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REVIEW ARTICLE

# Liver damage related to immune checkpoint inhibitors

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**Abstract**
Recently, immune checkpoint inhibitors are becoming one of the key agents of systemic treatment of cancer. The anti-cancer mechanism of this type of agent is totally different from that of conventional therapies; blockade of regulatory receptors and ligand of immune checkpoint molecules arose anti-tumor immunity with durable response. However, owing to its unique action to host immune system, immune checkpoint inhibitors sometimes induce immune-related adverse events (irAEs) which has not been observed for conventional chemotherapies. It has been reported that irAEs are manageable by discontinuation of immune checkpoint inhibitors and corticosteroid. However, severe irAEs might lead to the unsuccessful management of cancer treatment. It is conceivable that irAEs during the treatment of immune checkpoint blockade might mimic the autoimmune disease of the specific organ, such as autoimmune hepatitis (AIH). However, detail of the pathogenesis of irAEs has not been well estimated. In this review, we specially focused on this important issue and discussed the liver toxicity of this type of agent in the context of comparison of clinical and pathological findings of liver damage related to irAEs and AIH.

**Keywords** Liver damage · Immune checkpoint inhibitors · Autoimmune hepatitis · Hepatocellular carcinoma · Granuloma

## Introduction

Immune checkpoint inhibitors exert anti-tumor effect by blocking the interaction between regulatory receptors and ligand of checkpoint molecules on T cells, antigen-resenting cells and tumor cells [1]. These are expected to restore the anti-cancer immunity and are becoming one of the key agents for the treatment of cancers [2–4]. Currently, anti-programmed cell death (PD)-1, anti-PD-ligand 1 (PD-L1), and anti-cytotoxic T-lymphocyte associated antigen (CTLA-4) antibodies are available for several types of malignancies, including melanoma, renal cell carcinoma, non-small cell lung cancer, Hodgkin lymphoma, cervical cancer, and gastric cancer. In addition, combination therapies of immune checkpoint inhibitors, such as anti-PD-1 and anti-CTLA-4 combination, are approved for the treatment of advanced melanoma, and under clinical trials for many types of cancers [5, 6].

On the other hand, owing to the unique action of immune checkpoint inhibitors on immune system, this type of agent causes immune-related adverse events (irAEs) that mainly involve digestive system, lung, skin, endocrine glands, liver but can potentially affect any tissue. So far, it has been reported that irAEs caused by immune checkpoint monotherapies were manageable under steroid therapy and/or discontinuation of the agent [7–10]. However, it should be noted that irAEs induced by combination therapies, that aim to enhance the anti-tumor response, have not been well estimated [11–13].

It has been suspected that irAEs mimic the autoimmune disorders that target specific organs in terms of its pathogenesis. However, recent reports suggested that irAEs could represent a different feature compared to the autoimmune disorders [14]. In this review, we focused on the liver damage induced by immune checkpoint inhibitors and discussed the similarity and difference of clinical and pathological feature between irAEs of liver and autoimmune hepatitis (AIH).

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## Hepatotoxicity by immune checkpoint inhibitors

The frequencies of liver damage related to immune checkpoint inhibitors have been reported in the clinical trial of several types of cancers [15, 16]. Generally, it is reported that onset of liver damage was observed mainly within 3 months after the treatment but can emerge anytime during the treatment [17]. On the other hand, incidence of increase of aspartate transaminase (AST) or alanine transaminase (ALT) was observed in 2–5% of the cases and grade 3/4 increase of transaminase was detected in 1–4% [16, 17]. We summarized the frequencies of elevation of AST or ALT for melanoma patients treated with immune checkpoint inhibitor in Table 1. Although the dose and agent differed among the studies, the total frequencies of AST or ALT abnormalities ranged from 1.8–6.2%, and frequencies of grade 3/4 abnormalities were reported as 1.1–1.8% for the treatment of anti-PD-1 monotherapies [18–20]. On the other hand, the frequencies of liver damage related to the CTLA-4 monotherapy ranged from 1.2–14.6% for all grade, and 0.4–5.7% for grade 3/4 toxicity, suggesting that liver damage related to immune checkpoint inhibitors is more common in anti-CTLA-4 than in anti-PD-1 therapies [19–23].

