

Case Series

Running Title: Small-Bowel Metastasis in Lung Cancer

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Rare Small-Bowel Metastases from Lung Cancer: Diagnostic and Clinical Challenges

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Abstract

Lung cancer remains the leading cause of cancer-related mortality worldwide, with most patients diagnosed at a metastatic stage. The common metastatic sites include the brain, bone, adrenal glands, and liver. Advances in molecular profiling and the introduction of targeted therapies and immune checkpoint inhibitors have improved survival, leading to the occurrence of metastases in uncommon sites such as the small bowel. Small-bowel metastases from lung cancer are extremely rare and often present with nonspecific symptoms like anemia or abdominal pain, causing delayed diagnosis. These patients may develop life-threatening complications, including obstruction, perforation, or bleeding, requiring urgent surgery.

In this paper, we report two patients with lung cancer who developed symptomatic small-bowel metastases. The first, a 54-year-old woman with metastatic poorly differentiated lung carcinoma, achieved prolonged disease control with chemotherapy and nivolumab but later presented with melena and obstruction. Imaging revealed an ileal mass, and surgical resection confirmed metastasis of poorly differentiated carcinoma consistent with pulmonary origin.

The second, a 74-year-old man with SMARCA4-deficient undifferentiated carcinoma, responded partially to chemoimmunotherapy but later developed ileal perforation requiring emergency surgery, which confirmed metastatic spread.

Small-bowel metastases from lung cancer are exceedingly rare but clinically significant. Although prognosis is generally poor, timely surgical intervention integrated with systemic therapy can provide symptom relief and, in selected cases, extend survival. Clinicians should remain alert to the possibility of gastrointestinal metastases in lung cancer patients presenting with abdominal symptoms, as early recognition may be lifesaving.

Keywords: Lung neoplasms, Intestinal neoplasms, Secondary, Intestinal perforation, Neoplasm metastasis

Introduction

According to the most recent global cancer statistics (2022), lung cancer accounts for

approximately 2.48 million new cases and 1.82 million deaths worldwide, remaining the leading cause of cancer-related mortality in both men and women.¹ Despite advances in prevention, approximately 50% of cases present with metastasis at the time of diagnosis.²

Recent analyses show that in lung cancer, the most frequent metastatic sites are the brain (~29%), bone (~25%), adrenal glands (~15%), and liver (~13%).³

Recent advances in molecular profiling have enabled more personalized treatment approaches in lung cancer, with current systemic strategies primarily based on targeted agents and immune checkpoint inhibitors that have significantly improved survival outcomes. The prolonged survival achieved with these novel therapies has facilitated the occurrence of atypical metastases, such as small intestinal involvement, in the long-term disease course.²

Among patients with lung cancer, the clinical incidence of gastrointestinal (GI) metastases is <2%, whereas autopsy series report rates of 5%–14%; the small bowel is the most commonly affected segment.^{4, 5}

Clinically apparent GI metastases from lung cancer are considered rare. GI metastasis is frequently discovered only after severe complications—such as intestinal obstruction, perforation, bleeding, or intussusception—which may be life-threatening and necessitate emergency surgery.⁶

The prognosis for patients with small intestinal metastasis secondary to lung cancer is extremely poor. However, timely diagnosis and appropriate treatment may prolong survival. Due to its low incidence and diagnostic difficulty, there is still no consensus regarding the optimal management of these patients, who often present with high mortality.

A better understanding of the clinical course of primary lung cancer cases with small-bowel metastases will help facilitate early diagnosis and more effective management. The present report describes two rare cases of small intestinal metastasis originating from lung cancer. This case series was written in accordance with the CARE (Case Report) guidelines and reporting checklist.

