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Editorial

Rare Entities and Emerging Issues in Gastrointestinal and Liver Pathology

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The Journal of Clinical and Translational Pathology has launch-ed a special issue on gastrointestinal (GI) and liver pathology. Although molecular and digital pathology have been increasingly applied to GI and liver diseases, histopathologic and immunohistochemical evaluations of GI mucosal biopsies, needle core biopsies of the liver and resection specimens provide essential information for the most appropriate clinical management for patients with GI or liver diseases. Diagnosing rare GI tumors and liver diseases and the emerging immune checkpoint inhibitors (ICIs)-induced GI and hepatic toxicity is often challenging. The five selected articles focusing on goblet cell adenocarcinoma, esophageal verrucous carcinoma and carcinoma cuniculatum, post-infantile giant cell hepatitis, ICI-associated hepatic toxicity, and recurrent primary biliary cholangitis in post-transplant patients are included in this special issue of GI and liver pathology. These articles will help to increase awareness and improve the diagnosis of these entities.

Goblet cell adenocarcinoma is a rare appendiceal epithelial neoplasm with unique histopathologic and clinical features.[1] This new term replaces the old and confusing term "goblet cell carcinoid" used since 1974 and in the fourth edition of the World Health Organization Classification of Tumors of the Digestive System Tumors. In the timely review by Dr. Hanlin L. Wang, the diagnostic criteria, the histologic features of low-grade and high-grade patterns, the grading schema, and the prognostic parameters of goblet cell adenocarcinoma were discussed. It is essential to recognize and quantify both low- and high-grade tumor components for the diagnosis and grading of goblet cell adenocarcinoma since the presence of the former is required for the diagnosis, and the percentage of high-grade components predicts the prognosis.[2] In addition, Dr. Wang discussed the histogenesis and the possible cellular origins of this rare tumor and the advantages and disadvantages of the current nomenclature. Given that the current term "goblet cell adenocarcinoma" may not accurately reflect the cellular origin of this rare entity, the alternative name "crypt cell carcinoma" is favored in this review.

Esophageal verrucous carcinoma and carcinoma cuniculatum are rare well-differentiated squamous cell carcinomas.[3,4] These entities are extremely difficult or impossible to diagnose on small superficial biopsy specimens. Deep biopsies or resections are often needed to establish these diagnoses. Dr. Liu and her colleagues systemically discussed their clinical presentations, histomorphologic features, and molecular alterations in reviewing these two rare entities and the conventional squamous cell carcinoma of the esophagus.[5] The review emphasized the utility of molecular testing for the early diagnosis, as verrucous carcinoma exhibits unique molecular signatures (TP53 wild-type and frequent SMARCA4 mutation), and carcinoma cuniculatum harbors recurrent hot spot somatic mutations in NOTCH1, TP53, PIK3CA, KRAS, HRAS, SETD2, and TLR2 genes. Improving awareness of these rare entities with the clinic-histopathological correlation and molecular profile will lead to early diagnosis and optimal treatments and improve clinical outcomes.

Post-infantile giant cell hepatitis (PIGCH) is a rare entity characterized by acute or chronic hepatic injury patterns and the presence of syncytial hepatic giant cells (hepatocytes with > 3 nuclei and abundant cytoplasm).[6] Through a literature review and meta-analysis of 68 cases of PIGCH, Dr. Zhang and his colleagues performed a comprehensive and systemic analysis of the patient characteristics, clinical presentations, etiologies, histologic features, laboratory findings, and factors associated with the poor prognosis of this rare entity.[7] Autoimmune liver disease and combined multifactorial etiology appear to be the most common causes of PIGCH, followed by viral infections, medication, malignancies, and others. In contrast to the prior reports that suggested the underlying etiology as the dictating factor for prognosis, the current study identified many factors that are significantly associated with poor prognoses, such as older age, lower platelets and albumin levels, higher total bilirubin level, and diffuse distribution pattern of giant cells on liver biopsy. The results from this meta-analysis have provided valuable information for the diagnosis, clinical management, and prognosis of patients with PIGCH.

In recent years, immune checkpoint inhibitors (ICIs) have become the standard of care. They have been widely used

Abbreviations: GI, gastrointestinal; ICIs, immune checkpoint inhibitors; PIGCH, Post-infantile giant cell hepatitis; PBC, primary biliary cholangitis.

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to treat many types of malignancies. The immune-related adverse effects associated with ICIs are common and may affect many organ systems, including the gastrointestinal tract, skin, liver, endocrine system, and lungs. The diagnosis of ICI-associated hepatic toxicity is often challenging. It must be distinguished from various etiologies given the complex medical history, oncological treatment history, and possible immune system deregulation in cancer patients.[8] The review by Dr. Wang and his colleagues summarized the available data from the literature on the clinical, radiographic, histopathologic features and patterns, differential diagnosis, and clinical management of ICI-associated hepatic toxicity.[9] The review is focused on different liver injury patterns and major morphological clues. The hepatitic pattern appears to be the most common ICI-associated hepatitic injury pattern, followed by the cholangitic pattern, mixed hepatitic and cholangitic patterns, and some uncommon patterns. Since the liver biopsies of ICI-induced hepatic injury often have non-specific histologic findings that overlap with other etiologies, the diagnosis of ICI-induced hepatic injury requires the careful correlation of the histologic findings with the clinical and laboratory results and effective communication with the hepatologist. This review provided valuable and practical information for prompt diagnosis and clinical management of ICI-induced hepatic injury.

As a chronic cholestatic liver disease, primary biliary cholangitis (PBC) is characterized by immune-mediated progressive destruction of the bile ducts, leading to advanced fibrosis and cirrhosis. Orthotopic liver transplantation is the treatment of choice for PBC-related decompensated liver disease. Post-transplant recurrence of PBC could be seen in 10.9–42.3% of PBC patients and shows significant overlapping morphological features with acute cellular or chronic rejection.[10] Dr. Lin and her colleagues systemically summarized the clinical presentation and histopathologic features that are useful in the differential diagnosis of recurrent PBC with acute cellular rejection, plasma cell-rich rejection, and chronic rejection, as well as the common pitfalls leading to misinterpretation of liver biopsies in post-transplant patients for PBC.[11] The features to distinguish recurrent PBC from acute cellular and chronic rejections are effectively presented in this review.

We want to express our sincerest thanks to all authors for their fantastic and timely work and to the reviewers and editors for their valuable recommendations and comments for all papers published in this special issue. This special issue will greatly interest practicing pathologists and trainees who may encounter these rare and challenging cases daily.

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Conflict of interest

HW has been an editorial board member of the *Journal of Clinical and Translational Pathology* since 2021. The authors have no other conflicts of interest related to this publication.

Author contributions

Yin F and Wang H wrote and finalized the manuscript. All authors have read and approved the final manuscript.

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