Title: Liver biopsy findings in patients on immune checkpoint inhibitors

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要旨：免疫チェックポイント阻害薬 (immune checkpoint inhibitor; ICI) は種々の悪性腫瘍に持続的な抗腫瘍効果をもたらすが、様々な免疫関連有害事象 (immune related adverse events; irAE) を引き起こす。本研究では、ICI 使用中の患者における肝生検での炎症のパターンと、ICI の種類、肝逸脱酵素の異常、画像所見、ステロイド反応性などの項目に一定の傾向が見られるかを検討した。肝生検では、組織像を実質傷害、胆管傷害、両者の混合型、脂肪性肝炎、その他の軽微な非特異的変化に分類した。

60 例中 28 例で実質傷害パターンがみられ、そのうち 11 例で肉芽腫を、10 例で静脈内皮炎を認めた。8 例では混合性パターンがみられ、そのうち 6 例で肉芽腫を、4 例で静脈内皮炎を認めた。16 例で胆管傷害パターンがみられた。3 例で脂肪性肝炎パターン、5 例は非特異的変化がみられた。

実質傷害、混合型、胆管傷害パターンを呈するものは、それぞれ肝逸脱酵素の上昇パターンがよく一致していた。胆管傷害パターンでは胆管拡張や狭窄が画像所見として認められた。組織所見の種類や程度からステロイド反応性を予測することは困難であった。

胆管傷害パターンでは胆汁うっ滞性肝障害型の肝逸脱酵素の上昇が見られるが、胆道閉塞やその他の薬物性肝障害でも同様のパターンが見られるので注意が必要である。

Take home message：肝生検でみられる組織像は臨床像をよく反映しており、なかには脂肪性肝炎や胆道閉鎖と類似した組織像を呈する場合がある。また、組織障害の程度から治療反応性の予測をすることは困難である。浸潤するリンパ球のパターンから AIH や DILI と鑑別する報告もあるが、組織像から ICI 関連肝傷害の可能性を否定しないことが肝要である。

担当：西谷

Table 1 Clinical features of 60 patients with abnormal liver tests in the setting of immune checkpoint inhibitor therapy.

Age range (mean)	28-85 years (61 years)
Male: Female	29:31
Malignancy	
Melanoma	41
Nonsmall cell lung carcinoma	5
Gastrointestinal adenocarcinoma	4
Pancreatobiliary adenocarcinoma	3
GYN malignancy	2
Glioblastoma	3
Acute myeloid leukemia	1
Cutaneous squamous cell carcinoma	1
Immune checkpoint inhibitor therapy	
Anti-PD1 only	15
Anti-CTLA4 only	4
Combination Anti-PD1/Anti-CTLA4	20
Sequential Anti-PD1 and Anti-CTLA4	8
Checkpoint inhibitor with other therapy	13
Median days on ICI therapy (range)	78 (12–917)
Grade of liver toxicity (CTCAE)	
1	2
2	5
3	44
4	9
Pattern of liver enzyme abnormality	
Hepatitic	30
Cholestatic	24
Mixed	6
Radiologic modalities ($n = 59$)	
CT or PET CT only	42
Ultrasound and CT	9
Ultrasound only	3
MRCP or ERCP (with or without other modalities)	5
Radiologic findings ($n = 59$)	
No relevant liver findings	30
Hepatic metastases	15
Bile duct dilatation or narrowing	5
Gallbladder thickening	5
Steatosis	5
Portal edema	2
Cirrhosis	1
Duration of steroids	
Not given[a]	9
Less than 1 month	19
1–3 months	14
Greater than 3 months[b]	18
Secondary immunosuppression[b]	12
Median days until resolution of LFTs (range)	44 (2-302)
Outcome	
Alive without disease	18
Alive with disease	18
Dead of disease	24

ICI immune checkpoint inhibitor, *CTCAE* common terminology criteria for adverse events, *LFT* liver function test.

[a]One patient was on chronic steroids, but the dose was not increased after the diagnosis of ICI hepatitis.

[b]Two patients required steroids and secondary immunosuppression for concurrent immune mediated colitis.

Table 3 Clinical features in 60 patients biopsied for suspected immune checkpoint inhibitor liver injury by histologic pattern.

