Portal Hypertensive Enteropathy, Occult Bleeding, and Capsule Endoscopy: Where Do We Go from Here?

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Portal hypertension (PH) has many complications, some life-threatening. Historically, esophageal (EV) and gastric varices (GV), portal hypertensive gastropathy (PHG), and ascites were associated with PH [1]. Until just over a decade ago, the endoscopic examination of the small intestine was limited by its length. At the dawn of the millennium, deep enteroscopy (wireless or device-assisted) has been advanced by the advent of double-balloon technique and wireless capsule endoscopy (CE) [2, 3]. Since then, deep enteroscopy has identified portal hypertensive enteropathy (PHE) as a potentially significant complication of PH [4]. Due to its inherent advantages, CE has the latter has become the preferred method for PHE detection, particularly in the West [2].

Patients with advanced liver disease run an increased risk of gastrointestinal (GI) bleeding. In cirrhotic patients with chronic GI blood loss, with no obvious bleeding source visualized with bidirectional digestive endoscopy, PHE should be considered [5]. Nevertheless, whether it is necessary to routinely perform pan-enteroscopy in patients with PH with no evidence of obscure gastrointestinal bleeding (OGIB) is still a matter of continuing clinical research [6].

Documentation of PHE with small bowel CE is becoming more frequent [4, 5]. A consensus has emerged with regard to the type and distribution of small intestine mucosal abnormalities that constitute PHE [4, 5, 7]. The characteristic lesions of PHE include red spots indicative of arteriovenous malformations, patchy mucosal erythema,

diffuse mucosal edema (so-called ‘herring-rope’ appearance), varices, and spontaneous mucosal bleeding [8, 9]. However, the prevalence of PHE ranges between 20 and 90 % [4, 5]. Furthermore, only a few studies have considered other clinical factors associated with the presence of PHE with conflicting results.

In 2005, De Palma et al. were one of the first groups to use CE to study the type and prevalence of PH-related small intestinal lesions in a group of patients with liver cirrhosis of different etiologies, complicated by PH and anemia. In comparison with a control population diagnosed with irritable bowel syndrome, they essentially redefined PHE in the era of CE, reporting that large esophageal varices, PHG, portal hypertensive colopathy (PHC), and severe liver disease (Child–Pugh class C) are associated with the presence of PHE [7]. Conversely, the etiology of liver cirrhosis, patient gender, and history of EV hemorrhage were not associated with the presence of PHE. More recently, another landmark study by Abdelaal et al. [10] reported that CE findings consistent with PHE were present in 67.7 % of patients with liver cirrhosis. They were more common in patients with high liver stiffness as measured by FibroScan®, higher Child–Pugh score, large EVs, PHG, and a history of endoscopic EV sclerotherapy or band ligation. Furthermore, they refined the currently used classification of PHE CE findings into four main types: (1) red spots; (2) angiectasia; (3) small intestinal varices; and (4) inflammatory-like lesions [4, 8–10]. More importantly, however, Abdelaal et al. introduced the concept of combining auxiliary data such as transient elastography with more conventional clinical data in an attempt to select a patient population in risk for PHE. Takahashi et al. [11] reported that in CE, mucosal edema, unlike red spots and angiectasia, correlated well with the hepatic venous pressure gradient (HVPG). The latter had no significant

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correlation with either the presence or the stage of small intestine findings, the number of indirect signs of PH, or the type of intra-abdominal collaterals [12].

In PH, EVs and GVs conduct ~90 % of the portal blood flow, increasing in number and caliber over time, following the law of Laplace governing flow rate and diameter [5]. By inference, small intestine varices should follow a similar natural history. Additionally, abdominal computed tomography (CT) data, quantitative and non-invasive, should facilitate a more accurate classification of small intestine PHE-related CE findings such as mucosal and mural edema and varices.

