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Case Report

Rapid Malignant Transformation of Tubulovillous Adenoma, Initially Presenting as McKittrick-Wheelock Syndrome: A Case Report

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Keywords
Tubulovillous adenoma · Malignant transformation · Kirsten rat sarcoma viral oncogene homolog · McKittrick-Wheelock syndrome · Inflammation

Abstract
Most cases of colorectal cancer develop from adenomatous polyps, slowly progressing within an average period of 8–10 years. McKittrick-Wheelock syndrome (MKWS) is a rare manifestation of tubulovillous adenoma. It generally presents as hypersecretory diarrhea with severe electrolyte and fluid depletion. Roughly, 5% of the published cases have reported malignant histopathology associated with MKWS, with little to no data regarding the malignant transformation process of those patients. Our patient was a 53-year-old Asian woman suffering from chronic secretory diarrhea, resulting in severe volume, electrolyte depletion, and prerenal azotemia, consistent for MKWS. Her symptoms initially improved with sulfasalazine but eventually worsened. She demonstrated signs of systemic (elevated leukocyte, CRP, and LDH) and local inflammation (dense lymphocyte infiltration in colorectal tissue) throughout the course of her disease. Serial pathological results showed rapid neoplastic progression of adenomatous polyp to

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adenocarcinoma within 1 year period. Surgical resection resulted in complete symptom resolution. Molecular examination showed a favorable profile of exon 4 Kirsten rat sarcoma viral oncogene homolog mutation, normal NRAS, BRAF, CDX2, and CK20 expressions. Her molecular pattern did not reflect the profile of an aggressive disease, suggesting the possibility of oncogenic processes outside the major pathways of adenoma to carcinoma progression. Chronic inflammation is a well-established risk factor for colorectal cancer, and prostaglandin E2 (PGE2) has been observed as one of the key regulators of tumor initiation and growth. PGE2 is also responsible for hypersecretory diarrhea associated with MKWS.

Introduction

Most cases of colorectal cancer develop from adenomatous polyps, slowly progressing within an average period of 8–10 years [1]. Adenoma to carcinoma sequence of colorectal cancer has been extensively studied, identifying three major pathways: chromosomal instability, microsatellite instability (MSI), and serrated neoplasia [2]. However, some patients develop carcinoma without driver mutation associated with any of the three major pathways [3]. Additional factors such as inflammation and tumor microenvironment (TME) also play significant roles in the carcinogenesis of colorectal cancer [4]. An uncommon symptom of adenomatous polyp, secretory diarrhea is associated with villous and tubulovillous adenomas. In rare cases, it might cause severe electrolyte and fluid depletion, commonly referred to as McKittrick-Wheelock syndrome (MKWS) [5]. A potentially lethal disease, symptoms of MKWS usually resolve completely after tumor resection [6]. Roughly 5% of the published cases have reported malignant histopathology associated with MKWS, with little to no data regarding the malignant transformation process of those patients [7]. Our patient was a 53-year-old woman with tubulovillous colorectal adenoma, presenting with MKWS. Despite a favorable tumor molecular profile, she experienced a rapid malignant transformation of tubulovillous adenoma.

Case Report

A 53-year-old Asian woman complained of roughly 6–8 times/day watery diarrhea for the past 5 weeks, with blood occasionally observed in her stool. She also experienced recurrent abdominal cramps, decreased appetite, and unintentional weight loss of roughly 4 kg. She had no significant past medical and familial history, including malignancy. Her physical examination was unremarkable. Laboratory examination showed severe hypokalemia (1.7 mEq/L), severe hyponatremia (112 mEq/L), prerenal azotemia (BUN 60 mg/dL), and leukocytosis (24 × 103/μL) which recovered completely with IV fluid and electrolyte replacement. Her CEA level was 6.4 ng/mL. On colonoscopy, a 5 cm circular rectal mass was observed 7 cm from the anorectal with a pedunculated polyp measuring 1.5 × 2.5 cm located 50 cm from the anorectal (Fig. 1). Pathological examination showed proliferative tissue glands with tubulovillous pattern and mild dysplasia (Fig. 2). She was prescribed sulfasalazine 500 mg b.i.d, resulting in significant symptomatic relief. However, her symptoms never completely disappeared and eventually worsened. Five months after the initial colonoscopy, her diarrhea frequency increased to around ten times/day, resulting in the recurrence of hypokalemia (1.9 mEq/L), hyponatremia (109 mEq/L), prerenal azotemia (BUN 78.9 mg/dL),