	Hepatitic Pattern ($n = 28$)	Mixed hepatitic and cholangitic ($n = 8$)	Cholangitic pattern ($n = 16$)	Steatotic pattern ($n = 3$)	Mild and nonspecific changes ($n = 5$)
Checkpoint therapy					
Anti-PD1 only	5	2	5	2	1
Anti-CTLA4 only	4	0	0	0	0
Combination ICI	10	3	7	0	0
Sequential ICI	5	0	1	1	1
ICI and other	4	3	3	0	3
Pattern of LFT abnormalities					
Hepatocellular	22	2	2	1	3
Cholestatic	3	6	12	2	1
Mixed hepatocellular and cholestatic	3	0	2	0	1
Grade of liver toxicity (CTCAE)					
1	0	0	1	1	0
2	4	0	1	0	0
3	19	6	12	2	5
4	5	2	2	0	0
Radiologic findings					
Normal or nonspecific findings	19	4	5	2	4
Steatosis	4	0	0	1	0
Hepatic metastases	4	3	7	1	0
Bile duct dilatation/narrowing	1	0	4	0	0
Gallbladder thickening	1	1	2	0	1
Duration of steroids					
Not given	4	1	2	1	2
<1 month	8	2	6	1	2
1–3 months	8	2	4	0	0
>3 months	9	3	4	1	1
Secondary immunosuppression	5[a]	3	2	1	1
Median days to resolution of LFTs (range)	52 (10–160)	35 (2–110)	47 (14–268)	180 (59–302)	32 (20–364)
Outcome					
Alive without disease	10	1	4	1	2
Alive with disease	9	3	4	1	1
Dead of disease	9	4	8	1	2
Competing explanation for LFTs	0	1	10	1	[1]

ICI immune checkpoint inhibitor, *CTCAE* common terminology criteria for adverse events, *LFT* liver function test.

[a]Two patients received infliximab for concurrent colitis.

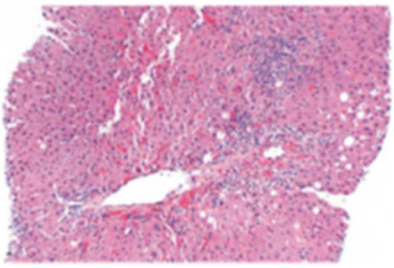

Fig. 1 Zone 3 hepatitis and necrosis with numerous histiocytes adjacent to an injured central vein. Note the mild steatosis colocalizing to the area of injury.

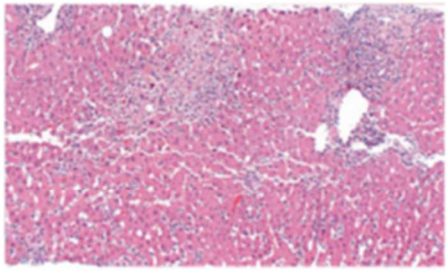

Fig. 2 Medium power view of a liver biopsy with panlobular inflammation, but with focal area of necrosis in the lobule. The portal tract in this view is moderately expanded by inflammatory cells, but the bile duct is not significantly injured.

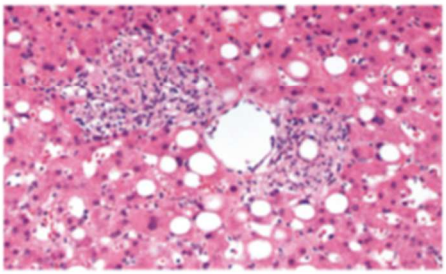

Fig. 3 Steatosis in an area of injury around a central vein with aggregates of histiocytes surrounding an injured vein. Note the lipid vacuole in the histiocyte aggregate, reminiscent of an early fibrin ring type granuloma.

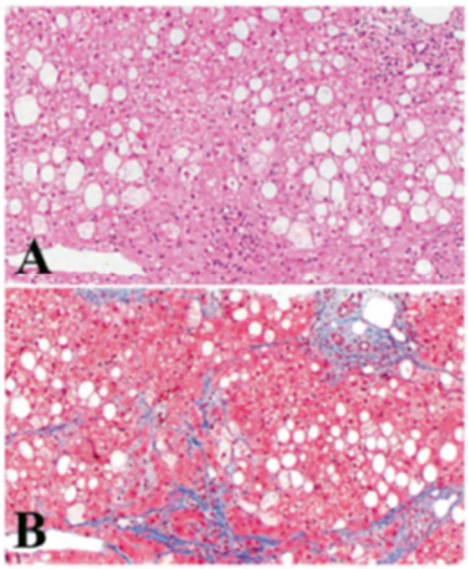

Fig. 8 Medium power view of a liver biopsy demonstrating a steatohepatitic pattern of injury. a Hematoxylin and eosin stained section. There is moderate macrovesicular steatosis, hepatocyte ballooning with Mallory-Denk bodies, and focal lobular mononuclear cell infiltrate. **b** Trichrome stain of the same area of the biopsy shows sinusoidal fibrosis in zone 3, as well as delicate septae extending from the portal tract, consistent with stage 2 of 4 fibrosis (Brunt stage).