Case Presentation

Case 1

A 54-year-old woman with a history of hypertension and a family history of leukemia (sister) and breast cancer (aunt) was diagnosed in April 2023 with metastatic poorly-differentiated lung carcinoma after presenting with a subcutaneous lesion in the left upper abdominal wall. The assay used was next-generation sequencing. Additionally, the programmed death-ligand 1 (PD-L1) tumor proportion score, assessed using Dako immunohistochemistry (IHC), was less than 1%. Both tests were performed at Baskent University Ankara Hospital. Initial staging with positron emission tomography-computed tomography (PET-CT) demonstrated a 3.3 × 2.7 cm necrotic mass encasing the right lower lobe bronchus, multiple subcutaneous, intramuscular, and bone metastases. Chemotherapy with paclitaxel and carboplatin was initiated. After four cycles, radiographic progression was documented, and second-line nivolumab was initiated.

After 18 cycles of nivolumab, the patient presented to the emergency department with acute loss of consciousness. Comprehensive evaluation indicated immune-mediated encephalitis attributable to immunotherapy. Concurrent imaging demonstrated disease progression, and systemic therapy was subsequently discontinued. Pemetrexed was initiated as third-line therapy. In March 2025, she presented with melena,

vomiting, and anemia (hemoglobin: 7.7 g/dL). Abdominal CT revealed a 6 × 4.6 cm enhancing intraluminal mass within the ileum, associated with secondary dilatation of the proximal jejunal segments and prominent air–fluid levels (Figure 1).

The lesion was accompanied by necrotic mesenteric lymphadenopathy and newly developed liver metastases. Given the obstructive and hemorrhagic features, she underwent urgent segmental ileal resection with primary anastomosis.

Histopathological examination revealed a malignant epithelial neoplasm infiltrating from the serosal surface toward the mucosal epithelium of the small intestine, accompanied by extensive surface erosion and ulceration. The tumor consisted of markedly pleomorphic cells with abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli. Diffuse lymphatic invasion was evident. The neoplastic proliferation displayed a solid and diffusely infiltrative growth pattern without glandular differentiation in the examined sections.

Immunohistochemical analysis demonstrated strong membranous and cytoplasmic positivity for Pan-cytokeratin (PanCK) in the tumor cells (Figure 2).

Taken together, the histomorphological features and immunophenotype were consistent with a poorly-differentiated carcinoma exhibiting a diffuse infiltrative pattern. Given the patient's clinical history of primary pulmonary carcinoma, and the morphologic concordance with the previously obtained lung biopsy specimen, the lesion was interpreted as a small-bowel metastasis originating from the primary poorly-differentiated lung carcinoma.

After surgery, the patient's Eastern Cooperative Oncology Group (ECOG) performance status deteriorated, and she was transitioned to best supportive care. On April 10, 2025, the patient was admitted to the

intensive care unit with septic shock and subsequently died.

Case 2

A 74-year-old man with a 50 pack-year smoking history, prior coronary artery bypass surgery, and chronic kidney disease presented in April 2024 with a persistent cough and left-sided chest pain. Chest CT revealed multiple nodular lesions in the left lung, the largest measuring 40 × 37 mm. PET-CT demonstrated hypermetabolic activity in the lung, adrenal glands, and bone. Transthoracic biopsy did not reveal definitive adenocarcinoma or squamous differentiation. Immunohistochemical analysis showed synaptophysin positivity, findings consistent with SMARCA4-deficient undifferentiated carcinoma. Molecular profiling using next-generation sequencing was negative for *EGFR*, *ALK*, *ROS1*, and *BRAF* mutations. The PD-L1 tumor proportion score, evaluated using Dako IHC, was 20%.

Both tests were performed at Baskent University Ankara Hospital. First-line systemic therapy with pemetrexed, carboplatin, and pembrolizumab was initiated in May 2024. After three cycles, partial radiographic regression was observed. Following six cycles, treatment was modified to pembrolizumab and pemetrexed due to renal dysfunction, as nephrology consultation excluded immune-related nephropathy.