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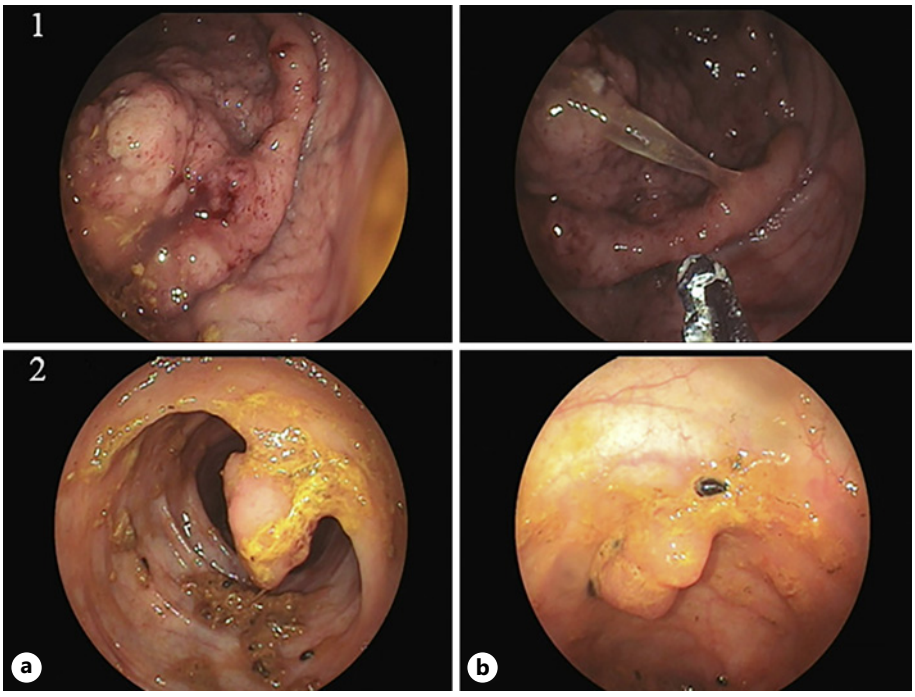

Fig. 1. Initial colonoscopy showing a 5 cm circular rectal mass was observed 7 cm from the anorectal (1 **a**, **b**) with a pedunculated polyp measuring 1.5 × 2.5 cm located 50 cm from the anorectal (2 **a**, **b**).

and leukocytosis (24 × 103/μL), which again recovered completely with IV fluid and electrolyte replacement. Her CEA level increased to 8.05 ng/mL with elevated CRP (65 mg/dL) and LDH (648 unit/L). Repeat colonoscopy found a 7 cm ulcerative circular rectal mass 5 cm from the anorectal and multiple pedunculated polyps 65–75 cm from the anorectal, measuring 1.5 × 2 cm in diameter (Fig. 3). Polypectomy was performed, and pathological examination showed villous adenoma with moderate dysplasia (Fig. 4). Endoscopic resection of the rectal mass was not feasible due to the tumor size. She was diagnosed with MKWS with a high risk of malignancy. Surgical resection was planned, which she initially refused.

