, Hajime Isomoto

ORCID number: Takumi Onoyama (0000-0003-0310-0720); Yohei Takeda (0000-0003-1096-5909); Taro Yamashita (0000-0003-2726-3356); Wataru Hamamoto (0000-0003-2220-9916); Yuri Sakamoto (0000-0001-9682-6410); Hiroki Koda (0000-0003-4000-6899); Soichiro Kawata (0000-0002-2194-0582); Kazuya Matsumoto (0000-0002-5680-4791); Hajime Isomoto (0000-0001-8998-7865).

Author contributions: Onoyama T and Takeda Y contributed equally to the work; Matsumoto K and Isomoto H conceptualized and designed the review together with Onoyama T; Onoyama T, Yamashita T, Koda H, Hamamoto W, Sakamoto Y and Kawata S carried out the analysis; Onoyama T drafted the initial manuscript; all authors reviewed and approved the final manuscript as submitted.

Conflict-of-interest statement: All the authors declare that they have no competing interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to

Takumi Onoyama, Yohei Takeda, Taro Yamashita, Wataru Hamamoto, Yuri Sakamoto, Hiroki Koda, Soichiro Kawata, Hajime Isomoto, Division of Medicine and Clinical Science, Department of Multidisciplinary Internal Medicine, Faculty of Medicine, Tottori University, Tottori prefecture 683-8504, Japan

Kazuya Matsumoto, Internal Medicine, Irisawa Medical Clinic, Shimane prefecture 690-0025, Japan

Corresponding author: Takumi Onoyama, MD, PhD, Doctor, Division of Medicine and Clinical Science, Department of Multidisciplinary Internal Medicine, Faculty of Medicine, Tottori University, 36-1 Nishi-cho, Yonago, Tottori prefecture 683-8504, Japan. golf4to@yahoo.co.jp

Abstract

BACKGROUND

Programmed cell death-1 (PD-1) inhibitor has been indicated for many types of malignancies. However, these inhibitors also cause immune-related adverse events. Hepatobiliary disorder is a phenotype of immune-related adverse event affecting 0%–4.5% of patients treated with PD-1 inhibitors. Recent studies have reported PD-1 inhibitor-related sclerosing cholangitis (SC); however, the associated clinical and pathological features are unclear.

AIM

To evaluate the clinical and pathological features of PD-1 inhibitor-related SC through a systematic review of the literature.

METHODS

The review, conducted using electronic databases in PubMed, was restricted to the period from January 2014 to September 2019 and focused on case reports/series on PD-1 inhibitor-related SC published in English. We scanned the references of the selected literature to identify any further relevant studies. Six cases previously studied by us, including three that have not yet been published, were included in this review.

RESULTS

Thirty-one PD-1 inhibitor-related SC cases were evaluated. Median age of patients was 67 years (range, 43–89), with a male to female ratio of 21:10. The main disease requiring PD-1 inhibitor treatment was non-small cell lung cancer. Agents that caused PD-1 inhibitor-related SC were nivolumab (19 cases),

distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: November 23, 2019

Peer-review started: November 23, 2019

First decision: December 23, 2019

Revised: January 7, 2020

Accepted: January 11, 2020

Article in press: January 11, 2020

Published online: January 21, 2020

P-Reviewer: Uhlmann D, Yang L

S-Editor: Zhang L

L-Editor: A

E-Editor: Xing YX



pembrolizumab (10 cases), avelumab (1 case), and durvalumab (1 case). The median number of cycles until PD-1 inhibitor-related SC onset was 5.5 (range, 1–27). Abdominal pain or discomfort (35.5%, 11/31) was the most frequent symptom. Blood serum tests identified liver dysfunction with a notable increase in biliary tract enzymes relative to hepatic enzymes, and a normal level of serum immunoglobulin G4. Biliary dilation without obstruction (76.9%, 20/26), diffuse hypertrophy of the extrahepatic biliary tract (90.5%, 19/21), and multiple strictures of the intrahepatic biliary tract (30.4%, 7/23) were noted. In 11/23 (47.8%) cases, pathological examination indicated that CD8+ T cells were the dominant inflammatory cells in the bile duct or peribiliary tract. Although corticosteroids were mainly used for PD inhibitor-related SC treatment, the response rate was 11.5% (3/26).

CONCLUSION

Some clinical and pathological features of PD-1 inhibitor-related SC were revealed. To establish diagnostic criteria for PD-1 inhibitor-related SC, more cases need to be evaluated.

Key words: Nivolumab; Pembrolizumab; Avelumab; Durvalumab; Atezolizumab; Programmed cell death-1 inhibitor; Immune-related adverse events; Cholangitis

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This study systematically reviewed the literature on the programmed cell death-1 inhibitor-related sclerosing cholangitis. Biliary dilation without obstruction, diffuse hypertrophy of the extrahepatic biliary tract and/or multiple strictures of intrahepatic biliary tract, liver dysfunction with a notable increase in biliary tract enzymes relative to hepatic enzymes, normal level of the serum immunoglobulin G4, and a moderate to poor response to steroid therapy, and CD8+ T cell infiltration in the biliary tract were clinical and pathological features of programmed cell death-1 inhibitor-related sclerosing cholangitis.

Citation: Onoyama T, Takeda Y, Yamashita T, Hamamoto W, Sakamoto Y, Koda H, Kawata S, Matsumoto K, Isomoto H. Programmed cell death-1 inhibitor-related sclerosing cholangitis: A systematic review. *World J Gastroenterol* 2020; 26(3): 353-365

URL: <https://www.wjgnet.com/1007-9327/full/v26/i3/353.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v26.i3.353>

INTRODUCTION

The programmed cell death-1 (PD-1) receptor is expressed on activated T cells, whereas the programmed cell death-ligand 1 (PD-L1) is overexpressed on specific types of cancer cells. When bound by PD-L1, PD-1 causes the suppression of T cell cytotoxic immune responses. This repression pathway is an essential immune prevention mechanism from host immunity and is upregulated in many malignant tumors and their surrounding microenvironment^[1]. Recently, developments in immunotherapy have demonstrated efficacy for the treatment of various malignancies. PD-1 inhibitors were also indicated for many types of malignancies, such as non-small cell lung cancer, melanoma, Hodgkin lymphoma, renal cell cancer, bladder cancer, gastric cancer, and esophageal cancer^[2-12]. Moreover, pembrolizumab has been indicated for solid carcinoma with mismatch repair deficiency^[13,14]. Therefore, many patients with malignant disease will be treated with a PD-1 inhibitor. Although PD-1 inhibitors are beneficial for the treatment of malignancies, it has been noted that immune-related adverse events (irAEs) result from dysregulation of the host immune system^[15]. Hepatobiliary disorders are irAEs that affect 0%–4.5% of patients treated with PD-1 inhibitors^[16-18]. Recently, PD-1 inhibitor-related sclerosing cholangitis (SC) and its clinical features have been reported^[19,20]. However, the diagnostic criteria for PD-1 inhibitor-related SC have not been clarified. We also have experience of six cases of suspected of PD-1 inhibitor-related SC.

