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Primary ileal squamous cell carcinoma: A case report and review of literature

Li QQ *et al.* A case report of PISCC

Abstract

BACKGROUND

Primary ileal squamous cell carcinoma (PISCC) is a rare malignant tumor of the ileum. Its development is an exceptional phenomenon, as the ileal mucosa is lined exclusively by simple columnar epithelium, with no native squamous epithelium under physiological conditions. PISCC accounts for fewer than 0.001% of all intestinal malignancies. As of 2025, only 12 confirmed cases have been documented in the global literature, predominantly as isolated case reports.

CASE SUMMARY

A 47-year-old female developed abdominal pain two years after chemotherapy for ovarian low-grade serous carcinoma (International Federation of Gynecology and Obstetrics stage IC1). Positron emission tomography/computed tomography showed localized thickening of the small intestinal wall in the right pelvic region with increased metabolic activity, suggesting implantation metastasis. The patient underwent partial ileal resection, intestinal anastomosis, appendectomy, omentectomy, and pericolic lymphadenectomy. Histopathological and immunohistochemical analyses confirmed a primary ileal low-grade squamous cell carcinoma. Postoperatively, the patient received intravenous doxorubicin plus carboplatin combined with anti-angiogenic targeted therapy. After six cycles, the regimen was changed to paclitaxel plus carboplatin with bevacizumab. Following five cycles, maintenance therapy with intravenous bevacizumab monotherapy was initiated, supplemented with adjunctive hepatoprotective agents. At the 30-month postoperative follow-up, the patient remained progression-free with no clinical or radiologic evidence of recurrence or distant metastasis.

CONCLUSION

Accurate diagnosis of PISCC requires integration of clinical history, systemic examination, histopathology, and immunohistochemical profiling to reduce misdiagnosis and missed diagnosis.

Key Words: Small intestinal neoplasms; Ileal squamous cell carcinoma; Immunophenotype; Clinical characteristics; Pathogenesis; Clinicopathology; Case report

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Core Tip: Primary ileal squamous cell carcinoma represents a paradox, as it arises in the ileal mucosa that lacks native squamous epithelium. With an incidence of less than 0.001% among intestinal malignancies and only 12 confirmed cases worldwide (as of 2025), this rare entity remains poorly characterized in the literature. Here, we report a newly diagnosed case of primary ileal squamous cell carcinoma and synthesize its clinicopathologic features, clinical presentation, therapeutic management, and the patient's outcome and prognosis, with particular emphasis on diagnostic dilemmas and treatment efficacy.

INTRODUCTION

The small intestine has vital roles in digestion and nutrient assimilation. Although it comprises approximately ¹75% of the total length of the gastrointestinal tract and nearly 90% of the mucosal surface area of the digestive system, it has remarkably low malignancy rates compared with other gastrointestinal regions[1], with small intestinal neoplasms constituting only 1%-5% of all gastrointestinal malignancies[2]. These tumors can be classified histologically into four principal subtypes: Adenocarcinoma (30%-40%), neuroendocrine neoplasms (35%-44%), lymphoma (10%-20%), and gastrointestinal stromal tumors (12%-18%)[3,4].

Primary small intestinal malignancies account for only 0.1%-0.3% of all cancers, or 1%-3% of gastrointestinal malignancies[5]. Although metastases to the small intestine from squamous cell carcinoma at other sites occur, primary squamous cell carcinoma (PISCC) of the small intestine is extremely rare[6]. Development of PISCC is clinically uncommon, as the ileal mucosa consists of simple columnar epithelium and typically lacks squamous epithelium under physiological conditions. Diagnosis relies on exclusion of metastatic squamous cell carcinoma. Essential steps include obtaining a detailed clinical history, performing a whole-body positron emission tomography/computed tomography (PET-CT) scan to detect extraintestinal primary tumors, and conducting a histopathologic evaluation of the tumor's growth architecture. In this report, we describe a case of PISCC in a 47-year-old woman. We also present a comprehensive review of clinicopathological characteristics, clinical manifestations, therapeutic strategies, and prognostic profiles of PISCC. The objective was to increase awareness of this rare malignancy among clinicians and pathologists, thereby improving diagnostic accuracy and optimizing therapeutic management.