During the subsequent month of observation, she further experienced recurrent diarrhea and electrolyte imbalances. Her CEA level increased to 12.8 ng/mL. Laparotomy resection of descending colon-rectum with colostomy was performed. Complete resection was not possible due to tumor infiltration to pelvic wall, leaving a residual mass on the distal rectum. We could not perform transanal endoscopic microsurgery as we did not have the necessary equipment. Pathological examination of resected tissue showed tubulovillous adenoma with adenocarcinoma infiltrating the submucosal layer with dense infiltration of lymphocytes (Fig. 5). Molecular examination showed KRAS (Kirsten rat sarcoma viral oncogene homolog) mutation on exon 4, normal NRAS, BRAF, CDX2, and CK20 expressions (Fig. 6). After surgery, her symptoms completely resolved with no notable treatment-related adverse event. She felt that she would have avoided months of suffering if she had agreed to undergo surgery earlier. After surgery, her CEA level decreased to 5.1 ng/mL; her serum electrolyte and blood urea nitrogen remained stable at normal levels. One month after surgery, an abdominal CT scan with contrast showed a residual mass on the distal rectum (Fig. 7). She was planned to receive adjuvant chemotherapy but requested to be transferred to another healthcare facility for convenience reasons.

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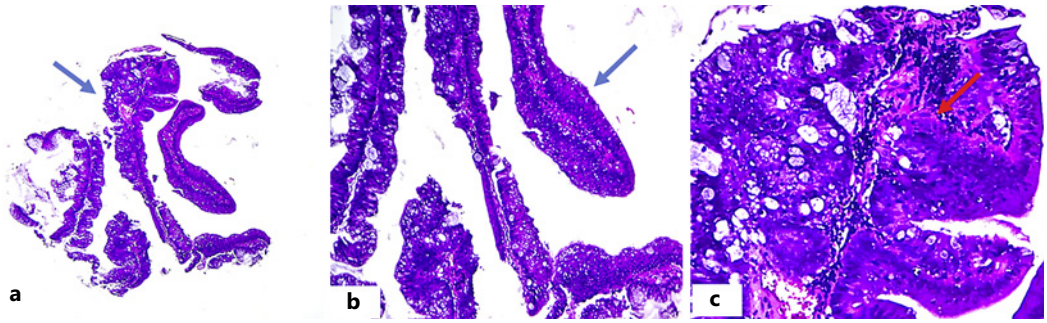

Fig. 2. Histopathological features of a biopsy specimen from initial colonoscopy with ×4 (**a**), ×10 (**b**), and ×40 (**c**) magnifications, showing proliferative tissue glands with tubulovillous pattern (blue arrow) and mild dysplasia (red arrow).