The objective of this work was to perform a systematic review of cases of PD-1 inhibitor-related SC, and to evaluate the clinical and imaging features of PD-1

inhibitor-related SC.

MATERIALS AND METHODS

Literature search strategy

We identified relevant studies in the literature by searching the databases of PubMed. The review was restricted to the period from January 2014 to September 2019 and focused on case reports or case series with PD-1 inhibitor-related SC that were published in English. The search terms consisted of the words ["Programmed cell death 1" (All Fields) and "cholangitis" (All Fields)], ["Programmed cell death ligand 1" (All Fields) AND "cholangitis" (All Fields)], ["Nivolumab" (All Fields) and "cholangitis" (All Fields)], ["Pembrolizumab" (All Fields) and "cholangitis" (All Fields)], ["Cemiplimab" (All Fields) and "cholangitis" (All Fields)], ["Atezolizumab" (All Fields) and "cholangitis" (All Fields)], ["Avelumab" (All Fields) and "cholangitis" (All Fields)], and ["Durvalumab" (All Fields) and "cholangitis" (All Fields)]. We also read the reference lists of the selected studies to manually identify further relevant studies.

Articles were excluded from this review if: (1) The article was a review, basic research, commentary, or clinical study; (2) The study had insufficient information and descriptions; and (3) The full text was unavailable.

We have also investigated six cases of PD-1 inhibitor-related SC, three of which have not yet been published. We have included these three cases in this case review.

RESULTS

The process of the literature selection is presented in [Figure 1](#). The literature search of the databases of PubMed identified 70 studies that met the search terms. We found an additional three relevant articles in the references of those studies. After the removal of duplicate studies, we evaluated 56 studies by screening the titles and abstracts to check that they met the search criteria. Consequently, we excluded 20 basic research studies, 3 review articles, 3 editorial letters, and 10 clinical studies. Moreover, two studies were case reports about same patient with PD-1 inhibitor-related SC; therefore, one of these studies was excluded. Finally, 19 studies, which included 5 case series and 14 case reports, were assessed in this review^[19-37]. One case series reported 10 patients with hepatobiliary disorder caused by PD-1 inhibitors, which included two patients with PD-1 inhibitor-related SC^[37]. With the inclusion of our three cases, a total of 31 cases of PD-1 inhibitor-related SC were evaluated.

The characteristics of patients with PD-1 inhibitor-related SC are shown in [Tables 1-3](#). The median age at the onset of PD-1 inhibitor-related SC was 67 years (range, 43-89). PD-1 inhibitor-related SC appeared to be more prevalent in men, with a male-to-female ratio of 21:10. The patients' primary diseases that were an adaptation disease for the treatment of PD-1 inhibitor were non-small cell lung cancer (20 cases), melanoma (4 cases), gastric cancer (3 cases), bladder cancer (2 cases), small cell lung cancer (1 case), and epithelioid mesothelioma (1 case). The agents that caused PD-1 inhibitor-related SC were nivolumab (19 cases), pembrolizumab (10 cases), avelumab (1 case), and durvalumab (1 case). The median number of cycles until onset of PD-1 inhibitor-related SC was 5.5 (range, 1-27). Abdominal pain or discomfort (35.5%, 11/31) was the most frequent symptom, followed by fever (19.4%, 6/31) and jaundice (12.9%, 4/31). Eight patients did not have any symptoms, but did have liver dysfunction (25.8%, 8/31). The median levels of total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase were 0.75 mg/dL (range, 0.3-15.9), 129.0 U/L (range, 49-961), 125.0 U/L (range, 31-1536), 1543.0 U/L (range, 237-5066), and 452.0 U/L (range, 114-2094), respectively. Of the 13 patients tested for immunoglobulin G4 (IgG4), almost all patients were negative (92.3%, 12/13).

Biliary stenosis occurred in 8 patients (34.8%, 8/23); 7 had stenosis in the intrahepatic biliary tract, which included 4 patients with multiple strictures in the biliary tract. Biliary dilation was observed in 20 patients (76.9%, 20/26). Twenty patients had hypertrophy of the biliary tract (95.2%, 20/21), of which 19 cases were diffuse ([Figure 2](#)).

Peroral cholangioscopy was performed in only 5 cases^[26,33,38]. Multiple scarred lesions and band-like narrowing were found in 4 patients, and 2 patients with PD-1 inhibitor-related SC showed diverticulum-like outpouching^[33,38]. Ulcerative lesions with many black spots (*e.g.*, "burned-out" epithelium) and yellow plaque were found in 1 patient^[26].

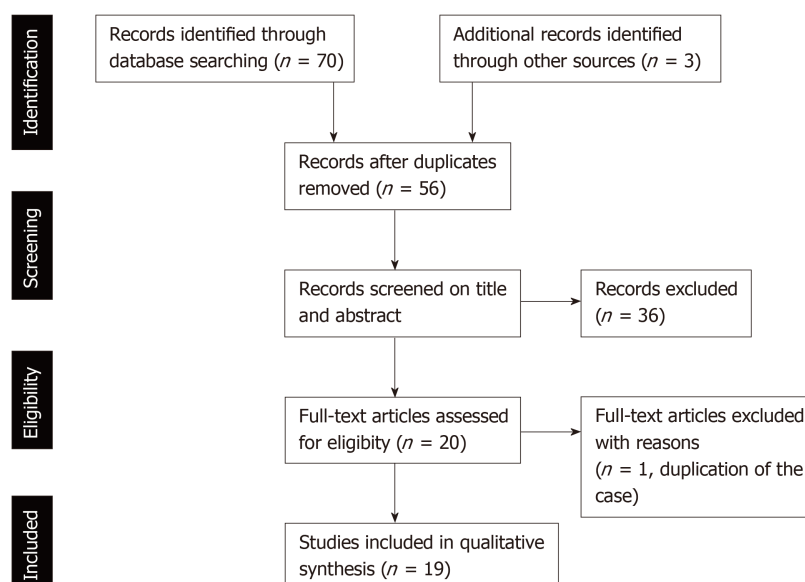


Figure 1 PRISMA 2009 Flow diagram describing the selection of the studies reporting programmed cell death-1 inhibitor-related cholangitis for our review.

In total, 23 patients underwent pathological evaluation; of these, 15 patients underwent liver biopsy. Fourteen patients had inflammatory changes in the bile duct and/or peribiliary tract, and CD8+ T cells were dominant in the inflammatory cells in 8 of these patients (53.3%, 8/15). Lobular hepatitis was found in 2 patients (13.3%, 2/15).

Transpapillary biopsy of the biliary tract with biopsy forceps was performed for 8 patients, and these pathological findings revealed inflammatory cells infiltration in the bile duct. In 2 patients, CD8+ T cells were the dominant inflammatory cells in the bile duct.

Of the 6 patients that underwent biliary drainage, 5 did not respond.

