REVIEW

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Adenocarcinoma of the ileum: literature insights on pyloric gland metaplasia

BOGDAN STANCU[1)], RĂZVAN ALEXANDRU CIOCAN[2)], MARIUS GEORGE TEODORESCU[3)], DOINIŢA CRIŞAN[4)], FLORIN VASILE MIHĂILEANU[1)], ŞTEFAN URSU[2)], LIVIU TARTACOVSCHI[5)], ŞTEFAN LUCIAN POPA[6)], CLAUDIA DIANA GHERMAN[2)], OCTAVIAN AUREL ANDERCOU[1)]

[1)]*Second Department of Surgery, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania*

[2)]*Department of Surgery–Practical Abilities, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania*

[3)]*Department of Morphological Sciences, Emergency County Clinical Hospital, Cluj-Napoca, Romania*

[4)]*Department of Morphological Sciences, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania*

[5)]*Second Department of General Surgery, Emergency County Clinical Hospital, Cluj-Napoca, Romania*

[6)]*Second Department of Internal Medicine, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania*

Abstract

Adenocarcinoma (ADK) of the ileum is an infrequent cancer that poses significant diagnostic and treatment difficulties. This article analyses the existing case literature to investigate the correlation between pyloric gland metaplasia (PGM) and the onset of ileal ADK. PGM, defined by the atypical transformation of intestinal epithelial cells into gastric-type mucosa, has been recognized as a possible precursor lesion in the spectrum of several gastrointestinal malignancies. We intend to clarify the clinical characteristics, histological results, and outcomes linked to ileal ADK originating from PGM through an exhaustive examination of recorded cases. Our findings indicate that early identification of metaplastic alterations may be essential for enhancing prognosis and informing therapeutic choices. This study emphasizes the need for additional research to elucidate the mechanisms driving this transition and to improve diagnostic precision in clinical practice.

Keywords: adenocarcinoma, ileum, pyloric gland metaplasia, gastrointestinal cancer, precursors, histology.

Introduction

Small bowel adenocarcinoma (ADK) is a rarely encountered entity that accounts for <5% of all gastrointestinal (GI) tract malignancies. Its etiology is indeed vast, including specific dietary habits, chronic inflammatory disorders and hereditary syndromes associated with an increased risk of developing intestinal polyps [1]. Chronic inflammation has been previously linked to variation in intestinal tumor morphology, with ADKs arising in an inflammatory bowel disease (IBD) setting often displaying a gastric phenotype. However, this behavior was scarcely observed in association with tumors affecting individuals with no prior history of bowel disease [2, 3].

Pyloric gland metaplasia (PGM) has been increasingly recognized as a potential precursor to ADK in the ileum, especially in patients without a prior history of chronic IBD. The transformation of intestinal epithelium into gastric mucosa, particularly the pyloric gland type, is thought to occur as a response to injury or inflammation, creating a microenvironment that may promote carcinogenesis [4, 5]. Despite this, the role of PGM in the development of ileal ADK remains underexplored in medical literature. Through a detailed analysis of reported cases, we seek to elucidate the histopathological features, clinical presentation, and potential diagnostic markers of this rare but significant association. By enhancing our understanding of this relationship, we hope to provide insights into early diagnosis and improved management of ileal ADK, a cancer that is often detected at advanced stages and associated with poor prognosis.

Aim

The aim of this article was to provide a detailed understanding of the link between PGM and ileal ADK, while also identifying gaps in current research that warrant further investigation.

Study selection for systematic review

Articles published in English in the online databases *PubMed* (*Medline*), *Embase*, and *Clarivate Web of Science* were analyzed from January 2014 to September 2024.

The study utilized the keywords: "ileum adenocarcinoma" OR "small bowel adenocarcinoma" AND "pyloric gland" AND "metaplasia," employing "AND" and "OR" as Boolean operators among the specified terms. All English titles published during a specific 10-year period were evaluated for eligibility by two independent researchers based on title and abstract to eliminate duplicates.

Inclusion criteria: all papers containing information regarding the pathophysiology, histology, and clinical manifestations of ileal ADK; study classification: original paper, clinical trial, and randomized controlled trial; subject categories: patients, cell cultures, or animals (Figure 1).