Imaging for treatment response demonstrated two new bone metastases, a solitary frontal brain lesion, and focal fluorodeoxyglucose (FDG) uptake in the terminal ileum. During multidisciplinary tumor board discussion, the disease was determined to represent oligoprogression. Stereotactic radiotherapy was administered to the bone and brain lesions, followed by the continuation of pemetrexed and pembrolizumab. Colonoscopy revealed only hyperplastic colonic polyps, and capsule endoscopy was deferred; the ileal lesion was managed with surveillance.

In March 2025, PET-CT showed enlargement and increased FDG avidity of the small-bowel lesion, while pulmonary disease remained stable (Figure 3a).

On March 9, the patient presented with acute abdominal pain and vomiting. Abdominal CT demonstrated pneumoperitoneum consistent with intestinal perforation, jejuno-ileal dilatation with air–fluid levels, and a distal ileal mass measuring 13.7×3.4 cm (Figure 3c,d). Emergency laparotomy with small-bowel resection and primary anastomosis was performed. Histopathological examination of the resected proximal ileum–jejunum tumor revealed malignant epithelial tumor cells infiltrating from the serosal surface into the subepithelial layers of the small intestine. The tumor cells appeared pleomorphic, possessing abundant eosinophilic cytoplasm, vesicular nuclei, and one to two conspicuous nucleoli, with numerous mitotic figures identified. Extensive lymphatic invasion was also observed within the tumor. Immunohistochemically, the neoplastic cells exhibited membranous and cytoplasmic positivity for Pan-cytokeratin (PanCK), epithelial membrane antigen (EMA), and Ber-EP4 epithelial antigen (BerEp4) (Figure 4).

In correlation with the morphological appearance, immunohistochemical profile, and the patient's clinical information, the lesion was interpreted as a poorly-differentiated carcinoma with undifferentiated features, considered most consistent with metastasis from the primary pulmonary tumor.

At postoperative follow-up, the patient's ECOG performance status returned to baseline, and treatment with pemetrexed and pembrolizumab was resumed. Subsequent progression with new liver lesions and

enlargement of pulmonary disease prompted initiation of paclitaxel plus carboplatin, with response assessment planned after three cycles.

Ethics statement

This case series was approved by the Başkent University Institutional Review Board/Ethics Committee (Approval No. KA25/393). Owing to the non-interventional and anonymized design of this case series, the requirement for written informed consent for participation was waived by the Ethics Committee. Nevertheless, written informed consent for publication of clinical data and images was obtained from both patients included in this case series. For the deceased patient, written informed consent for publication of clinical data and images was obtained from the patient's next of kin.

Discussion

Small-bowel metastasis from primary lung cancer is exceedingly rare but clinically significant, as delayed recognition can result in catastrophic complications. In the past ten years, only sporadic case reports have been published, underscoring how easily this pattern of spread may be overlooked in daily practice. Our two cases add to this limited evidence, emphasizing that GI metastasis should be considered whenever lung-cancer patients develop unexplained abdominal symptoms.

GI metastases are generally absent at the time of initial lung cancer diagnosis and more commonly emerge during disease progression or follow-up, making recognition challenging until symptoms evolve. Cross-sectional imaging such as CT or PET-CT may reveal enhancing or hypermetabolic intraluminal lesions, yet sensitivity is limited for subtle disease; moreover, distinguishing whether such lesions represent a second primary malignancy or metastatic disease is often not possible on imaging alone. Invasive

investigations, including device-assisted enteroscopy, can occasionally provide histologic confirmation when bleeding is obscure; motorized spiral enteroscopy has recently been reported as a decisive tool in otherwise elusive cases.⁷