On the other hand, several systemic therapies are found to be effective in advanced HCC cases [24–27] and several critical trials of immune checkpoint inhibitors are ongoing [28, 29]. Although number of the patients treated with this type of agents is much smaller in HCC than in melanoma cases, liver damage is more frequently observed in HCC cases, where 9–15% of the cases showed increase of ALT, and grade 3/4 toxicity was observed in 4–6% for anti-PD-1 treatment [28, 29]. Furthermore, anti-CTLA-4 antibody, tremelimumab, induced liver damage in 55% for all grades and 25% for grade 3/4 toxicity in the HCC patients, respectively [30]. Therefore, increase of ALT should be carefully monitored during the treatment of immune checkpoint inhibitors in HCC cases, although all liver damages were manageable by discontinuation of the agent and corticosteroid. On the other hand, grade 3/4 liver damage was much more severe for the combination of anti-PD-1 and anti-CTLA4 antibodies: 17.6–21% for all grades and 8.3–11% for grade 3/4 toxicity in melanoma cases [18, 21–23].

**Table 1** Frequencies of liver damage in the treatment with immune checkpoint inhibitors

| Agent (dose per infusion) | Tumor type | Number of the patients | Incidence of liver damage (%) | | References |
|---|---|---|---|---|---|
| | | | Total | Grade ¾ | |
| Anti-PD-1 antibody | | | | | |
| Pembrolizumab (10 mg/kg) | Melanoma | 277 | 1.8 | 1.8 | Robert et al. [19] |
| Nivolumab (3 mg/kg) | Melanoma | 313 | 3.8 | 1.3 | Larken et al. [18] |
| Nivolumab (3 mg/kg) | Melanoma | 313 | 4 | 1 | Wolchok et al. [23] |
| Nivolumab (3 mg/kg) | Melanoma | 452 | 6.2 | 1.1 | Weber et al. [20] |
| Nivolumab[a] | HCC | 48 | 15 | 6 | El-Khoueiry et al. [28] |
| Pembrolizumab[b] | HCC | 104 | 9 | 4 | Zhu et al. [29] |
| Anti-CTLA-4 antibody | | | | | |
| Ipilimumab (3 mg/kg) | Melanoma | 256 | 1.2 | 0.4 | Robert et al. [19] |
| Ipilimumab (3 mg/kg) | Melanoma | 311 | 3.9 | 1.6 | Larken et al. [18] |
| Ipilimumab (3 mg/kg) | Melanoma | 311 | 4 | 2 | Wolchok et al. [23] |
| Ipilimumab (10 mg/kg) | Melanoma | 453 | 14.6 | 5.7 | Weber et al. [20] |
| Tremelimumab (15 mg/kg)[c] | HCC | 20 | 55 | 25 | Sangro et al. [30] |
| Anti-PD-1 + anti-CTLA-4 antibodies | | | | | |
| Nivolumab + ipilimumab[d] | Melanoma | 53 | 21 | 11 | Wolchok et al. [22] |
| Nivolumab + ipilimumab[e] | Melanoma | 313 | 17.6 | 8.3 | Larken et al [18] |
| Nivolumab + ipilimumab[e] | Melanoma | 313 | 19 | 9 | Wolchok et al. [23] |

For the trial on melanoma, cases positive for hepatitis B (HBV) and hepatitis C virus, (HCV) were excluded

[a]Nivolumab 0.1–10 mg/kg. Among 48 patients, 15 and 10 were positive for HBV and HCV, respectively