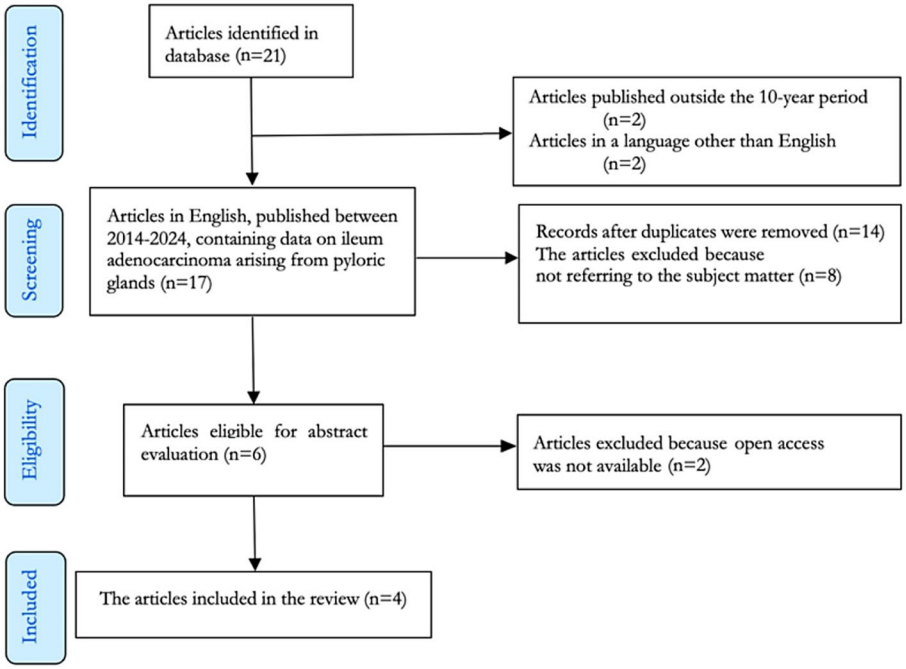

Figure 1 – ***PRISMA flow diagram for the selected studies included in the systematic review (records identified from PubMed, Embase and Web of Science–Clarivate Analytics databases). PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses.***

Exclusion criteria: articles published prior to 2014, irrelevant to the topic, letters to the editor, brief reports, meta-analyses, systematic reviews, narrative reviews, non-English publications, patients under 18 years of age, and articles unrelated to the subject matter.

During a time, window of 10 years, after searching the combination of keywords mentioned, and eliminating those published outside the timeline and the ones not written in English, a number of 17 articles were found. All duplicated articles, publications not referring to the matter, systematic reviews and open access restriction papers were eliminated, thus making four scientific papers eligible for this study containing data on pathogenesis, histopathology and clinical presentation of the small bowel ADK arising from pyloric glands.

Clinical and pathological aspects

This section discusses the clinical, pathological, and molecular features observed in patients with ileal ADK originating from PGM. The patients' clinical presentation, encompassing symptoms and diagnostic imaging, necessitates surgical intervention in most cases, thus facilitating a comprehensive pathological assessment. The principal histological characteristics, immunohistochemical (IHC) profiles, and tumor staging are described, emphasizing the tumor's correlation with PGM. Additionally, the analysis highlights the significance of human epidermal growth factor receptor 2 (HER2/neu) overexpression and its potential implications for treatment strategies.

Usually, the patients present weight loss and diffuse abdominal pain with a tendency of localization to the right lumbar and iliac regions, associated with episodic abdominal distension and changes in bowel habits. On physical examination, the abdomen is soft, with palpation evidencing localized tenderness of the right iliac region.

Esophagogastroduodenoscopy is unrevealing. The endoscopic evaluation of the large intestine does not find any pathological process but the impossibility to intubate and progress into the terminal ileum. An abdominal computed tomography scan is mandatory revealing a circumferential, non-obstructive thickening of the distal ileal wall, unmasking a potential intraluminal mass. An exploratory laparotomy identifies the protrusive mass located more often in the distal ileum, proximally from the ileocecal valve and an ileo-colectomy with primary anastomosis is the surgical procedure of election.

The ileal lumen contains an exophytic, well-demarcated, grey-white tumor, with the adjacent ileal mucosa displaying thickened plicae when compared to the normal ileal mucosal folds (Figure 2).