In our series, the first patient presented with melena and anemia accompanied by radiologic evidence of small-bowel obstruction, which led to urgent surgical resection and histologic confirmation of pulmonary metastasis. The second patient had been under radiologic surveillance when he developed acute abdominal pain; subsequent imaging revealed pneumoperitoneum and an ileal mass, and the diagnosis of small-bowel metastasis was established at surgery and confirmed pathologically. These presentations—GI bleeding with obstructive features in one case and radiologically detected perforation in the other—closely parallel the spectrum described in the literature, where most patients present either with overt bleeding or with acute abdomen due to obstruction or perforation.⁸⁻¹²

In both of our cases, surgical pathology provided definitive confirmation of small-bowel metastasis. In the first patient, histology and IHC demonstrated an intraluminal ileal tumor consistent with pulmonary adenocarcinoma. In the second patient, the resected proximal ileum–jejunum specimen revealed an undifferentiated tumor with synaptophysin positivity, morphologically and immunophenotypically concordant with the pulmonary primary. Histologically, adenocarcinoma remains the most common lung cancer subtype to metastasize to the small bowel, but pleomorphic carcinoma and small-cell carcinoma have also been implicated, often in cases with aggressive presentations.^{8, 11, 13}

Regarding anatomic distribution, the ileum and jejunum are the most frequently affected sites, while duodenal involvement, though

rare, has also been described.^{14, 15} The small bowel is in fact recognized as the most common site of GI involvement by lung cancer metastases, whereas gastric and colonic lesions are distinctly uncommon.¹²

This pattern was mirrored in our series, one patient harboring an ileal lesion and the other a proximal ileum–jejunum mass. An apparent propensity for distal small-bowel involvement has been attributed to the rich submucosal vascular network that may facilitate hematogenous dissemination, although this remains speculative. Much of this knowledge has been derived from accumulated case reports in which surgical exploration, intraoperative findings, and subsequent histopathology enabled precise localization. Advances in modern imaging, particularly PET-CT, has further contributed to the detection of metabolically active intraluminal disease, while device-assisted enteroscopy has on occasion permitted direct visualization and biopsy. Collectively, these complementary approaches have deepened our understanding of the distribution and biological behavior of small-bowel metastases from lung cancer.

Treatment strategy is driven by clinical urgency. Most patients require emergency surgical resection due to bleeding, obstruction, or perforation, with the dual goals of palliation and histologic confirmation.^{10, 11} Both of our patients underwent urgent resection for life-threatening complications, which not only alleviated symptoms but also permitted continuation of systemic therapy. Although overall prognosis remains poor once small-bowel metastases occur, recent reports suggest that timely surgery can stabilize patients sufficiently to allow further systemic treatment, thereby improving quality of life and, in selected cases, extending survival.^{9, 12} These observations, together with our experience, indicate that aggressive local management of GI complications, when

combined with modern systemic therapy, may offer substantial benefit even in the setting of disseminated lung cancer.

In conclusion, small-bowel metastases from lung cancer are exceedingly rare but clinically significant, most often manifesting with bleeding, obstruction, or perforation during the course of disease progression. Our review of recent reports, together with two illustrative cases, highlights that the ileum and jejunum are the most frequent sites of involvement, whereas gastric and colonic metastases are distinctly uncommon. Diagnosis is often delayed due to nonspecific presentation and limitations of imaging, yet surgical pathology and IHC remain crucial for confirmation. Although overall prognosis is poor, timely surgical intervention integrated with systemic therapy can provide symptom relief and, in selected cases, extend survival.

Conclusion

Small-bowel metastases from lung cancer are exceedingly rare but clinically significant. Prognosis is generally poor, yet timely surgical intervention integrated with systemic therapy can provide symptom relief and, in selected cases, extend survival. Clinicians should remain alert to the possibility of GI metastases in lung cancer patients presenting with abdominal symptoms, as early recognition may be lifesaving.

Informed Consent

Written informed consent was obtained from both patients included in this case series. For the deceased patient, informed consent for publication of clinical data and images was obtained from her next of kin.