[b]Pembrolizumab 200 mg

[c]Nivolumab 0.1–10 mg/kg. All patients showed chronic HCV infection

[d]Nivolumab 0.3–3 mg/kg + ipilimumab 1–3 mg/kg

[e]Nivolumab 1 mg/kg + ipilimumab 3 mg/kg

## Difference of clinical and pathological feature between autoimmune hepatitis and liver damage induced by immune checkpoint inhibitors

De Martin et al. reported 16 cases with liver injury related to immune checkpoint inhibitors; 7 cases were treated with anti-CTLA-4 antibody or anti-PD-1 and anti-CTLA-4 combination, and 9 cases underwent anti-PD-1 monotherapy. Among them, 6 cases (37.5%) were accompanied by high fever (mainly observed in the cases with anti-CTLA-4 or combination therapy); five cases (31.3%) showed skin rash [31]. In contrast to the cases of autoimmune hepatitis (AIH), no female predominance was reported for the incidence of liver damage of irAEs (Table 2). In addition, the characteristic findings of serological examination of AIH, such as increase of γ-globulin and appearance of antinuclear antibody (ANA) and anti-smooth muscle antibody (SMA), were not always observed in the case with liver damage related to immune checkpoint inhibitors [31].

Differences of histological features between AIH and liver damage of irAEs have also been described. Histology of the liver related to irAEs is heterogeneous that should be attributed to the complexity of pathogenesis, including lobular hepatitis, steatosis and steatohepatitis, as well as bile duct injury [32, 33]. In addition to the autoimmune-like hepatitis in liver parenchyma [34], damage in ductal and endothelial cells is observed, suggesting that cellular rejection may be induced by this type of agent; the cases with liver allograft failure have been reported in association with immune checkpoint inhibitors [35–37].

Liver parenchymal damage induced by anti-PD-1 antibody is mainly represented lobular hepatitis with mild lobular infiltration [38]. It may be accompanied by cholangiolitis, bile duct injury and endothelialitis [14, 38, 39]; although the degree of liver injury was milder compared to that induced by anti-CTLA-4 antibody. Portal fibrosis was also reported

**Table 2** Comparisons of liver damage related to immune checkpoint inhibitors and autoimmune hepatitis

| | AIH | Liver damage related to immune checkpoint inhibitors | | |
|---|---|---|---|---|
| | | Anti-PD-1 | Anti-CTLA4 | Anti-PD-1 + anti-CTLA-4 |
| Clinical manifestations | | | | |
| Sex | Female predominant | Not particular | | |
| History | History of autoimmune disorders, preceded viral infection etc | Administration of immune checkpoint inhibitors | | |
| Symptom | Malaise, jaundice | Fever (37.5%), diffuse maculopapular rash (31.2%) | | |
| Serological marker | | | | |
| ANA, SMA | Positive[a] | Negative or low titer | | |
| γ-Globulin | Increased[a] | Normal range | | |
| Histological feature | | | | |
| Hepatitis | Interface hepatitis[a]<br>Fibrosis<br>Liver cirrhosis | Lobular hepatitis with mild portal infiltration<br>Portal fibrosis (44%) | Pan-lobular hepatitis<br>Centrilobular hepatitis<br>Granulomatous hepatitis | Granulomatous hepatitis with sever centrilobular necrosis |
| Cell infiltration | Plasma cell predominant | Histiocyte predominant | Histiocyte predominant (sinusoidal distribution) | |
| Lymphocytes | $CD4^+$ and $CD8^+$ | $CD4^+$ and $CD8^+$ | $CD8^+$ predominant | |
| Neutrophils | Rare | | Scattered | |
| Others | Rosette formation | Patchy necrosis, acidophilic body (microgranuloma without fibrin) | Microgranuloma by macrophages with fibrin deposit | Fibrin ring granuloma[b] |
| | Overlap with PBC (possible) | Bile duct injury (≥ 50%)[c] | | |
| | No other atypical change | | Endothelialitis[d] | |
| | | Steatosis/steatohepatitis | | |