Corticosteroids were the main treatment for PD inhibitor-related SC (83.8%, 26/31). Only 3 patients who the levels of liver and biliary enzymes were improved to normal level with steroid therapy, so that the response rate to corticosteroids was 11.5% (3/26). Eight patients with PD-1 inhibitor-related SC had poor response, no improvement of liver and biliary enzymes, to steroid therapy. In 15 patients who received steroid therapy, the levels of liver and biliary enzymes were improved, although normalization of enzyme activities was not achieved (*i.e.* only a moderate response occurred).

DISCUSSION

PD-1/PD-L1 inhibitors are used widely for the treatment of many types of malignancies. However, irAEs, including cardiac, respiratory, endocrine, gastrointestinal, musculoskeletal, skin, and, importantly, hepatobiliary disorders, were also reported^[15-18]. However, the reasons for the occurrence of irAEs, including cholangitis, are unclear, although it may involve the T cell, antibody, and cytokine responses^[39].

Gelsomino *et al*^[20,21] reported the first case of PD-1 inhibitor-related SC; subsequently, this group and Kawakami *et al*^[19] suggested the clinical features of PD-1 inhibitor-related SC. However, PD-1 inhibitor-related SC is still not well known. Kawakami *et al*^[19] reported SC related to the PD-1 inhibitor nivolumab was characterized by: (1) Localized extrahepatic bile duct dilation without obstruction; (2) Diffuse hypertrophy of the extrahepatic bile duct wall; (3) A dominant increase in the biliary tract enzymes alkaline phosphatase and gamma-glutamyl transpeptidase relative to hepatic enzymes aspartate aminotransferase and alanine aminotransferase; (4) Normal or reduced levels of the serum immunological markers, such as antinuclear antibody, antimitochondrial antibody, smooth muscle antibody, and IgG4; (5) The pathological finding of biliary tract CD8+ T cell infiltration from liver biopsy; and (6) A moderate to poor response to steroid therapy. In our study, some clinical features, such as biliary dilation without obstruction, diffuse hypertrophy of the

Table 1 Demographic characteristics of patients with programmed cell death-1 inhibitor-related sclerosing cholangitis

Patient characteristics	Value
Age, median (range, yr)	67.0 (43–89)
Sex, male/female	21/10
Primary disease	
NSCLC	20
Melanoma	4
GC	3
BC	2
SCLC	1
Epithelioid mesothelioma	1
Drugs	
Nivolumab	19
Pembrolizumab	10
Avelumab	1
Durvalumab	1
Atezolizumab	0
Treatment cycles until onset	5.5 (1–27)
Symptoms	
Abdominal pain or discomfort	11
Fever	6
Jaundice	4
Vomiting	2
Appetite loss	2
Diarrhea or soft stool	2
Skin disorder	2
General fatigue	1
Backache	1
None (liver dysfunction)	8
Liver functional test	
T-Bil, median (range, mg/dL)	0.75 (0.3–15.9)
AST, median (range, U/L)	129.0 (49–961)
ALT, median (range, U/L)	125.0 (31–1536)
ALP, median (range, U/L)	1543.0 (237–5066)
GGT, median (range, U/L)	452.0 (114–2094)
Serological test	
IgG, median (range, U/L)	1230.0 (1050–1789)
IgA, median (range, U/L)	297.5 (199–474.4)
IgM, median (range, U/L)	64.0 (38–94)
IgG4, ≥ 135 U/L / < 135 U/L	1/12
Antinuclear antibody, ≥ 40 / < 40	7/12
Imaging findings	
Biliary stenosis	8
Intrahepatic bile duct	3
Extrahepatic bile duct	1
Multiple	4
Absence	15
Biliary dilation	
Presence/Absence	20 / 6
Hypertrophy of the biliary tract	20
Diffuse	19
Gallbladder	1
Absence	1
Pathological findings	

Liver	15
Inflammation	15
Biliary or peribiliary tract	14
-CD 8+ T cells dominant	8
Lobular hepatitis	2
Bile duct	8
Inflammation	8
-CD 8+ T cells dominant	2
Gallbladder	2
Inflammation	2
-CD 8+ T cells dominant	1
Therapy	
Corticosteroid	26
UDCA	13
MMF	6
Tacrolimus	1
Bezafibrate	1
Response to steroid therapy	
Good	3
Moderate	15
Poor	8

NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer; GC: Gastric cancer; BC: Bladder cancer; MCC: Merkel cell carcinoma; RPC: Renal pelvis cancer; T-Bil: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; IgG4: Immunoglobulin G4; Mpsl: Methylprednisolone; PSL: Prednisolone; UDCA: Ursodeoxycholic acid; MMF: Mycophenolate mofetil.

extrahepatic biliary tract, liver dysfunction with a dominant increase in the biliary tract enzymes relative to hepatic enzymes, normal level of serum IgG4, and a moderate to poor response to steroid therapy, were similar to those reported by Kawakami *et al*^[19]. In contrast, Gelsomino *et al*^[20] suggested that there were different types of PD-1 inhibitor-related SC, such as large duct cholangitis and small ducts cholangitis, and that those types have different clinical presentation and biochemical evolution and were associated with various outcomes. Indeed, in our case review, 15 patients had diffuse extrahepatic biliary hypertrophy without biliary stenosis (extrahepatic type). Three patients had multiple stenoses, especially in the intrahepatic bile duct, without extrahepatic biliary hypertrophy (intrahepatic type). Moreover, four patients had diffuse biliary tract hypertrophy with multiple stenoses of the intrahepatic and extrahepatic bile ducts (diffuse type). The clinical implications of these types of PD-1 inhibitor-SC is uncertain, but may be clarified by more cases in the future.

Zen *et al*^[40] reported that CD8+ T lymphocytes were the predominant infiltrates in the bile duct of patients with PD-1 inhibitor-related SC, similar to hepatic irAEs. Moreover, they reported the clinical features and detailed pathological findings of 10 cases of hepatobiliary disorders caused by PD-1 inhibitors. In that study, the ratio of CD8+ to CD4+ cells was significantly higher than that in autoimmune hepatitis or idiosyncratic drug-induced liver injury^[37]. Although CD8+ T cell infiltration is one of the clinical features of irAEs, in the pathological findings of PD-1 inhibitor-related SC, CD8+ T cells were not necessarily dominant, especially in the bile duct biopsy. Other inflammatory cells, such as eosinophils, neutrophils, plasma cells, and macrophages, were also observed in the biliary tract. Although this finding may be used for auxiliary diagnosis for PD-1 inhibitor-SC, it may not always be observable.