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Authors' Contributions

A.F. contributed to the study conception and design, collected and interpreted the clinical data, and drafted the manuscript. D.M. reviewed and interpreted the radiological findings and critically revised the manuscript. A.O. and O.A. contributed to the study design, supervised the work, and critically reviewed the manuscript for important intellectual content. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

None declared.

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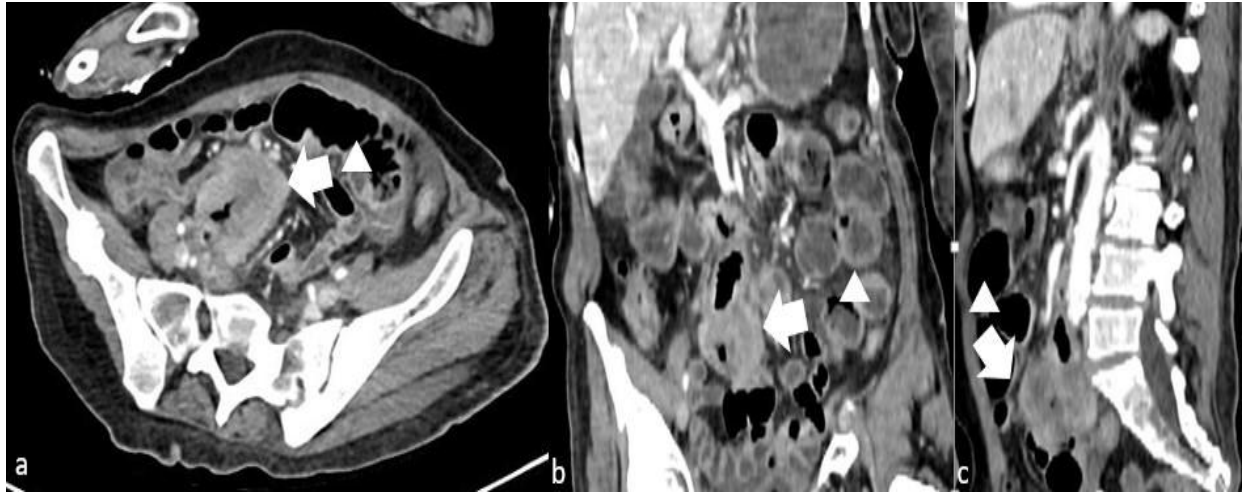


Figure 1. Axial (a), coronal (b), and sagittal (c) contrast-enhanced CT images obtained during the portal venous phase with soft-tissue windowing demonstrate a necrotic mass measuring 6×4.6 cm in the distal ileal segment (white arrows). The regions marked by triangles in panels a, b, and c indicate dilatation of proximal small-bowel loops and air–fluid levels secondary to obstruction caused by the mass.