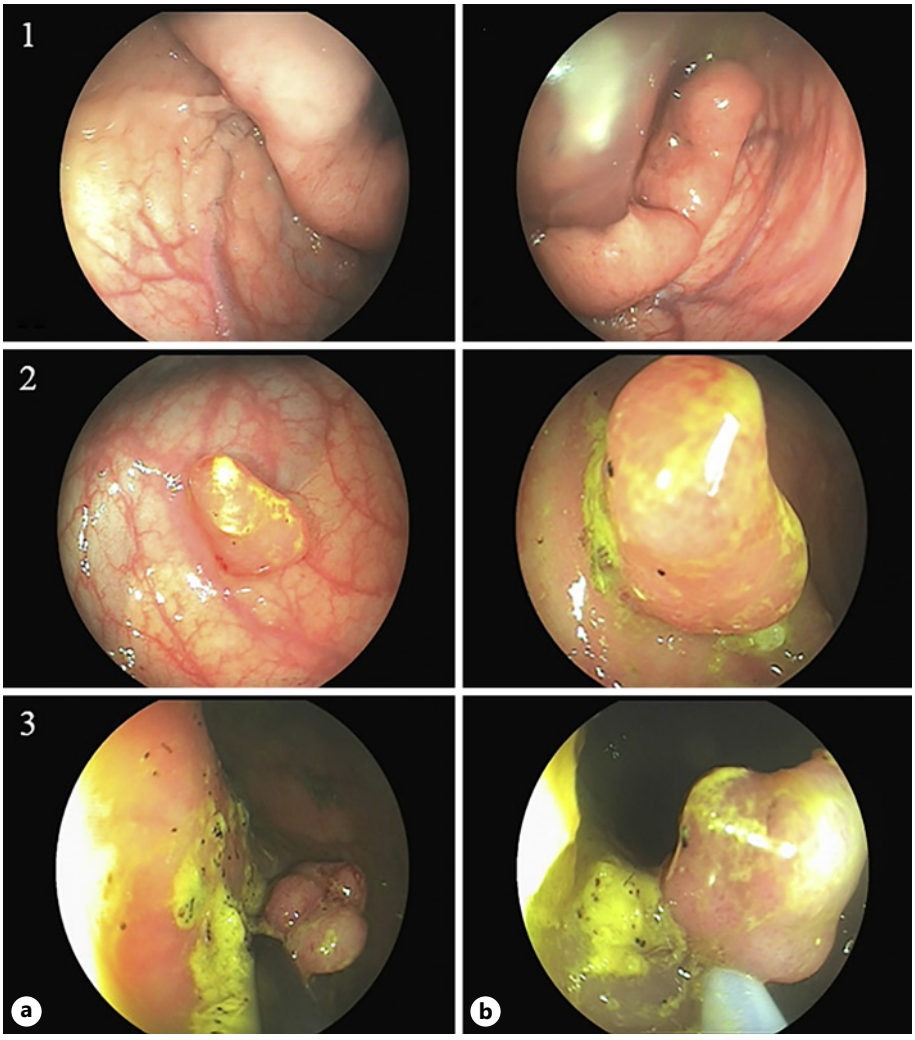

Fig. 3. Repeat colonoscopy found a 7 cm ulcerative circular rectal mass 5 cm from the anorectal (1 **a**, **b**), the first polyp located 65 cm from the anorectal (2 **a**, **b**), and the second polyp located 75 cm from the anorectal (3 **a**, **b**). Both polyps measured 1.5 × 2 cm.

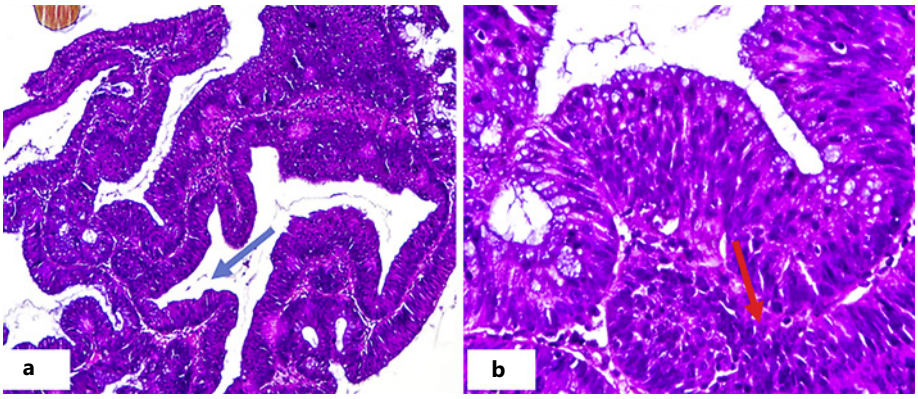

Fig. 4. Morphological feature of biopsy specimens from second colonoscopy with ×10 (**a**), and ×40 (**b**) magnifications, showing villous pattern (blue arrow) and moderate dysplasia (red arrow).

Discussion

The adenoma progression and malignant transformation in our patient were unusually rapid. We attempted to examine the major pathways of adenoma to carcinoma progression in colorectal cancer to predict the contributing factors of progression and as a guide for choosing the appropriate treatment approach. We examined KRAS mutation for chromosomal instability pathway, showing mutation on exon 4. However, our facility was not able to provide the allele frequency data. KRAS mutation is common in villous and tubulovillous adenomas [8]. KRAS has an extensive role in the carcinogenesis of colorectal cancer, including in cell proliferation, transformation, invasion, metastasis, and resistance toward therapy, leading to a worse prognosis [9]. Most KRAS mutation in colorectal cancer occurs in exon 2, 12, 13, with limited data on exon 4 mutation due to its rare occurrence [10–12]. Research by Guo et al. [13] reported that KRAS exon 4 mutation was associated with older age at diagnosis, rectal tumor origin, adenocarcinoma pathology, and higher tumor grade, albeit with better overall survival.