In general, steroid therapy was recommended for the treatment of irAEs^[41,42], however, corticosteroids were not useful for the treatment of PD-1 inhibitor-related SC. Although four patients received high-dose steroid therapy (methylprednisolone, 500–1000 mg/d), a good response was not shown. Therefore, at least in our study, steroid therapy was not recommended for the treatment of PD-1 inhibitor-related SC. However, the response to steroid therapy may be dependent on the type of PD-1 inhibitor-related SC, as described above. Although 15 patients with extrahepatic and diffuse type PD-1 inhibitor-related SC received steroid therapy in our case review, a good response occurred only in one case (6.7%, 1/15). Meanwhile, only two patients

Table 2 Baseline characteristics of cases of programmed cell death-1 inhibitor-related sclerosing cholangitis

Case	Ref.	Age	Sex	Primary disease	Drug	Cycles until onset	Symptoms
1	Gelsomino <i>et al</i> ^[21]	79	M	NSCLC	Nivolumab	4	Itching, jaundice
2	Kawakami <i>et al</i> ^[19]	64	M	NSCLC	Nivolumab	9	Fever, abdominal discomfort
3	Kawakami <i>et al</i> ^[19]	73	F	NSCLC	Nivolumab	6	Fever, vomiting, abdominal discomfort, diarrhea
4	Kawakami <i>et al</i> ^[19]	82	F	NSCLC	Nivolumab	12	Fever, general fatigue
5	Kashima <i>et al</i> ^[22]	63	M	NSCLC	Nivolumab	24	Epigastric pain, soft stool
6	Doherty <i>et al</i> ^[23]	49	F	Melanoma	Pembrolizumab	1	Jaundice
7	Doherty <i>et al</i> ^[23]	59	F	Melanoma	Nivolumab	3	None (liver dysfunction)
8	Doherty <i>et al</i> ^[23]	76	M	epithelioid mesothelioma	Pembrolizumab	1	Jaundice
9	Cho <i>et al</i> ^[24]	69	M	NSCLC	Avelumab	21	Right upper abdominal discomfort
10	Hamoir <i>et al</i> ^[25]	71	M	NSCLC	Nivolumab	NA (11 mo)	None (liver dysfunction)
11	Kuraoka <i>et al</i> ^[26]	69	M	NSCLC	Nivolumab	3	Pruritic rash, liver dysfunction
12	Ogawa <i>et al</i> ^[27]	73	M	Melanoma	Pembrolizumab	NA (3 mo)	None (liver dysfunction)
13	Kono <i>et al</i> ^[28]	69	F	GC	Nivolumab	2	Jaundice
14	Noda-Narita <i>et al</i> ^[29]	57	F	NSCLC	Nivolumab	NA (12 mo)	Abdominal pain
15	Sawada <i>et al</i> ^[30]	76	M	GC	Nivolumab	4	None (liver dysfunction)
16	Taltec <i>et al</i> ^[31]	56	F	NSCLC	Nivolumab	16 (9 mo)	Myalgia, skin thickening
17	Oda <i>et al</i> ^[32]	43	M	GC	Nivolumab	1	Fever, tachycardia, appetite loss, malaise
18	Koya <i>et al</i> ^[33]	66	M	SCLC	Pembrolizumab	5	Epigastric pain
19	Fouchard <i>et al</i> ^[34]	52	M	NSCLC	Nivolumab	8	Abdominal pain
20	Fouchard <i>et al</i> ^[34]	NA	M	NSCLC	Durvalumab (+ tremelimumab)	4	Fever, abdominal pain
21	Fouchard <i>et al</i> ^[34]	61	M	NSCLC	Pembrolizumab	17	None (liver dysfunction)
22	Clugreanu <i>et al</i> ^[35]	43	F	Melanoma	Nivolumab	27	Epigastralgia, anorexia,
23	Anderson <i>et al</i> ^[36]	67	M	NSCLC	Nivolumab	8	Right upper abdominal pain
24	Zen <i>et al</i> ^[37]	68	M	NSCLC	Pembrolizumab	NA (5.5 mo)	Abdominal pain, vomiting
25	Zen <i>et al</i> ^[40]	67	M	NSCLC	Pembrolizumab	NA (1 mo)	Fever, malaise
26	Our case	61	M	BC	Pembrolizumab	5	Fever
27	Our case	89	M	BC	Pembrolizumab	4	None (liver dysfunction)
28	Our case	63	M	NSCLC	Pembrolizumab	7	None (liver dysfunction)
29	Our case	55	M	NSCLC	Nivolumab	11	Abdominal pain
30	Our case	81	F	NSCLC	Nivolumab	25	Backache
31	Our case	82	F	NSCLC	Nivolumab	2	None (liver dysfunction)

NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer; GC: Gastric cancer; BC: Bladder cancer; NA: Not available.

Table 3 Clinical, imaging, and pathological findings of cases of programmed cell death-1 inhibitor-related sclerosing cholangitis

Case	T-Bil/AST/ALT/ALP/GGT/IgG4	Biliary stenosis/dilation	Hypertrophy of biliary tract	Pathological findings	Treatment (Dosage)	Steroid response
1	Grade 4/NA/Grade 3; Grade 3/Grade 4/NA	NA	NA	Liver: CD8+ T cells infiltration in bile duct	mPSL (1 mg/kg), + UDCA (15 mg/kg)	Moderate
2	0.7/142/144; 1769/902/normal	-/+	Diffuse	Liver: CD8+ and CD4+ T cells infiltration in Glisson's capsule	PSL (0.5 mg/kg)	Poor
3	3.8/89/101; 1947/804/normal	-/+	Diffuse	NA	PSL (0.5 mg/kg), Biliary drainage	Moderate
4	0.8/108/70; 2996/813/normal	-/+	Diffuse	Liver: CD8+ and CD4+ T cells infiltration in Glisson's capsule	Biliary drainage	-
5	NA/88/92; 1543/NA/NA	Distal bile duct/+	Diffuse	Bile duct: Interstitial fibrosis, neutrophils infiltration in mucosa	PSL (2 mg/kg) Biliary drainage	Moderate
6	NA/961/1536; 237/2094/NA	NA/-	NA	Liver: Severe steatohepatitis, absence of bile ducts	1 st PSL (1 mg/kg), 2 nd PSL + UDCA (NA) + MMF (2 g)	Poor
7	NA/NA/>300; >1000/NA/NA	NA	NA	Liver: Degenerative bile duct atypia and periductal fibrosis	1 st PSL (1 mg/kg), 2 nd PSL + UDCA (NA)	Poor
8	NA/NA/>500; >700/NA/NA	NA	NA	Liver: Attenuated bile duct, cellular and canalicular cholestasis in parenchyma	mPSL (2 mg/kg) + cholestyramine (NA) + MMF (1 g) + UDCA (NA)	Poor
9	0.6/Grade 1/Grade 1; Grade 2/Grade 2/NA	-/+	Diffuse	NA	mPSL (1 mg/kg)	Moderate
10	Normal/129/135; 558/984/NA	Multiple/-	None	Liver: CD8+ T cell infiltration in the periportal zone and cholangitis	mPSL (0.5 mg/kg), + UDCA (10 mg/kg)	Good
11	NA/NA/NA; NA/NA/NA	-/+	Diffuse	Bile duct: Inflammatory cells and lymphocytes infiltration in epithelium	1 st PSL (60 mg), 2 nd mPSL (500 mg)	Poor
12	NA/58/77; 1111/461/NA	Multiple/+	Diffuse	Bile duct: Destruction of epithelium, fibrosis with CD8+ T cell infiltration in submucosa	Discontinuation of Pembrolizumab	-
13	15.9/454/NA; 5066/NA/20.2	Intrahepatic bile duct/-	Gall bladder	NA	Biliary drainage	-
14	NA/NA/NA; 1065/304/normal	-/+	Diffuse	NA	UDCA (300 mg)	-
15	0.8/69/68; 2427/252/41.0	-/+	NA	Liver: Eosinophil, CD8+, and CD4+ T cell infiltration in the portal tract. Eosinophil infiltration in the epithelial linings of the bile duct	PSL (0.5 mg/kg), + UDCA (NA)	Good
16	Normal/272/516; 615/442/NA	NA	Diffuse	NA	Corticosteroid (NA)	Good
17	3.7/49/31; 598/151/90	-/-	NA	Liver: CD8+ T cells and macrophage infiltration in bile duct	1 st PSL (1 mg/kg), 2 nd m PSL (1 g), 3 rd PSL + MMF (2 g)	Poor