CT: Computed tomography

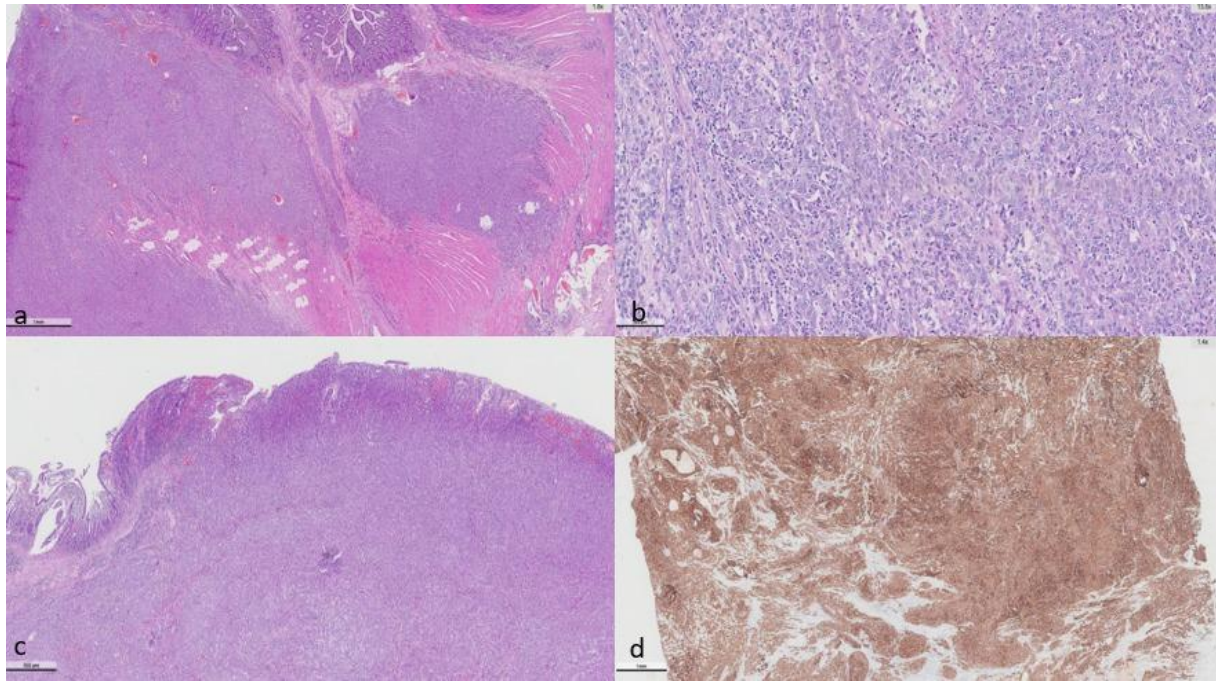


Figure 2. (a–c) H&E staining demonstrates malignant epithelial infiltration extending from the serosal surface into the subepithelial layers of the small intestine. The tumor displays marked pleomorphism, abundant eosinophilic cytoplasm, vesicular nuclei, prominent nucleoli, frequent mitoses, and evident lymphatic invasion (original magnification $\times 200$). (d) Immunohistochemical staining for PanCK demonstrates diffuse membranous and cytoplasmic positivity, supporting epithelial lineage (original magnification $\times 200$).