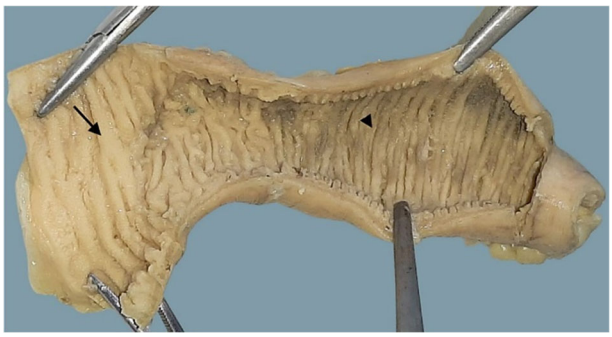

Figure 2 – ***Macroscopic appearance of the distal ileum. Markedly thickened mucosal folds (arrow) situated adjacent to the tumor (not depicted) in comparison to the normal ileal mucosa (arrowhead).***

On microscopic examination, there is an ADK with a mixed, tubular, papillary and solid, growth pattern (Figure 3, A and B), that infiltrates the intestinal wall, reaching the serosal adipose tissue. The *lamina propria* at the tumor periphery is occupied by multiple, Periodic Acid–Schiff (PAS)+, pyloric-type mucous glands abutting the *muscularis mucosae* (Figure 4, A and B).

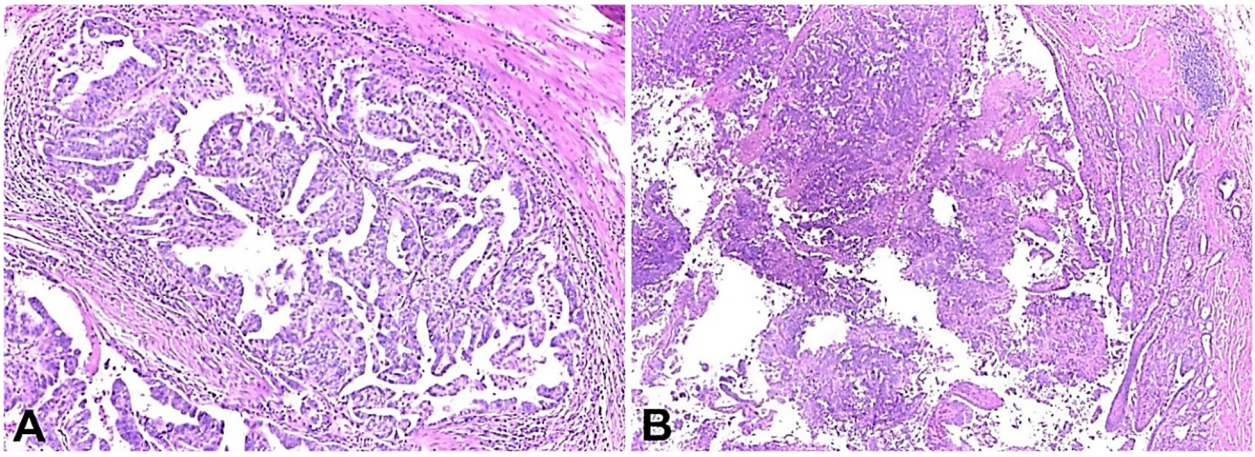

Figure 3 – ***Histopathological findings of the ileal mass: (A) Epithelial malignant proliferation displaying tubular and papillary morphology; (B) Photomicrograph showing solid growth areas within the same tumor; the adenocarcinomatous infiltration is apparent in the muscularis propria (serosal adipose tissue extension not depicted). HE staining: (A) ×100; (B) ×40. HE: Hematoxylin–Eosin.***