18	1.1/313/296; 2241/868/normal	Intrahepatic bile duct/+	Diffuse	Liver: CD8+ T cell and eosinophil infiltration in the periportal zones, Bile duct: CD8+ T cell infiltration and fibrosis in submucosa	1 st UDCA (900 mg) + bezafibrate (400 mg), 2 nd m PSL (0.5 g) followed by PSL (1 mg/kg), Biliary drainage	Poor
19	Normal/>100/>100; >900/>500/NA	-/+	NA	Gall bladder: Inflammatory cell infiltration	PSL (0.5 mg/kg) + UDCA (NA), Cholecystectomy	Moderate
20	NA/>100/>300; >800/>1700/normal	-/+	NA	Gall bladder: CD8+ T cell infiltration	PSL (120 mg) + UDCA (NA), Cholecystectomy	Moderate
21	Normal/NA/>100; >400/>1400/NA	NA	NA	NA	PSL (1 mg/kg)	Moderate
22	Normal/52/126; 545/1007/NA	Multiple/+	NA	Liver: CD3+ and CD8 T cell infiltration in the bile duct	PSL (1 mg/kg)	Moderate
23	NA/>300/NA; 793/NA/NA	Multiple/+	Diffuse	Liver: Fibrosis and inflammation in the portal tract, lobular inflammation, mild macrovesicular steatosis	mPSL (NA) following PSL (50 mg), MMF (NA), Tacrolimu (NA)s	Poor
24	0.5/67/68; 2107/279/59	NA/-	Diffuse	Liver: Cholangiopathologic change, CD8/CD4 ratio 12:7, Bile duct: Lymphocyte, eosinophil and plasma cell infiltration	PSL (50 mg)	Moderate
25	1.2/198/233; 1540/332/78	NA/-	Diffuse	Liver: Lobular hepatitis with cholangiopathic change, CD8/CD4 ratio 17:2	PSL (40 mg)	Moderate
26	0.3/91/65; 1683/159/80.4	-/+	Diffuse	Bile duct: Inflammatory cell infiltration	PSL (1 mg/kg) + UDCA (600 mg)	Moderate
27	0.4/245/124; 1245/114/352	-/+	Diffuse	Bile duct: Neutrophil and lymphocyte infiltration	UDCA (600 mg)	-
28	0.6/184/254; 1783/452/128	-/+	Diffuse	Bile duct: Inflammatory cell infiltration	PSL (1 mg/kg) + UDCA (600 mg)	Moderate
29	0.3/64/245; 1328/448/67.3	Intrahepatic bile duct/+	Diffuse	NA	mPSL (2 mg/kg) + MMF (2 g)	Moderate
30	1.3/284/248; 3029/1070/NA	-/+	Diffuse	NA	mPSL (2 mg/kg) + MMF (2 g), Biliary drainage	Moderate
31	0.7/294/85; 4635/829/NA	-/+	Diffuse	Liver: Lymphocyte infiltration in Glisson's capsule, hydropic degeneration of hepatocytes	mPSL (1.6 mg/kg)	Moderate

T-Bil: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; IgG4: Immunoglobulin G4; mPSL: Methylprednisolone; PSL: Prednisolone; UDCA: Ursodeoxycholic acid; MMF: Mycophenolate mofetil; AZA: Azathioprine; NA: Not available.

with intrahepatic type PD-1 inhibitor-related SC received steroid therapy: One patient's liver function was improved and the other had a moderate response, with a response ratio of 1:1. This finding is still uncertain in a few cases.

Ursodeoxycholic acid (UDCA) was used for treatment of PD-1 inhibitor-related SC in 13 patients. Two patients received only UDCA, with discontinuation of nivolumab, and displayed a moderate response. In contrast, no response was found in the single