We examined BRAF mutation as it is the earliest event in the serrated pathway and a negative prognostic marker in colorectal cancer, which was not detected in our patient [14, 15]. MSI and MLH1 examinations were not available in our country. However, the literature suggests MSI is uncommon in villous and tubulovillous adenoma, including in MKWS, as reported in a case series by Droy-Dupré et al. [16]. NRAS mutation is associated with proliferation and metastasis in colorectal cancer through mitogen-activated protein kinase pathway [17]. NRAS mutation is less prevalent in the Asian population and was not observed in our patient [18]. Loss of CDX2 and CK20 is more commonly observed in microsatellite-unstable colorectal cancer and is associated with a worse cancer profile and prognosis [19, 20]. Our patient had well-differentiated cancer cells on biopsy with normal expression of CDX2 and CK20, suggesting favorable prognosis. Our patient's molecular pattern did not reflect the profile of an aggressive disease, suggesting the possibility of oncogenic processes outside the major pathways of adenoma to carcinoma progression.

Our patient initially presented with chronic hypersecretory diarrhea, resulting in severe fluid and electrolyte imbalances, also known as MKWS [21]. Although MKWS is associated with tubulovillous adenoma, it is a rare presentation of tubulovillous adenoma. Most cases of tubulovillous adenoma are asymptomatic, and large TVA lesions more commonly present with obstructive symptoms and GI bleeding. The presence of MKWS was clinically significant, as it is a potentially lethal syndrome if left untreated [22]. The underlying pathologic process of MKWS is mediated by prostaglandin E2 (PGE2), which is elevated in rectal secretion, as

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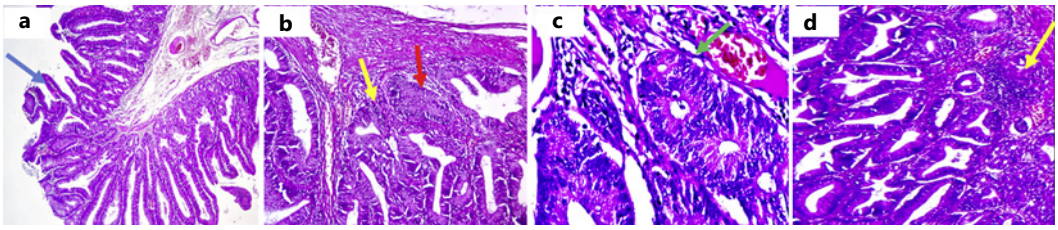

Fig. 5. Histopathological features of descending colon and rectum from surgical resection with ×4 (**a**), ×4 (**b**), ×10 (**c**), and ×40 (**d**) magnifications, showing tubulovillous adenoma component (blue arrow) with partly adenocarcinoma component in another area (red arrow). Tumor cells are characterized by atypical shape, large size, scanty cytoplasm, and prominent nucleoli, infiltrated submucosa layer (green arrow). Dense lymphocyte infiltration was observed in the surrounding tumor nest (yellow arrow).

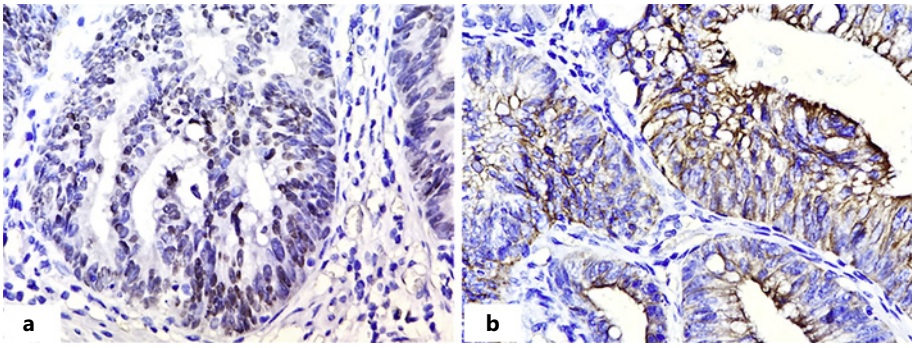

Fig. 6. The immunohistochemical examination of CDX2 and CK20 showed the nuclear positivity of CDX2 (**a**) and the membrane-cytoplasmic positivity of CK20 (**b**).