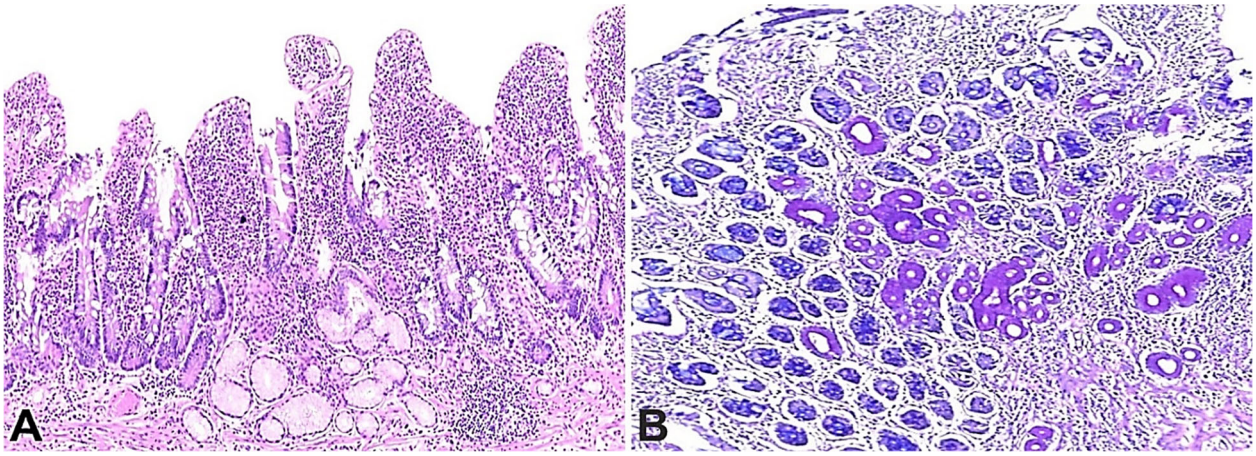

Figure 4 – ***Microscopic aspect of the peritumoral ileal mucosa: (A) Multiple foci of pyloric gland metaplasia abutting the muscularis mucosae; (B) Pyloric-type glands stained with PAS, in contrast to the AB affinity of the adjacent intestinal glands. HE staining: (A) ×100. PAS–AB staining: (B) ×100. AB: Alcian Blue; HE: Hematoxylin–Eosin; PAS: Periodic Acid–Schiff.***

IHC profile of the ADK is cytokeratin (CK)7+/CK20- (Figure 5, A and B), whereas the adjacent small bowel mucosa shows a weak, patchy reaction for CK7 and is CK20+ (Figure 6, A and B).

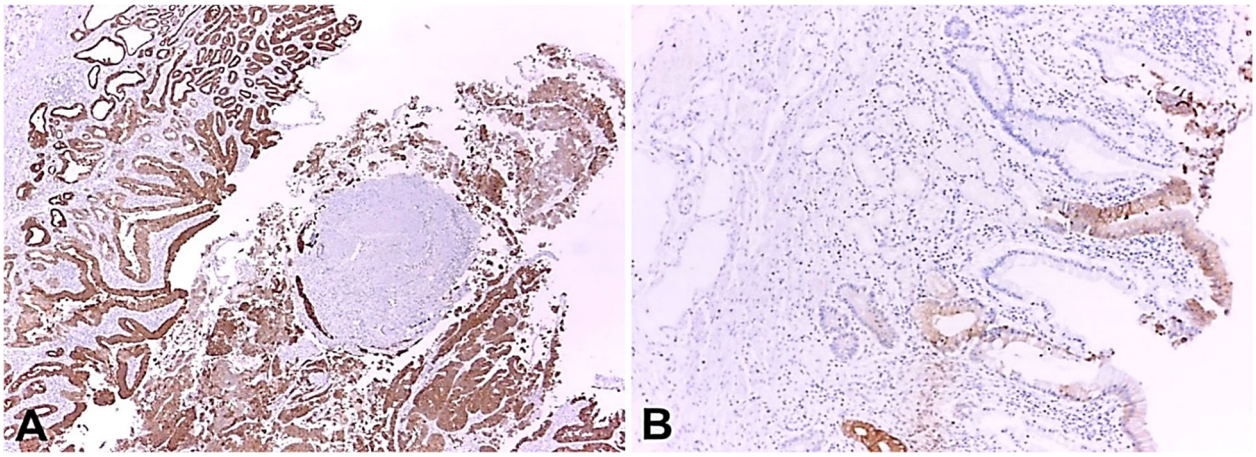

Figure 5 – ***Immunoreactivity for CK7: (A) The tumor showed a strong, diffuse reaction for CK7; (B) The adjacent intestinal mucosa was weakly and patchy positive for the same marker. Anti-CK7 antibody immunomarking: (A) ×40; (B) ×100. CK7: Cytokeratin 7.***