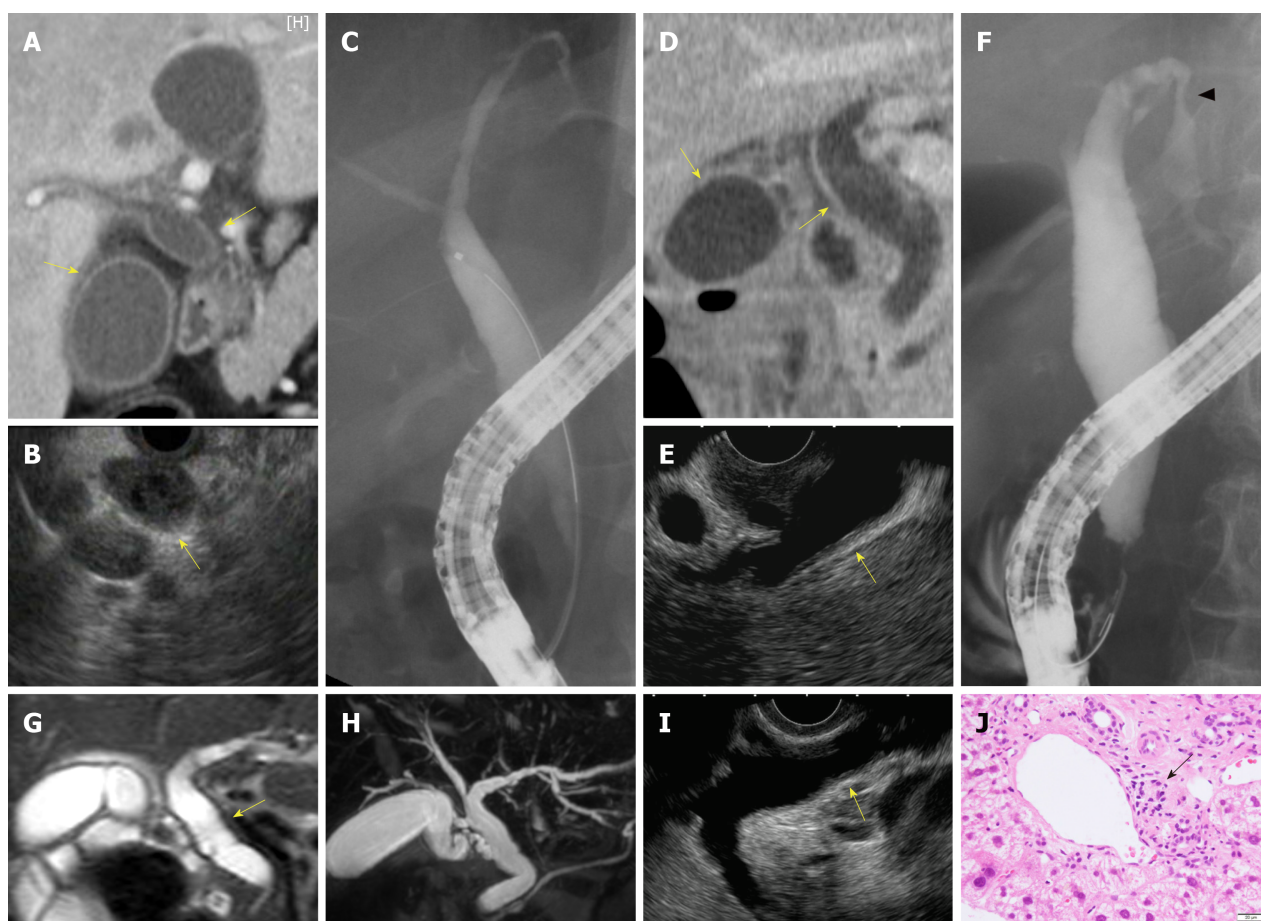


Figure 2 Our cases with sclerosing cholangitis caused by nivolumab (Case 29, A–C; Case 30, D–F; Case 31, G–J). A, D: Computed tomography; G, H: Magnetic resonance imaging; B, E, I: Endoscopic ultrasonography. Revealed diffuse hypertrophy of biliary tract (yellow allows) in all cases. C, F: Endoscopic retrograde cholangiopancreatography revealed biliary stenosis of the intrahepatic bile duct (arrow-head) in Case 30. J: In Case 31, liver biopsy showed lymphocyte infiltration in Glisson's capsule (black arrow).

patient who received UDCA with bezafibrate. Seven patients received combination therapy of steroids and UDCA. The response rate to that therapy was 28.6% (2/7). Three patients received steroid therapy first; when no improvement was observed, UDCA was added and a moderate response was observed in these patients. Although the efficacy was insufficient, UDCA was considered a treatment for PD-1 inhibitor-related SC owing to the low rate of adverse events^[43].

Other anti-inflammatory agents, including immunomodulators or infliximab were sometimes considered to using for treatment of irAEs^[44]. Tacrolimus, an immunomodulator, was also used for one case of PD-1 inhibitor-related SC; however, the response was insufficient. Infliximab was used for some irAEs, such as colitis and pneumonitis. In our case review, infliximab was not used for the treatment of PD-1 inhibitor-related SC. More cases may be needed to evaluate the usefulness of these drugs for PD-1 inhibitor-related SC.

This study had some limitations. First, there are no current diagnostic criteria for PD-1 inhibitor-related SC. Second, some clinical cases, for which blood test data, image findings, and pathological evaluation were not presented, were included in this study. Therefore, our study may include different diseases that cause sclerosing cholangitis.

In conclusion, some clinical features of PD-1 inhibitor-related SC, such as biliary dilation without obstruction, diffuse hypertrophy of the extrahepatic biliary tract and/or multiple strictures of intrahepatic biliary tract, liver dysfunction with a dominant increase in biliary tract enzymes relative to hepatic enzymes, normal level of serum IgG4, and a moderate-to-poor response to steroid therapy, were revealed, although there were many unsolved questions in our study. To establish the diagnostic criteria for PD-1 inhibitor-related SC, more cases, for which clinical data including hepatobiliary enzymes, immunological marker, image findings, and pathological evaluation were presented clearly, need to be evaluated. Although CD8+ T cell infiltration is one of the pathological features of PD-1 inhibitor-related SC, it is not enough to exclude different diseases that cause sclerosing cholangitis. We will

have to find more specific features of PD-1 inhibitor-related SC.

ARTICLE HIGHLIGHTS

Research background

Programmed cell death-1 (PD-1) inhibitor has been indicated for many types of malignancies. On the other hands, these inhibitors cause immune-related adverse events (irAEs). Hepatobiliary disorder is a phenotype of irAEs that affect 0%–4.5% of patients treated with PD-1 inhibitors.

Research motivation

Recently, PD-1 inhibitor-related sclerosing cholangitis (SC), one of the irAEs, have been reported. However, the clinical and pathological features of PD-1 inhibitor-related SC are uncertain.

Research objectives

The objective of this study to evaluate the clinical and pathological features of PD-1 inhibitor-related SC through a systematic review of the literature.

Research methods

We conducted an electronic search through databases of PubMed. The review was restricted to the period from January 2014 to September 2019 and focused on case reports/series on PD-1 inhibitor-related SC published in English. The reference lists of the identified papers were also scanned to find out further relevant studies. Six cases previously studied by us, including three that have not yet been published, were included in this review.

Research results

Thirty-one PD-1 inhibitor-related SC cases were evaluated. The median number of cycles until PD-1 inhibitor-related SC onset was 5.5 (range, 1–27). Abdominal pain or discomfort (35.5%, 11/31) was the most frequent symptom. Liver dysfunction with a notable increase in biliary tract enzymes relative to hepatic enzymes, and a normal level of serum IgG4 were shown in blood serum test. Biliary dilation without obstruction (76.9%, 20/26), diffuse hypertrophy of the extrahepatic biliary tract (90.5%, 19/21), and multiple strictures of the intrahepatic biliary tract (30.4%, 7/23) were noted. CD8+ T cells were the dominant inflammatory cells in the bile duct or peribiliary tract in 11/23 (47.8%) cases. The response rate of corticosteroids for PD inhibitor-related SC was 11.5% (3/26).

Research conclusions

Some clinical features of PD-1 inhibitor-related SC, such as biliary dilation without obstruction, diffuse hypertrophy of the extrahepatic biliary tract and/or multiple strictures of intrahepatic biliary tract, liver dysfunction with a dominant increase in biliary tract enzymes relative to hepatic enzymes, normal level of serum IgG4, and a moderate-to-poor response to steroid therapy, were revealed.

Research perspectives

To establish the diagnostic criteria for PD-1 inhibitor-related SC, more cases, for which clinical data including hepatobiliary enzymes, immunological marker, image findings, and pathological evaluation were presented clearly, need to be evaluated. We will have to find more specific features of PD-1 inhibitor-related SC.

ACKNOWLEDGEMENTS

We wish to thank to our colleagues in the Departments of Gastroenterology and Hepatology, and Pathology at Tottori University Faculty of Medicine (Tottori, Japan).