Fig. 1. 組織球浸潤を伴う中心静脈周囲炎および壊死。軽度の脂肪変性を伴う。

Fig. 2. 汎小葉の炎症パターン。門脈域は炎症細胞浸潤により拡大している。壊死は少なく胆管傷害は目立たない。

Fig. 8. 脂肪性肝炎パターン。a. ballooning と Mallory-Denk 小体がみられる。炎症細胞浸潤が実質に軽度認められる。b. 中心静脈域において、類洞（肝細胞）周囲の線維化を認める。門脈域周囲にも繊細な線維化がみられ Brunt stage 2 の像である。

参考資料

表. CTCAE について

CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alkaline phosphatase increased	＞ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	＞2.5 - 5.0 x ULN if baseline was normal; ＞2.5 - 5.0 x baseline if baseline was abnormal	＞5.0 - 20.0 x ULN if baseline was normal; ＞5.0 - 20.0 x baseline if baseline was abnormal	＞20.0 x ULN if baseline was normal; ＞20.0 x baseline if baseline was abnormal	-
Blood bilirubin increased	＞ULN - 1.5 x ULN if baseline was normal; ＞ 1.0 - 1.5 x baseline if baseline was abnormal	＞1.5 - 3.0 x ULN if baseline was normal; ＞1.5 - 3.0 x baseline if baseline was abnormal	＞3.0 - 10.0 x ULN if baseline was normal; ＞3.0 - 10.0 x baseline if baseline was abnormal	＞10.0 x ULN if baseline was normal; ＞10.0 x baseline if baseline was abnormal	-
Hepatic failure	-	-	Asterixis; mild encephalopathy; drug-induced liver injury (DILI); limiting self care ADL	Life-threatening consequences; moderate to severe encephalopathy; coma	Death

CTCAE: common terminology criteria for adverse events

ULN: upper limit normal limit

図. ICI 関連肝障害、自己免疫性肝炎（AIH)、薬物性肝障害（DILI）の鑑別

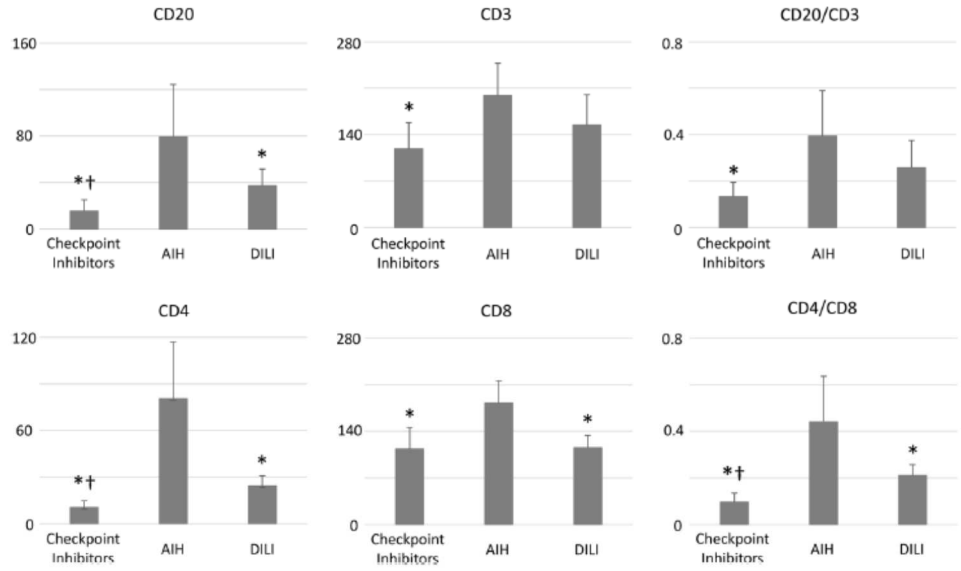

Fig. 3 Characterization of infiltrating inflammatory cells in checkpoint inhibitor-induced liver injury, autoimmune hepatitis (AIH), and drug-induced liver injury (DILI). The absolute numbers of lymphocytes positive for CD20, CD3, CD4, or CD8 were counted per high power field. The ratios of CD20+/CD3+ or CD4+/CD8+ cells were also calculated. *$p < 0.05$ vs. AIH; †$p < 0.05$ vs. DILI

ICI 関連では CD3>CD20 かつ、CD4<CD8 であり、浸潤する T, B リンパ球の種類により AIH, DILI と鑑別が可能である。

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. より抜粋

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