In the retrospective multicenter study of Jeon et al. [13] published in this issue of *Digestive Diseases and Sciences*, the investigators formulated a clinically useful correlation between PHE (diagnosed by CE) and the presence of predictive factors associated with background liver disease. More importantly, they introduced a CT scan score—based on the presence of EV, GV, peri-umbilical collaterals, PHG, PHC, portal hypertensive cholecystopathy, splenomegaly, and ascites—as predictor of PHE in CE. Although the population size is typical of most single-center studies [4, 5], this remains the first collaborative effort in this area. Going through the Korean Nationwide CE registry for a 10-year period, the authors identified 45 patients with cirrhosis and no underlying small intestine disease, no concomitant severe cardiopulmonary or renal end-stage disease or any prior use of anticoagulants or non-steroidal anti-inflammatory drugs, who were then divided into two subgroups; those with PHE visualized with CE ($n = 18$) and those with no CE evidence of PHE ($n = 27$). The authors used validated scores to grade EVs, PHG, and small intestine CE findings.

As expected, there was heterogeneity of the type of capsule endoscopes used and the type of pre-procedure small intestine preparation. In the univariate analysis, Child–Pugh class C and a CT score >3 points were significantly associated with PHE. Nonetheless, in the multivariate analysis, only a high CT score was significantly associated with PHE [odds ratio (OR) 11.19, 95 % confidence interval (CI), 1.59 – ∞ , $p = 0.040$]. Furthermore, no difference between the two subgroups was present with regard to the indication for the CE procedure, the type of CE model used, the pre-procedure small intestine preparation, the quality of CE images obtained, and the completion rate of CE. There were more P2-grade CE findings [14], i.e., lesions considered to have a high potential for bleeding in the PHE subgroup, as compared with those present in the subgroup of patients with liver cirrhosis but no PHE. In concordance with previous studies, PHE-related CE findings were more common in those with severe liver disease (Child–Pugh C), EV, GV, PHG, and PHC, despite not reaching statistical significance. However, the

overall prevalence of PHE was 40 %, much lower than reported in recent studies. This is likely due to prior over-interpretation of CE findings or use of varying CE criteria. Arguably, the presence of small intestine varices in the PHE group is similar to that reported previously [10, 11]. Since red spots and small intestine wall edema are major components of congestive enteropathy, these subtle findings can be underreported [15].

The authors admit to a number of study limitations. First and foremost, the number of patients seems small for a multicenter study. Secondly, there was lack of a control group. Thirdly, they report a possible selection bias as the Korean Nationwide Database includes only tertiary referral centers. Lastly, the components of the proposed CT score have not been validated. However, a novel aspect of this study—for which the authors should be praised—is their correlation of PHE CE findings with CT scan findings, resulting in the formulation of a composite selection tool. The composite CT scan score correlated well with the presence of PHE findings in patients with liver disease who underwent CE. This is probably because the components of the CT score i.e., EV, GV, peri-umbilical collaterals, PHG, PHC, portal hypertensive cholecystopathy, splenomegaly, and ascites are well-known clinical indicators of PH.

Further questions still remain unanswered. All studies (including the one by Jeon et al.) have small numbers of patients, ‘clouding’ the clinical significance of PHE. In patients with cirrhosis and obscure GI bleeding or chronic anemia, PHE provides a plausible explanation for GI blood loss; yet, its prognostic value and correlation with morbidity and mortality remain unclear. With the advent of the SmartPill®, data regarding intestinal transit times in patients with decompensated liver disease are gradually becoming available. Therefore, it is expected that such data will likely enhance the understanding of PHE pathogenesis [16]. On the other hand, CE luminal, two-dimensional images of a structure which twists and curls constantly, impairing interpretation. Moreover, inherent weaknesses of the current CE technology, such as lack of insufflation and/or three-dimensional imaging, are extra factors that may interfere with the diagnostic accuracy of wireless endoscopy. In the recently launched Sonopill® project, ultrasound imaging will likely extend the diagnostic capabilities of future capsule models [17]. This is supported by extensive pre-clinical studies demonstrating the complementary nature of ultrasonic and optical imaging. Furthermore, studies on multimodal diagnosis capsule devices manoeuvrability as they traverse the GI tract, are necessary. Therefore, the multifunctional capsule of the future will likely be able to provide a wealth of data currently only collected from separate studies. Studies like the one authored by Jeon et al. remind us, more than anything else, of the need to press ahead on this path.

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