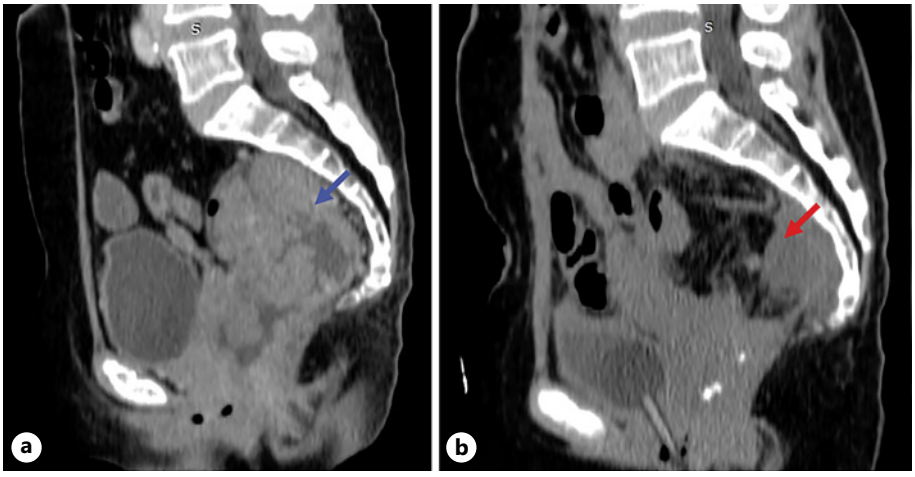

Fig. 7. Abdominal CT scan with contrast, showing presurgical (**a**) rectal mass (blue arrow) and the corresponding postsurgical (**b**) residual tumor on distal rectum (red arrow).

reported by previous studies [23, 24]. Unfortunately, PGE2 examination was unavailable in our country. PGE2 is a potent inflammatory mediator responsible for acute and chronic inflammation [25]. Our patient demonstrated signs of chronic systemic inflammation, such as elevated leukocyte on repeated complete blood examinations, elevated CRP and LDH. She also

had signs of localized inflammation, demonstrated by the dense infiltration of lymphocytes on the pathologic examination of her colorectal tissue (Fig. 5). She also experienced initial symptomatic improvement with sulfasalazine, further supporting the role of inflammation. Chronic inflammation is a well-established risk factor for colorectal cancer, and PGE2 has been observed as one of the key regulators of tumor initiation and growth [4, 26]. The role of PGE2 in colorectal tumorigenesis is through direct cell stimulation and modification of the TME. PGE2 stimulates cancer cell proliferation via EP receptors, which activate NF-κB signaling [26]. PGE2 also creates TME favorable for tumorigenesis by switching macrophages and neutrophils to pro-tumor phenotype, inhibiting T cells and NK cells, and affecting macrophage polarization [27]. Unfortunately, direct inhibition of PGE2 using nonsteroidal anti-inflammatory drugs in these patients is limited by the severe adverse events associated with long-term use, and surgery remains the best approach. Our case report is limited by the diagnostic modalities available in our country. We did not have the facility to examine RAS allelic frequency, MSI, and MLH1, which might be widely available in resourceful countries, limiting the implementation of the findings from our case to other patients. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531992).

Conclusion

Despite favorable molecular profile, malignant transformation of tubulovillous adenoma can occur in patients with MKWS, possibly due to chronic inflammation mediated by PGE2.

Acknowledgments

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Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case report and the accompanying data. Ethical approval was waivered by the Ethics Committee of Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University because this is an anonymized case report.

Conflict of Interest Statement

The authors declare no conflicting interests.

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Author Contributions

I.P., B.L., and N.R. were responsible for conceptualization, data acquisition, data curation, visualization, writing-original draft, and writing-review and editing; B.P.U., I.S., and E.K.D. were responsible for visualization, data acquisition, data curation, and writing-review and editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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