REFERENCES

- 1 Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev* 2010; **236**: 219–242 [PMID: 20636820 DOI: 10.1111/j.1600-065X.2010.00923.x]
- 2 Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, Segal NH, Ariyan CE, Gordon RA, Reed K, Burke MM, Caldwell A, Kronenberg SA, Agunwamba BU, Zhang X, Lowy I, Inzunza HD, Feely W, Horak CE, Hong Q, Korman AJ, Wigginton JM, Gupta A, Sznol M. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 2013; **369**: 122–133 [PMID: 23724867 DOI: 10.1056/NEJMoa1302369]
- 3 Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, Linette GP, Meyer N, Giguere JK, Agarwala SS, Shaheen M, Ernstoff MS, Minor D, Salama AK, Taylor M, Ott PA, Rollin LM, Horak C, Gagnier P, Wolchok JD, Hodi FS. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med* 2015; **372**: 2006–2017 [PMID: 25891304 DOI: 10.1056/NEJMoa1414428]
- 4 Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocho E, Savage KJ, Hernberg MM, Lebbé C, Charles J, Mihalcioiu C, Chiarion-Sileni V, Mauch C, Cognetti F, Arance A, Schmidt H, Schadendorf D, Gogas H, Lundgren-Eriksson L, Horak C, Sharkey B, Waxman IM, Atkinson V, Ascierto PA. Nivolumab in previously untreated melanoma without

- BRAF mutation. *N Engl J Med* 2015; **372**: 320-330 [PMID: 25399552 DOI: 10.1056/NEJMoa1412082]
- 5 **Brahmer J**, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* 2015; **373**: 123-135 [PMID: 26028407 DOI: 10.1056/NEJMoa1504627]
- 6 **Borghaei H**, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhäufel M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crinò L, Blumenschein GR, Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med* 2015; **373**: 1627-1639 [PMID: 26412456 DOI: 10.1056/NEJMoa1507643]
- 7 **Ansell SM**, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, Schuster SJ, Millenson MM, Cattray D, Freeman GJ, Rodig SJ, Chapuy B, Ligon AH, Zhu L, Grosso JF, Kim SY, Timmerman JM, Shipp MA, Armand P. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med* 2015; **372**: 311-319 [PMID: 25482239 DOI: 10.1056/NEJMoa1411087]
- 8 **Motzer RJ**, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gurney H, Donskov F, Bono P, Wagstaff J, Gauder TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM, Sharma P; CheckMate 025 Investigators. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2015; **373**: 1803-1813 [PMID: 26406148 DOI: 10.1056/NEJMoa1510665]
- 9 **Powles T**, Eder JP, Fine GD, Braith FS, Loriot Y, Cruz C, Bellmunt J, Burris HA, Petrylak DP, Teng SL, Shen X, Boyd Z, Hegde PS, Chen DS, Vogelzang NJ. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature* 2014; **515**: 558-562 [PMID: 25428503 DOI: 10.1038/nature13904]
- 10 **Kang YK**, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, Chung HC, Chen JS, Muro K, Kang WK, Yeh KH, Yoshikawa T, Oh SC, Bai LY, Tamura T, Lee KW, Hamamoto Y, Kim JG, Chin K, Oh DY, Minashi K, Cho JY, Tsuda M, Chen LT. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **390**: 2461-2471 [PMID: 28993052 DOI: 10.1016/S0140-6736(17)31827-5]
- 11 **Kato K**, Cho BC, Takahashi M, Okada M, Lin CY, Chin K, Kadowaki S, Ahn MJ, Hamamoto Y, Doki Y, Yen CC, Kubota Y, Kim SB, Hsu CH, Holtved E, Xynos I, Kodani M, Kitagawa Y. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019; **20**: 1506-1517 [PMID: 31582355 DOI: 10.1016/S1470-2045(19)30626-6]
- 12 **Robert C**, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A; KEYNOTE-006 investigators. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 2015; **372**: 2521-2532 [PMID: 25891173 DOI: 10.1056/NEJMoa1503093]
- 13 **Le DT**, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409-413 [PMID: 28596308 DOI: 10.1126/science.aan6733]
- 14 **Le DT**, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015; **372**: 2509-2520 [PMID: 26028255 DOI: 10.1056/NEJMoa1500596]
- 15 **Friedman CF**, Proverbs-Singh TA, Postow MA. Treatment of the Immune-Related Adverse Effects of Immune Checkpoint Inhibitors: A Review. *JAMA Oncol* 2016; **2**: 1346-1353 [PMID: 27367787 DOI: 10.1001/jamaoncol.2016.1051]
- 16 **Villadolid J**, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. *Transl Lung Cancer Res* 2015; **4**: 560-575 [PMID: 26629425 DOI: 10.3978/j.issn.2218-6751.2015.06.06]
- 17 **Spain L**, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev* 2016; **44**: 51-60 [PMID: 26874776 DOI: 10.1016/j.ctrv.2016.02.001]
- 18 **Raschi E**, Mazzearella A, Antonazzo IC, Bendinelli N, Forcesi E, Tuccori M, Moretti U, Poluzzi E, De Ponti F. Toxicities with Immune Checkpoint Inhibitors: Emerging Priorities from Disproportionality Analysis of the FDA Adverse Event Reporting System. *Target Oncol* 2019; **14**: 205-221 [PMID: 30927173 DOI: 10.1007/s11523-019-00632-w]
- 19 **Kawakami H**, Tanizaki J, Tanaka K, Haratani K, Hayashi H, Takeda M, Kamata K, Takenaka M, Kimura M, Chikugo T, Sato T, Kudo M, Ito A, Nakagawa K. Imaging and clinicopathological features of nivolumab-related cholangitis in patients with non-small cell lung cancer. *Invest New Drugs* 2017; **35**: 529-536 [PMID: 28317087 DOI: 10.1007/s10637-017-0453-0]
- 20 **Gelsomino F**, Vitale G, Ardizzoni A. A case of nivolumab-related cholangitis and literature review: how to look for the right tools for a correct diagnosis of this rare immune-related adverse event. *Invest New Drugs* 2018; **36**: 144-146 [PMID: 28631096 DOI: 10.1007/s10637-017-0484-6]
- 21 **Gelsomino F**, Vitale G, D'Errico A, Bertuzzi C, Andreone P, Ardizzoni A. Nivolumab-induced cholangitic liver disease: a novel form of serious liver injury. *Ann Oncol* 2017; **28**: 671-672 [PMID: 27993797 DOI: 10.1093/annonc/mdw649]
- 22 **Kashima J**, Okuma Y, Shimizuguchi R, Chiba K. Bile duct obstruction in a patient treated with nivolumab as second-line chemotherapy for advanced non-small-cell lung cancer: a case report. *Cancer Immunol Immunother* 2018; **67**: 61-65 [PMID: 28913619 DOI: 10.1007/s00262-017-2062-3]
- 23 **Doherty GJ**, Duckworth AM, Davies SE, Mells GF, Brais R, Harden SV, Parkinson CA, Corrie PG. Severe steroid-resistant anti-PD1 T-cell checkpoint inhibitor-induced hepatotoxicity driven by biliary