CASE PRESENTATION

Chief complaints

A 47-year-old woman was admitted with a 6-month history of persistent abdominal pain that had worsened during the preceding two weeks.

History of present illness

In 2020, the patient underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy. Postoperatively, low-grade serous ovarian carcinoma (International Federation of Gynecology and Obstetrics stage IC1; staged according to the 2014 International Federation of Gynecology and Obstetrics classification system) was confirmed.

History of past illness

The patient had a 44-year history of congenital deafness. In 2021, a diagnostic colonoscopy revealed a suspicious lesion that was subsequently biopsied. Histopathological analysis confirmed sigmoid tubular adenoma; no further treatment was deemed clinically necessary at that time.

Personal and family history

The patient reported no significant family history of hereditary medical conditions.

Physical examination

Pelvic examination revealed localized thickening with tenderness at the cranial aspect of the vaginal stump, with right-sided predominance.

Laboratory examinations

Leukocytosis (white blood cell count $14.69 \times 10^9/L$) with neutrophilic predominance (81.4%) was noted, accompanied by moderate anemia (hemoglobin 77 g/L). Tumor marker analysis showed carbohydrate antigen 125 (CA125) at the borderline of the normal range (18.67 U/mL; reference < 35 U/mL), whereas human epididymis protein 4 remained within age-appropriate reference ranges (35.20 pmol/L; premenopausal threshold < 70 pmol/L, postmenopausal threshold < 140 pmol/L).

Imaging examinations

PET-CT showed postoperative changes related to ovarian carcinoma and focal hypermetabolic small bowel wall thickening in the right pelvis. These findings were radiologically suggestive of implantation metastasis (Figure 1).

Pathological examination

The surgical specimen comprised a 42-cm resected ileal segment with luminal dimensions of 42 cm × 6 cm. An 8 cm × 5 cm × 3 cm ulcerated mass was located 8 cm

from the proximal resection margin and 29 cm from the distal margin. The cut surface of the lesion was firm with grayish-white discoloration (Figure 2A).

Histopathological examination revealed the following histomorphological features. Low-power architecture: Solid sheet-like growth (Figure 2B) and nested patterns lacking glandular differentiation (Figure 2C); High-power cytology: Neoplastic cells with abundant clear cytoplasm (Figure 2D), marked nuclear pleomorphism, hyperchromasia, and frequent typical and atypical mitoses (Figure 2E). Perineural infiltration was present (Figure 2F), but there was no lymphovascular invasion. The immunohistochemical staining results were as follows. Positive markers: P40 (Figure 3A), P63 (Figure 3B), cytokeratin (CK) 5/6 (Figure 3C), and CK7 (Figure 3D); negative markers: Estrogen receptor (ER), progesterone receptor (PR), CA125, wilms tumor 1 (WT-1), CK20, caudal-type homeobox protein 2, and villin; proliferative index: Ki-67 labeling index > 80%.

FINAL DIAGNOSIS

Following histopathological confirmation, a diagnosis of poorly differentiated squamous cell carcinoma involving the ileum was established, with transmural invasion extending to the subserosal adipose compartment and perineural involvement. All surgical margins - including proximal, distal, and mesenteric - were negative for neoplasia. No lymphovascular invasion was identified. Lymph node evaluation showed no metastatic involvement (0/35).

TREATMENT

After surgery, the patient received six cycles of first-line combination chemotherapy with liposomal doxorubicin (50 mg/m²) and carboplatin (0.6 g) with concurrent anti-angiogenic therapy. The regimen was then modified to second-line therapy with five cycles of nab-paclitaxel (240 mg/m²) plus carboplatin (0.6 g) in conjunction with bevacizumab (15 mg/kg). After review by the multidisciplinary tumor board and informed consent from the patient and/or legal representatives, maintenance therapy

was initiated with bevacizumab monotherapy (15 mg/kg every 3 weeks) with concomitant hepatoprotective support (oral reduced glutathione 600 mg three times daily).

OUTCOME AND FOLLOW-UP

At the 30-month postoperative follow-up, the patient remained progression-free, with no clinical or radiologic evidence of recurrence or distant metastasis.