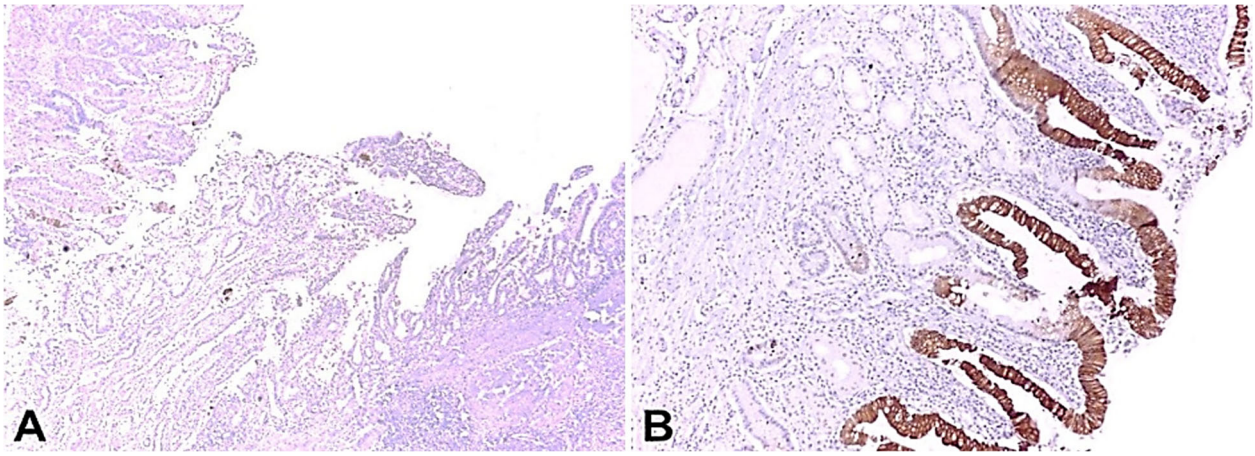

Figure 6 – ***Immunohistochemical study with CK20: (A) The malignant epithelial component was negative for CK20; (B) The adjacent intestinal mucosa was strongly positive for the same marker (left, center). Anti-CK20 antibody immunomarking: (A) ×40; (B) ×100. CK20: Cytokeratin 20.***

As a further matter, the malignant epithelial component is strongly positive (3+) for HER2/neu protein overexpression (Figure 7). Hereby, the diagnosis of invasive ADK, staged pT3, pN0 (0/21), pMx, G2, R0 according to the *American Joint Committee on Cancer* (AJCC) Staging Manual, accompanying multiple foci of PGM is performed.

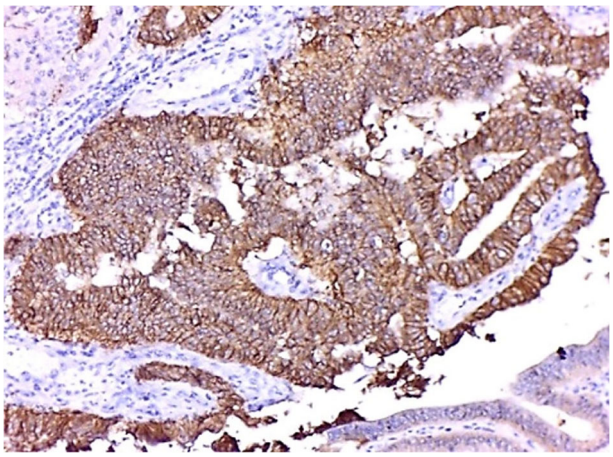

Figure 7 – ***HER2 oncoprotein overexpression. The tumor depicted a strong (3+) expression (right). Anti-HER2 antibody immunomarking, ×200. HER2: Human epidermal growth factor receptor 2.***

The pathological analysis demonstrates that the ADK exhibited tubular, papillary, and solid growth patterns, infiltrating the intestinal wall. The IHC study, particularly the strong HER2/neu positivity, suggests a molecular profile similar to gastric cancers, despite the tumor's ileal location. These findings reinforce the hypothesis that PGM, even without chronic inflammation, can undergo malignant transformation.

Discussions

The presence of ectopic gastric tissue throughout the small bowel, whether reported as heterotopic gastric mucosa (HGM) or gastric metaplasia (GM), is not a common occurrence, unless referred to as HGM in association with Meckel's diverticulum or other congenital abnormalities [2]. HGM is thought to be congenital in origin and histologically consists of gastric foveolar epithelium covering deeply situated gastric glands that usually contain parietal and chief cells; in contrast, GM (sometimes referred to as acquired HGM) is a rather postnatal attainment and can be further subdivided in a foveolar type and a pyloric gland type. While foveolar metaplasia is composed of epithelium harboring columnar cells with apical mucin vacuoles, the latter type cannot be reasonably distinguished from the mucinous glands found in the *lamina propria* of the pyloric mucosa [2, 6, 7]. Considering the above observations, it is plausible that our findings are part of the GM, pyloric gland-type spectrum.