- injury. *ESMO Open* 2017; **2**: e000268 [PMID: 29081991 DOI: 10.1136/esmoopen-2017-000268]
- 24 **Cho JH**, Sun JM, Lee SH, Ahn JS, Park K, Ahn MJ. Late-Onset Cholecystitis with Cholangitis after Avelumab Treatment in Non-Small Cell Lung Cancer. *J Thorac Oncol* 2018; **13**: e34-e36 [PMID: 29472055 DOI: 10.1016/j.jtho.2017.10.007]
 - 25 **Hamoir C**, de Vos M, Clinckart F, Nicaise G, Komuta M, Lanthier N. Hepatobiliary and Pancreatic: Nivolumab-related cholangiopathy. *J Gastroenterol Hepatol* 2018; **33**: 1695 [PMID: 29707809 DOI: 10.1111/jgh.14136]
 - 26 **Kuraoka N**, Hara K, Terai S, Yatabe Y, Horio Y. Peroral cholangioscopy of nivolumab-related (induced) ulcerative cholangitis in a patient with non-small cell lung cancer. *Endoscopy* 2018; **50**: E259-E261 [PMID: 29969801 DOI: 10.1055/a-0640-2392]
 - 27 **Ogawa K**, Kamimura K, Terai S. Antiprogrammed Cell Death-1 Immunotherapy-Related Secondary Sclerosing Cholangitis. *Hepatology* 2019; **69**: 914-916 [PMID: 30033637 DOI: 10.1002/hep.30189]
 - 28 **Kono M**, Sakurai T, Okamoto K, Masaki S, Nagai T, Komeda Y, Kamata K, Minaga K, Yamao K, Takenaka M, Watanabe T, Nishida N, Kudo M. Efficacy and Safety of Chemotherapy Following Anti-PD-1 Antibody Therapy for Gastric Cancer: A Case of Sclerosing Cholangitis. *Intern Med* 2019; **58**: 1263-1266 [PMID: 30626829 DOI: 10.2169/internalmedicine.1981-18]
 - 29 **Noda-Narita S**, Mizuno S, Noguchi S, Watanabe K, Nakai Y, Koike K, Kage H, Nagase T. Development of mild drug-induced sclerosing cholangitis after discontinuation of nivolumab. *Eur J Cancer* 2019; **107**: 93-96 [PMID: 30554074 DOI: 10.1016/j.ejca.2018.11.021]
 - 30 **Sawada K**, Shonaka T, Nishikawa Y, Hasegawa K, Hayashi H, Hasebe T, Nakajima S, Ikuta K, Fujiya M, Furukawa H, Okumura T. Successful Treatment of Nivolumab-related Cholangitis with Prednisolone: A Case Report and Review of the Literature. *Intern Med* 2019; **58**: 1747-1752 [PMID: 30799364 DOI: 10.2169/internalmedicine.2330-18]
 - 31 **Le Tallec E**, Ricordel C, Triquet L, Deniel A, Marcorelles P, Lena H, Jegou P, Belhomme N. An Original Case of an Association of Eosinophilic Fasciitis with Cholangitis Induced by Nivolumab. *J Thorac Oncol* 2019; **14**: e13-e15 [PMID: 30579548 DOI: 10.1016/j.jtho.2018.09.016]
 - 32 **Oda H**, Ishihara M, Miyahara Y, Nakamura J, Kozuka Y, Iwasa M, Tsunoda A, Yamashita Y, Saito K, Mizuno T, Shiku H, Katayama N. First Case of Cytokine Release Syndrome after Nivolumab for Gastric Cancer. *Case Rep Oncol* 2019; **12**: 147-156 [PMID: 31043953 DOI: 10.1159/000496933]
 - 33 **Koya Y**, Shibata M, Shinohara N, Nebuya S, Oe S, Honma Y, Senju M, Sato N, Harada M. Secondary sclerosing cholangitis with hemobilia induced by pembrolizumab: Case report and review of published work. *Hepatol Res* 2019; **49**: 950-956 [PMID: 30861263 DOI: 10.1111/hepr.13329]
 - 34 **Fouchard M**, Jantzen H, Quere G, Descourt R, Robinet G, Poureau PG. Three cases of immune cholangitis related to anti-programmed cell death and programmed cell death ligand agents for the treatment of non-small cell lung cancer. *Eur J Cancer* 2019; **115**: 107-110 [PMID: 31132740 DOI: 10.1016/j.ejca.2019.04.022]
 - 35 **Călugăreanu A**, Romptaux P, Bohelay G, Goldfarb L, Barrau V, Cucherousset N, Heidelberger V, Nault JC, Ziol M, Caux F, Maubec E. Late onset of nivolumab-induced severe gastroduodenitis and cholangitis in a patient with stage IV melanoma. *Immunotherapy* 2019; **11**: 1005-1013 [PMID: 31304833 DOI: 10.2217/imt-2019-0077]
 - 36 **Anderson B**, Dawe DE. Nivolumab-Induced Secondary Sclerosing Cholangitis with Deterioration Despite Immunosuppression. *J Thorac Oncol* 2019; **14**: e205-e206 [PMID: 31445738 DOI: 10.1016/j.jtho.2019.04.023]
 - 37 **Zen Y**, Chen YY, Jeng YM, Tsai HW, Yeh MM. Immune-related adverse reactions in the hepatobiliary system: second-generation check-point inhibitors highlight diverse histological changes. *Histopathology* 2019 [PMID: 31550390 DOI: 10.1111/his.14000]
 - 38 **Onoyama T**, Takeda Y, Kato M, Edano M, Tarumoto R, Matsumoto K, Isomoto H. Peroral cholangioscopy of programmed cell death-1 inhibitor-related sclerosing cholangitis: three case reports. *Endoscopy* 2019; **51**: E402-E403 [PMID: 31340390 DOI: 10.1055/a-0948-1271]
 - 39 **Postow MA**, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. *N Engl J Med* 2018; **378**: 158-168 [PMID: 29320654 DOI: 10.1056/NEJMr1703481]
 - 40 **Zen Y**, Yeh MM. Checkpoint inhibitor-induced liver injury: A novel form of liver disease emerging in the era of cancer immunotherapy. *Semin Diagn Pathol* 2019; **36**: 434-440 [PMID: 31358424 DOI: 10.1053/j.semdp.2019.07.009]
 - 41 **Haanen JBA**G, Carbone F, Robert C, Kerr KM, Peters S, Larkin J, Jordan K; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28**: iv119-iv142 [PMID: 28881921 DOI: 10.1093/annonc/mdx225]
 - 42 **Brahmer JR**, Lacchetti C, Thompson JA. Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline Summary. *J Oncol Pract* 2018; **14**: 247-249 [PMID: 29517954 DOI: 10.1200/JOP.18.00005]
 - 43 **Zhu GQ**, Shi KQ, Huang GQ, Wang LR, Lin YQ, Braddock M, Chen YP, Zhou MT, Zheng MH. A network meta-analysis of the efficacy and side effects of UDCA-based therapies for primary sclerosing cholangitis. *Oncotarget* 2015; **6**: 26757-26769 [PMID: 26378046 DOI: 10.18632/oncotarget.5610]
 - 44 **Puzanov I**, Diab A, Abdallah K, Bingham CO, Brogdon C, Dadu R, Hamad L, Kim S, Lacouture ME, LeBoeuf NR, Lenihan D, Onofrei C, Shannon V, Sharma R, Silk AW, Skondra D, Suarez-Almazor ME, Wang Y, Wiley K, Kaufman HL, Ernstoff MS; Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* 2017; **5**: 95 [PMID: 29162153 DOI: 10.1186/s40425-017-0300-z]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