[a]ANA and hyper γ-globulinemia may be absent for acute onset. Zone 3 necrosis may be present

[b]Fibrin ring granuloma: granuloma with central lipid vacuole surrounded by a red fibrin ring and a cluster of histiocytes

[c]Bile duct injury: lymphocytic cholangitis and ductal dystrophy

[d]Endothelialitis in both central and portal vein

for liver injury related to anti-PD-1 antibody. However, infiltration of plasma cell and lymphoid follicles, which was one of the characteristic findings of AIH, was rarely observed [31, 38, 40]. On the other hand, bile duct injury during the treatment using anti-PD-1 antibody may lead to vanishing bile duct syndrome that is attributed to lymphocytic cholangitis [32, 41, 42]. Reportedly, extrahepatic bile duct could also be involved, which represented dilatation of extrahepatic biliary [32]. Elevation of alkaline phosphatase, γ-glutamyl transpeptidase and bilirubin are predominant laboratory findings in the cases with cholangiopathy [43].

Liver injury related to anti-CTLA-4 antibody and its combination with anti-PD-1 antibody could be more severe and, reportedly, represented unique pathological features. The liver injury induced by anti-CTLA-4 may occur earlier than that induced by anti-PD-1 antibody [31]. Most patients showed pan-lobular hepatitis with infiltration of lymphocyte and histiocytes. The infiltrated T lymphocyte mainly represented $CD8^+$ in anti-CTLA-4 antibody-related liver injury, although both $CD4^+$ and $CD8^+$ T lymphocytes were observed in AIH as well as liver injury related to anti-PD-1 antibody [31, 44]. The centrilobular hepatitis, which had been described in AIH, could also be observed in anti-CTLA-4 related liver injury. Bile duct injury and steatohepatitis might take place, but not characteristic findings [31, 44]. In many cases, central vein endothelialitis and sinusoidal distribution of macrophage were reportedly detected. Everett et al. reported two cases of the fibrin ring granulomas in patients with liver damage related to ipilimumab and nivolumab combination therapy, which could be observed in a variety of liver injuries, such as induced by infectious and toxic agents [45]. It generally consists of several layers with a central lipid vacuole surrounded by macrophages, histiocytes and fibrin ring. De Martin et al. also reported that granulomatous hepatitis with fibrin deposit accompanied by severe lobular necrotic and inflammatory activity was frequently detected in the patients treated with anti-PD-1 and anti-CTLA-4 combination [31]. Endothelialitis in central and portal vein also occurred in patients treated with combination therapy [31, 44].

So far, there are no specific predictors that predict emergence of liver damage after the start of immune checkpoint inhibitors. Based on the previous analysis that analyzed 16 cases of liver damage associated with immune checkpoint inhibitors, 9 cases showed positive for ANA or SMA, although their titers are low [31]. Although previous report shows high flare rate of autoimmune disorders in patients with inactive status, risk of liver toxicity in patients with autoimmune liver disease has not been evaluated [33]. In addition, association between the presence of ANA and SMA and risk of emergence of liver damage on the treatment using immune checkpoint inhibitors has not been clarified yet. On the other hand, skin and gastrointestinal complication could be accompanied by liver damage; emergence of such symptom could be a precursor of liver complication [33].

## Conclusion

The treatment using immune checkpoint inhibitors is expanding; its liver toxicity is poorly understood [46]. It has been considered that immune checkpoint inhibitors arouse autoimmune reaction, but clinical and pathological feature of liver injury related to this type of agent is, in some respects, different from that of AIH [14]. The typical serological finding of AIH was not observed in liver injury related to irAEs, where major infiltrating cells are histiocyte and macrophage but not plasma cells. Severe interface hepatitis and rosette formation are rare, and granulomatous lobular hepatitis, fibrin ring granulomas, and endothelialitis and bile duct injury are more frequently observed compared to AIH.