DISCUSSION

PISCC is an exceptionally rare malignant neoplasm, with only 56 cases documented in the global medical literature since its initial description by Adair *et al*[7] in 1981. The present case brings the cumulative total to 57. We analyzed the cohort of reported PISCC patients (Table 1)[6-57] and found a male-to-female ratio of approximately 1.4:1 (33 males vs. 24 females) (Figure 4A). Age at diagnosis ranged from 39 to 91 years, with a median of 65 years and a mean of 64 years (Figure 4B). By anatomic site, the duodenum was most commonly affected (54%, $n = 31$), followed by the ileum (23%, $n = 13$) and jejunum (23%, $n = 13$) (Figure 4C).

The predominant clinical manifestations were abdominal pain (65%, $n = 37$), distension, nausea, vomiting, melena, and weight loss (Figure 4D). Abdominal pain, the most frequently reported presenting symptom, typically results from tumor-induced mechanical traction and associated intestinal dysmotility and therefore often becomes clinically apparent only in the advanced stage of disease. This delayed presentation poses significant challenges for early diagnosis and warrants increased diagnostic vigilance; for example, patients with unexplained abdominal pain should undergo timely multimodal evaluation, including cross-sectional imaging and endoscopic biopsy, to rule out occult malignancy. Among cases with available tumor size data ($n = 40$), approximately 45% had lesions measuring < 4 cm in maximum diameter. The largest recorded tumor measured 14 cm in greatest dimension, with a mean maximum diameter of 5.4 cm across the cohort (Figure 4E).

The pathogenesis of PISCC remains unclear. Four principal hypotheses are under active investigation: hypothesis 1 malignant transformation of ectopic squamous epithelium arising from embryonic remnants, as demonstrated by Adair *et al*[7] through histopathological analyses of intestinal duplication; hypothesis 2: Clonal evolution of adenocarcinoma with secondary squamous differentiation, substantiated by 11.6% ($n = 5$) of reported cases displaying hybrid adenosquamous histology[14,17,18,28,50]; hypothesis 3: Dysregulated differentiation of pluripotent stem cells, supported by immunohistochemical evidence from Barnhill *et al*[58] of multiphenotypic tumor differentiation; and hypothesis 4 chronic inflammation-mediated carcinogenesis *via* the metaplasia-dysplasia-carcinoma continuum, as conceptualized in Friedman's model of multistep oncogenesis[25].

In the present case, hypothesis 1 was considered implausible because of the absence of congenital malformations and a CDX2-negative immunophenotype, which together effectively exclude embryonic tissue. The histopathological findings did not support hypothesis 2, as the tumor showed pure squamous morphology without glandular elements. Hypothesis 3 was also unlikely, as the distinct histologic (serous *vs* squamous) and molecular profiles of the ovarian and ileal malignancies precluded a shared stem cell origin. Hypothesis 4 appeared most plausible: Chemotherapy-induced mucosal injury during prior ovarian cancer treatment may have initiated chronic inflammation, in which proinflammatory cytokines facilitated glandular squamous metaplasia. Subsequent accumulation of genetic alterations within this metaplastic epithelium could then have driven malignant transformation.

Further research is warranted to test this hypothesis, including comprehensive immunohistochemical profiling of inflammatory markers within the ileal tumor and comparative molecular analyses of the ovarian and intestinal neoplasms to delineate the underlying oncogenic pathways. Notably, molecular mechanisms involved in PISCC remain incompletely defined. There is an urgent need for additional molecular studies to elucidate the etiology of this rare condition and to guide the development of preventive measures and targeted therapeutic interventions.

