Metastatic Merkel Cell Carcinoma Presenting as Silent Infiltrative Liver Disease: A Lesson Emphasizing the Utility of Liver Biopsy in the Exclusion of Immune Checkpoint Inhibitor-Mediated Hepatotoxicity

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Clinical Significance

- In the initial evaluation of suspected immune checkpoint inhibitor (ICI)-mediated hepatobiliary toxicity, liver biopsy is not yet considered mandatory
- Several scenarios support diagnostic liver biopsy as part of the initial diagnostic work-up to exclude alternative causes of abnormal liver biochemical tests, such as metastatic disease in the liver, especially when the clinical picture is unclear

Introduction

- Merkel cell carcinoma (MCC) is a rare neuroendocrine tumor that arises on skin exposed to the sun; mortality is about 33% and disseminated disease suggests poor prognosis
- Metastasis to the liver is exceedingly rare, with only few reported cases presenting as infiltrative liver disease
- We present a case of MCC with "silent" infiltration in the liver effectively differentiated from suspected immune checkpoint inhibitor-mediated hepatotoxicity (IMH) by liver biopsy

Case Presentation

- A 76-year-old man with a history of metastatic MCC of the left distal thigh status-post stem cell transplant presented to a cancer care center for evaluation of fatigue, nausea, and dyspnea
- History of chronic alcohol use until 2 years prior
- MCC treatment: pembrolizumab and plinabulin (a phase I microtubule inhibitor) with radiation to the liver 2 months prior to presentation
- On admission, asymptomatic CTCAE grade 3 ALT elevation noted (**Table 1**)
- Liver imaging unrevealing for liver lesions
- Budesonide 9 mg/d + ursodiol 1000 mg/d were started empirically to treat presumed IMH, but without meaningful improvement in liver enzymes
- Parenchymal liver biopsy was performed to clarify diagnosis: Histology showed tumor cells strongly positive for synaptophysin, chromogranin, confirming metastatic MCC (**Figure 1**)
- Empiric steroids were discontinued after 4 days of empiric treatment; diagnosis was attributed to liver infiltration by MCC; patient passed away 3 months later from MCC

Laboratory Value	Normal ranges	Baseline on Immunotherapy	Day 1 of Admission	Day 1 After Steroids	Day 2 After Steroids	Day 3 After Steroids
Alanine Aminotransferase (ALT)	< 40 (U/L)	**46**	**315**	**267**	**257**	**240**
Aspartate Aminotransferase (AST)	< 41 (U/L)	**41**	**269**	**333**	**281**	**281**
Alkaline Phosphatase (ALP)	40-129 (U/L)	**87**	**226**	**243**	**231**	**227**
Total Bilirubin	< 1.2 (mg/dL)	**0.3**	**0.7**	**0.7**	**0.9**	**1.1**
International Normalized Ratio (INR)	0.90-1.10	**1.06**	**1.15**	**1.16**	**1.18**	**1.18**

Table 1. Liver biochemical lab trends. Prior to initiating immunotherapy, serum transaminases rose slowly but remained within 3× upper limit of normal (ULN). At the end of treatment, transaminases reached >5× ULN. No meaningful improvement was seen in liver enzymes after initiating empiric steroid therapy for suspected IMH.