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### Compliance with ethical standards

**Conflict of interest** Naoshi Nishida and Masatoshi Kudo have no conflicts of interest to disclose.

**Ethical approval and informed consent** This is not a research paper involving human participants and/or animals; informed consent is not required.

## References

1. Nishida N, Kudo M. Immunological microenvironment of hepatocellular carcinoma and its clinical implication. Oncology 2017;92(Suppl 1):40–49
2. Kudo M. Immune checkpoint blockade in hepatocellular carcinoma: 2017 update. Liver Cancer 2016;6:1–12
3. Kudo M. A new era of systemic therapy for hepatocellular carcinoma with regorafenib and lenvatinib. Liver Cancer 2017;6:177–184
4. Kudo M. Management of hepatocellular carcinoma in Japan as a world-leading model. Liver Cancer 2018;7:134–147
5. Kudo M. Immune checkpoint inhibition in hepatocellular carcinoma: basics and ongoing clinical trials. Oncology 2017;92(Suppl 1):50–62
6. Nishida N, Kudo M. Role of immune checkpoint blockade in the treatment for human hepatocellular carcinoma. Dig Dis 2017;35:618–622
7. 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
8. Huffman BM, Kottschade LA, Kamath PS, Markovic SN. Hepatotoxicity after immune checkpoint inhibitor therapy in