One particularly striking aspect is that the GM arose as a sporadic event, from any recorded long-standing inflammatory process involving the ileal wall. It is well documented that prolonged intestinal inflammation is often accompanied by GM changes as an adaptive response to chronic mucosal injury. One article demonstrated that a significant proportion of the malignant neoplastic processes that may concern the small bowel show gastric differentiation. The finding was strongly associated with Crohn's disease-related small bowel ADKs, whereas sporadic small bowel ADKs expressed a gastric phenotype only exceptionally. The authors identified one such sporadic tumorous growth located in the ileum, with gastric tubular/mucinous morphology and devoid of peritumoral GM foci, also mentioning a sporadic jejunal malignant mass that asseverated intestinal and gastric tubular features and was accompanied by nearby GM of the mucosa [2, 8–10].

Simpson *et al.* presented an ileal epithelial tumor with a poorly differentiated component associated with adjacent dysplastic pyloric glands in a Crohn's disease patient [10]. There has been one report of a jejunal primary ADK expressing gastric differentiation in association with HGM [7]. Ultimately, an ADK with ileal localization originated in heterotopic gastric tissue with secondary *gastritis cystica profunda* changes [7, 11–13].

In comparison to other studies, the ADK arising from PGM in the ileum reveals a rare occurrence, primarily due to the absence of a chronic inflammatory background. Similar studies, such as Whitcomb *et al.* (2014), link GM to Crohn's disease, whereas in other cases it may suggest that PGM can sporadically result in ADK without preceding inflammation [2]. Furthermore, strong HER2/neu over-

expression aligns with findings in gastric-type cancers but remains rare in small bowel ADKs.

Other reports, like Chan *et al.* (2010), identified HER2/neu positivity only in a small percentage of small bowel tumors [13]. Furthermore, other papers like Miwa *et al.* (2023) have documented ADK developing from HGM, particularly in conditions like Meckel's diverticulum. In these instances, gastric-type tissue located in the small intestine exhibits similar malignant potential to that of PGM, suggesting that these metaplastic changes, though typically associated with congenital anomalies, may also occur sporadically without chronic inflammation [14–16].

On the contrary, another publication revealed a strong, HER2 (3+) reaction by IHC analysis, although this finding was limited to as little as 3.2% of the total number of ADKs assessed [17]. A more recently published article showed that the incidence of overexpression and amplification of the *HER2/ERBB2* gene remarkably decreased from foregut to midgut located tumors [18]. It is conceivable that, in correlation with the other gastric differentiation markers expressed, ADK has its origin from tissue belonging to the upper GI tract. What is more, it is one of the very few ADKs associated with heterotopic gastric tissue, expressing a strong HER2 (3+) IHC profile, with another relevant example being confined to a small bowel duplication [19].

Furthermore, Frank's postulate from decades ago – that GM cells might possess an increased malignant transformation potential – remains of staggering actuality and should undoubtedly engage the necessity to clarify the mechanisms of malignant transformation from PGM and to enhance diagnostic precision in clinical practice [19].

Gastric cells metaplasia undergoes genetic changes that alter their cellular phenotype, migration, invasion and proliferation capacity, transforming into tumor cells [20]. They create a tumor microenvironment that allows them to increase their capacity for proliferation, local invasion and metastasis [21, 22].

Conclusions

The presence of PGM as a precursor to ileal ADK emphasizes the importance of recognizing and understanding metaplastic changes in the GI tract, particularly in patients without a prior history of bowel disease or chronic inflammation. The early identification of metaplastic alterations may be essential for enhancing prognosis and informing therapeutic choices for the ADK of the ileum arising from PGM. The rare association of strong HER2/neu protein overexpression suggests that early identification and histopathological analysis of metaplastic lesions could play a crucial role in improving prognosis and guiding treatment decisions.

Conflict of interests

The authors have no conflict of interests.

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Corresponding author

Răzvan Alexandru Ciocan, Lecturer, MD, PhD, Department of Surgery–Practical Abilities, Iuliu Haţieganu University of Medicine and Pharmacy, 23 Gheorghe Marinescu Street, 400337 Cluj-Napoca, Romania; Phone +40753–080 411, e-mail: razvan.ciocan@umfcluj.ro

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