Differential diagnosis of PISCC includes both primary and metastatic neoplastic entities. First, PISCC must be distinguished from poorly differentiated adenocarcinoma. In this case, the tumor showed a solid sheet-like or nested architectural pattern resembling adenocarcinoma; however, its immunophenotype (CK20-, caudal-type homeobox protein 2-, and Villin-negative; P40-, P63-, CK5/6-, and CK7-positive) confirmed squamous lineage differentiation. Second, it is necessary to exclude neuroendocrine carcinoma, which typically demonstrates nested, trabecular, or diffuse growth patterns with high nuclear-to-cytoplasmic ratios, finely granular chromatin, and strong expression of synaptophysin, chromogranin A, and CD5/6. By contrast, squamous markers (CK5/6-, P63-, and P40-positive) were observed in this case, with the absence of glandular markers (CK7- and CK20-negative). Third, the diagnosis requires exclusion of metastatic squamous cell carcinoma, common primary sites of which include the lung, esophagus, and cervix[59-62]. Essential diagnostic steps include comprehensive clinical history evaluation, whole-body PET-CT to identify potential extraintestinal primaries, and histopathological assessment of growth patterns (serosal implantation in metastases vs. mucosal-to-subserosal invasion in PISCC). Our patient had no prior history of squamous cell carcinoma, showed negative PET-CT findings for pulmonary, esophageal, and cervical lesions, and exhibited tumor progression from mucosa to subserosa. These observations, taken together, support the diagnosis of PISCC. Finally, metastatic ovarian serous carcinoma was considered because of the patient's history of low-grade serous carcinoma. Although ovarian serous carcinomas may exhibit solid growth patterns, their immunoprofile (ER-, PR-, WT-1-, and CA125-positive; P40- and P63-negative) is distinct from the findings in this case (ER-, PR-, CA125-, and WT-1-negative; P40-, P63-, CK5/6- and CK7-positive), which definitively ruled out metastatic disease.

Surgical intervention remains the primary therapeutic modality for PISCC. Radical resection - defined as *en bloc* excision of the primary tumor (≥ 2 cm macroscopic margins) combined with regional lymphadenectomy, has been shown to yield superior survival outcomes through complete oncologic clearance and reduced locoregional

recurrence rates (Figure 4F). Among 47 patients with well-documented treatment protocols, 74.5% ($n = 35$) underwent surgery as definitive therapy. Optimal management for resectable cases involves segmental bowel resection with systematic mesenteric lymph node dissection, facilitating precise TNM staging in accordance with the 8th edition of the AJCC criteria. Postoperative adjuvant chemotherapy was administered in 12.8% ($n = 6$) of patients, five of whom achieved disease-free survival without evidence of recurrence[7,17,32,54]. Fatal outcomes occurred in two cases: One patient survived 12 months[24], whereas the other developed metachronous metastases to the cervical region and left upper extremity, resulting in survival of 28 months[27]. Adjuvant chemoradiotherapy has been shown to significantly improve recurrence-free survival in patients with node-positive or locally advanced (T3/T4) disease compared with surgery alone[13,16,22,23]. However, current National Comprehensive Cancer Network guidelines do not include PISCC-specific systemic therapy recommendations. Consequently, clinical management often adopts established regimens used for squamous cell carcinomas at other sites, such as the esophagus or head and neck. The most frequently employed regimen consists of platinum-based agents combined with either 5-fluorouracil (5-FU) or a taxane. This combination is standard for head and neck as well as esophageal squamous cell carcinomas, owing to the synergy by which platinum agents, together with 5-FU or taxanes, disrupt DNA synthesis and impair cell division. In cases with high tumor burden or more aggressive disease, intensified regimens such as TPF (docetaxel + cisplatin + 5-FU) may be considered. The modified FOLFOX6 regimen (oxaliplatin + leucovorin + 5-FU) may also be selected because of potential suitability for the intestinal tumor microenvironment and a generally more manageable toxicity profile of oxaliplatin in some patients. The final treatment strategy should be determined through a comprehensive evaluation of tumor biology, patient performance status, and treatment goals[63].

CONCLUSION

A rare primary ileal poorly differentiated squamous cell carcinoma was diagnosed in a patient with a history of ovarian low-grade serous carcinoma (International Federation of Gynecology and Obstetrics stage IC1), treated with taxane-carboplatin chemotherapy 2 years earlier. Chemotherapy-induced intestinal mucosal injury and alterations in the local microenvironment may have served as initiating factors for squamous metaplasia. We systematically reviewed published cases and summarized the clinicopathological features of PISCC, the therapeutic modalities administered, and the associated prognostic outcomes. We also discussed putative pathogenic mechanisms and therapeutic strategies. Notably, the molecular pathways involved in PISCC remain incompletely understood. Thus, there is an urgent need for further molecular studies to elucidate the etiology of this rare condition and to guide the development of preventive measures and targeted therapeutic interventions.

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