H&E: Hematoxylin and eosin; PanCK: Pan-cytokeratin

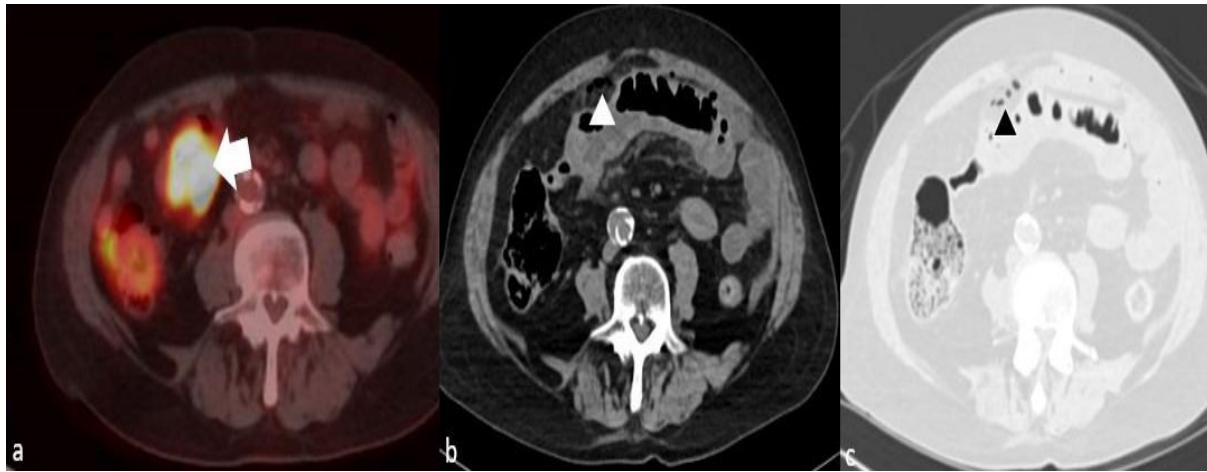


Figure 3. (a) Axial PET-CT image demonstrates intense FDG uptake within a necrotic mass located in the distal ileal segment (white arrow). (b) Axial non-contrast-enhanced abdominal CT reveals free air (white triangle) adjacent to the tumor, indicative of perforation. (c) Axial lung window image of the non-contrast CT more clearly visualizes the free air (black triangle).
PET-CT: Positron emission tomography-computed tomography; FDG: fluorodeoxyglucose; CT: computed tomography

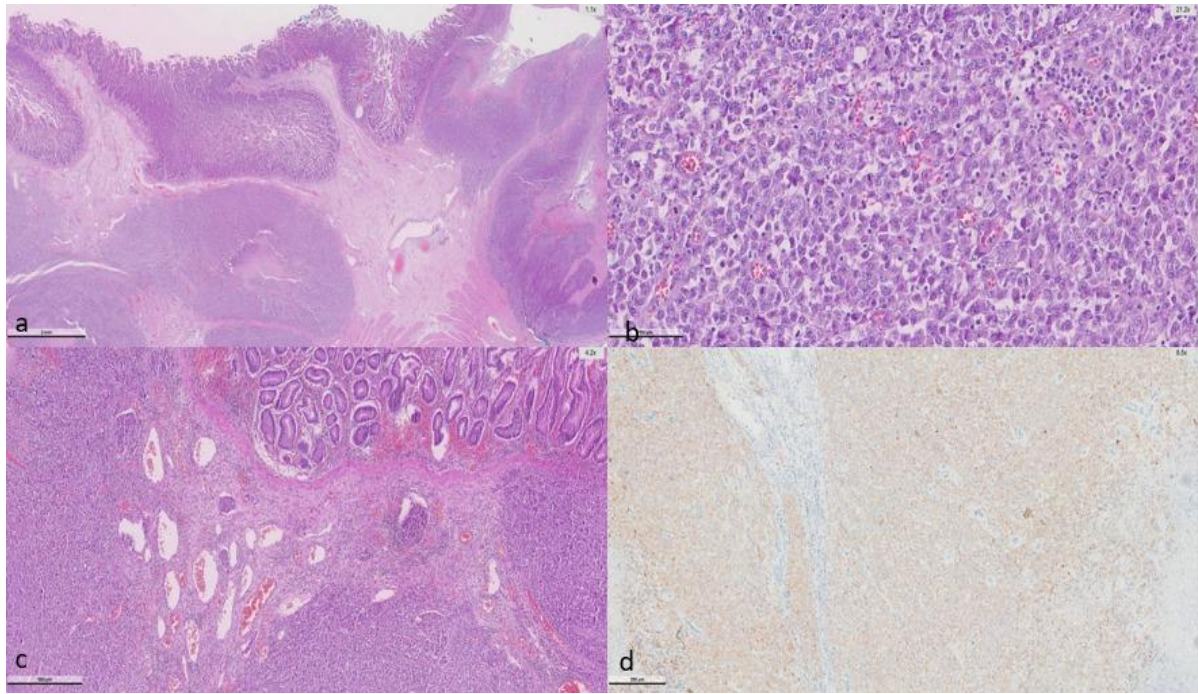


Figure 4. (a–c) H&E staining demonstrates malignant epithelial cells infiltrating from the serosal surface into the subepithelial layers of the small intestine, showing marked pleomorphism with eosinophilic cytoplasm, vesicular nuclei, and frequent mitoses (original magnification $\times 200$). (d) Immunohistochemical staining for PanCK demonstrates strong cytoplasmic and membranous positivity, confirming epithelial origin and supporting metastatic carcinoma (original magnification $\times 200$).

H&E: Hematoxylin and eosin; PanCK: Pan-cytokeratin