melanoma: natural progression and management. Am J Clin Oncol 2018;41:760–765
9. Johnson DB, Chandra S, Sosman JA. Immune checkpoint inhibitor toxicity in 2018. JAMA 2018;320:1702–1703
10. Sanjeevaiah A, Kerr T, Beg MS. Approach and management of checkpoint inhibitor-related immune hepatitis. J Gastrointest Oncol 2018;9:220–224
11. Nishida N, Kudo M. Oncogenic signal and tumor microenvironment in hepatocellular carcinoma. Oncology 2017;93(Suppl 1):160–164
12. Kudo M. Combination cancer immunotherapy in hepatocellular carcinoma. Liver Cancer 2018;7:20–27
13. Lin JJ, Chin E, Yeap BY, Ferris LA, Kamesan V, Lennes IT, et al. Brief report: Increased hepatotoxicity associated with sequential immune checkpoint inhibitor and crizotinib therapy in patients with non-small-cell lung cancer. J Thorac Oncol 2019;14:135–140
14. Zen Y, Yeh MM. Hepatotoxicity of immune checkpoint inhibitors: a histology study of seven cases in comparison with autoimmune hepatitis and idiosyncratic drug-induced liver injury. Mod Pathol 2018;31:965–973
15. Zhang X, Ran Y, Wang K, Zhu Y, Li J. Incidence and risk of hepatic toxicities with PD-1 inhibitors in cancer patients: a meta-analysis. Drug Des Dev Ther 2016;10:3153–3161
16. Wang W, Lie P, Guo M, He J. Risk of hepatotoxicity in cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis of published data. Int J Cancer 2017;141:1018–1028
17. Suzman DL, Pelosof L, Rosenberg A, Avigan MI. Hepatotoxicity of immune checkpoint inhibitors: an evolving picture of risk associated with a vital class of immunotherapy agents. Liver Int 2018;38:976–987
18. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and Ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34
19. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in advanced melanoma. N Engl J Med 2015;372:2521–2532
20. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017;377:1824–1835
21. Ribas A, Hodi FS, Callahan M, Konto C, Wolchok J. Hepatotoxicity with combination of vemurafenib and ipilimumab. N Engl J Med 2013;368:1365–1366
22. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369:122–133
23. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017;377:1345–1356
24. Ikeda K, Kudo M, Kawazoe S, Osaki Y, Ikeda M, Okusaka T, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. J Gastroenterol 2017;52:512–519
25. Kudo M, Hatano E, Ohkawa S, Fujii H, Masumoto A, Furuse J, et al. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma: Japanese subgroup analysis of the REACH trial. J Gastroenterol 2017;52:494–503
26. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317–370
27. Nishida N, Nishimura T, Kaido T, Minaga K, Yamao K, Kamata K, et al. Molecular scoring of hepatocellular carcinoma for predicting metastatic recurrence and requirements of systemic chemotherapy. Cancers (Basel) 2018;10:E367
28. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492–2502
29. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018;19:940–952
30. Sangro B, Gomez-Martin C, de la Mata M, Inarrairaegui M, Garralda E, Barrera P, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol 2013;59:81–88
31. De Martin E, Michot JM, Papouin B, Champiat S, Mateus C, Lambotte O, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol 2018;68:1181–1190
32. Reddy HG, Schneider BJ, Tai AW. Immune checkpoint inhibitor-associated colits and hepatitis. Clin Transl Gastroenterol 2018;9:180
33. Nadeau BA, Fecher LA, Owens SR, Razumilava N. Liver toxicity with cancer checkpoint inhibitor therapy. Semin Liver Dis 2018;38:366–378
34. Ziemer M, Koukoulioti E, Beyer S, Simon JC, Berg T. Managing immune checkpoint-inhibitor-induced severe autoimmune-like hepatitis by liver-directed topical steroids. J Hepatol 2017;66:657–659
35. Gassmann D, Weiler S, Mertens JC, Reiner CS, Vrugt B, Nageli M, et al. Liver allograft failure after nivolumab treatment-a case report with systematic literature research. Transpl Direct 2018;4:e376
36. Kuo JC, Lilly LB, Hogg D. Immune checkpoint inhibitor therapy in a liver transplant recipient with a rare subtype of melanoma: a case report and literature review. Melanoma Res 2018;28:61–64
37. Biondani P, De Martin E, Samuel D. Safety of an anti-PD-1 immune checkpoint inhibitor in a liver transplant recipient. Ann Oncol 2018;29:286–287
38. Karamchandani DM, Chetty R. Immune checkpoint inhibitor-induced gastrointestinal and hepatic injury: pathologists' perspective. J Clin Pathol 2018;71:665–671
39. Simonelli M, Di Tommaso L, Baretti M, Santoro A. Pathological characterization of nivolumab-related liver injury in a patient with glioblastoma. Immunotherapy 2016;8:1363–1369
40. Schmeltzer PA, Russo MW. Clinical narrative: autoimmune hepatitis. Am J Gastroenterol 2018;113:951–958
41. Doherty GJ, Duckworth AM, Davies SE, Mells GF, Brais R, Harden SV, et al. Severe steroid-resistant anti-PD1 T-cell checkpoint inhibitor-induced hepatotoxicity driven by biliary injury. ESMO Open 2017;2:e000268
42. Kawakami H, Tanizaki J, Tanaka K, Haratani K, Hayashi H, Takeda M, et al. Imaging and clinicopathological features of nivolumab-related cholangitis in patients with non-small cell lung cancer. Investig New Drugs 2017;35:529–536
43. Parlati L, Vallet-Pichard A, Batista R, Hernvann A, Sogni P, Pol S, et al. Incidence of grade 3–4 liver injury under immune checkpoints inhibitors: a retrospective study. J Hepatol 2018;69:1396–1397
44. Johncilla M, Misdraji J, Pratt DS, Agoston AT, Lauwers GY, Srivastava A, et al. Ipilimumab-associated hepatitis: clinicopathologic characterization in a series of 11 cases. Am J Surg Pathol 2015;39:1075–1084
45. Everett J, Srivastava A, Misdraji J. Fibrin ring granulomas in checkpoint inhibitor-induced hepatitis. Am J Surg Pathol 2017;41:134–137
46. Nishida N, Kudo M. Immune checkpoint blockade for the treatment of human hepatocellular carcinoma. Hepatol Res 2018;48:622–634