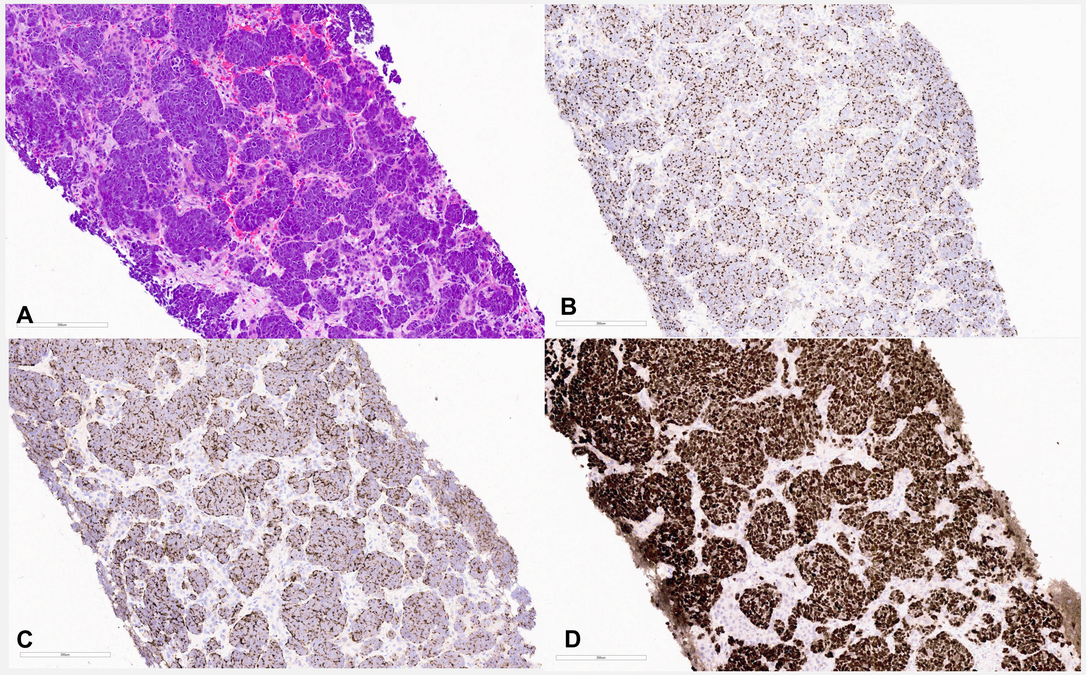

Figure 1. Liver histology from biopsy.

A) **H&E** - Solid nests and lobules of poorly differentiated neuroendocrine cells are seen in this liver biopsy; tumor cells show high nuclear to cytoplasmic ratios with hyperchromatic nuclei and irregular nuclear membranes indicating metastatic MCC

B) **Chromogranin stain** - Tumor cells are strongly and diffusely positive for chromogranin

C) **CK20 stain** - Tumor cells show perinuclear dot-like reactivity to Cytokeratin-20

D) **Synaptophysin stain** - Tumor cells are strongly and diffusely positive for neuroendocrine marker Synaptophysin

Discussion

- Traditionally, when there is high suspicion, IMH would be clinically diagnosed without expectation for upfront liver biopsy, and systemic corticosteroids are often prescribed upfront and empirically
- Guidelines suggest that if the patient's liver biochemical parameters do not improve after starting corticosteroids, to then subsequently consider liver biopsy to demonstrate if the diagnosis of IMH is correct
- One critique regarding the role of liver biopsy may be that histological features associated with IMH are nonspecific, with features of lobular to pan-lobular hepatitis
- However, the absence of an alternative findings on the biopsy confers additional confidence towards the diagnosis of IMH, akin to providing histologic data for input into a scoring system for the diagnosis of classic idiopathic autoimmune hepatitis, where a liver biopsy is accepted as mandatory
- There are no specific serological tests that support the diagnosis of IMH, and the onset of IMH is variable after ICI exposure; RUCAM scale will be difficult to interpret, and concurrent cancer treatment agents may confound the clinical picture
- In a recent study by Li et al. (2021) in *JAMA Oncology*, 11.2% of patients had the suspected diagnosis of IMH disproven by liver biopsy, which represents a subset of patients who should not be treated with steroids; this supports an approach that involves obtaining liver biopsy first before starting systemic corticosteroids to avoid unnecessary immunosuppression
- Our case highlights the importance of the diagnostic liver biopsy prior to immunosuppressive treatment for suspected IMH to exclude other differentials and guide the decision for empiric steroids

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