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Case Report

Iron Deficiency Leading to the Diagnosis of a Rectal Neuroendocrine Tumor: A Case Report

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ABSTRACT

Iron deficiency is common, particularly in young women, but persistent cases that do not respond to treatment require further investigation, especially within the gastrointestinal system. In this case report, we present a 35-year-old woman with chronic intermittent pruritus for 2 years and refractory iron deficiency ultimately diagnosed with a rectal neuroendocrine tumor (NET). After the tumor was identified through colonoscopy and pathology report, she underwent surgery, which led to the disappearance of pruritus and improvement in ferritin levels. This case underscores the importance of considering systemic causes for persistent pruritus and refractory iron deficiency, highlighting the need for comprehensive evaluation.

Keywords: Iron deficiency, Pruritus, Itching, Rectal neuroendocrine tumor, Refractory anemia, Case report

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INTRODUCTION

Iron deficiency anemia impacts over 1.2 billion individuals globally, and iron deficiency without anemia is even more widespread. There is a persistent misconception that iron deficiency anemia (IDA) and iron deficiency (ID) are interchangeable terms. However, ID is a broader condition and refers to inadequate iron stores that fail to meet the body's needs, with or without anemia (1).

The World Health Organization (WHO) defines anemia thresholds as 130 g/L for men, 120 g/L for non-pregnant women, and 110 g/L for pregnant women (2). Serum ferritin is the most specific biochemical marker for evaluating total body iron stores. Levels below 30 µg/L are widely recognized as the threshold indicating iron deficiency (3). ID without anemia (IDWA), despite having a straightforward cause and treatment, often escapes clinical attention (4). It also shows a significant connection to colorectal malignancies and should be examined with the same urgency as assessing iron deficiency anemia (IDA) (5).Neuroendocrine tumors (NETs) are rare among gastrointestinal (GI) malignancies that often remain undetected in early stages due to their vague and non-specific symptoms, which can mimic those of more common conditions, leading to delayed diagnosis (6). These neoplasms are a heterogeneous group of epithelial neoplastic proliferations ranging from indolent, well-differentiated neuroendocrine tumors (NETs) to very aggressive, poorly differentiated neuroendocrine carcinomas (NECs) (7). Neuroendocrine tumors (NETs) develop from neuroendocrine cells, which possess characteristics of both nerve cells and hormone-producing endocrine cells. These tumors are classified as functional or non-functional based on their ability to produce hormone-like substances. Regardless of functionality, all NETs are classified as cancerous NETs can originate in various parts of the body, with the GI tract accounting for 43% of cases, the lungs for 30%, and the pancreas for 7% (8).

Chronic pruritus can be a distressing symptom arising from a variety of conditions, including dermatological, neurological, psychiatric, or systemic issues (9). It may sometimes be an early sign of malignancy. A comprehensive diagnostic evaluation is essential in cases with a strong suspicion of a malignancy. However, the exact mechanisms driving malignancy-associated itch remain poorly understood and require further investigation (10).

This case emphasizes the importance of investigating systemic causes for persistent pruritus and refractory iron deficiency, underscoring the need for a comprehensive evaluation.

CASE REPORT

A 35-year-old woman with no significant medical history and no known family history was referred to a gastroenterologist due to persistent iron deficiency that did not respond to supplementation. She had been experiencing intermittent pruritus, mainly on her trunk and limbs, for two years. She described it as bothersome and diffuse, without a consistent pattern or specific triggers. The itching was not associated with other noticeable symptoms, and she did not experience skin rashes. Initially, she sought help from a dermatologist, but no specific cause was identified, leading her to discontinue follow-up. Two months before her referral to the gastroenterologist, she experienced heavy menstrual bleeding and consulted a gynecologist. Laboratory investigations, including a complete blood count (CBC) and ferritin levels, showed normal hemoglobin but low ferritin and iron levels. An ultrasonography of the uterus and ovaries yielded unremarkable results. She was prescribed ferrous sulfate at a dosage of 100 mg three times daily.After two months of treatment, follow-up tests indicated no improvement in ferritin levels despite continued supplementation. An occult blood test was conducted and returned negative (Table 1). She continued iron supplementation for an additional month without any change in her ferritin levels. Consequently, she was referred to a gastroenterologist for further evaluation.

Table 1. Laboratory findings at initial presentation and follow-up after 2 months demonstrated persistent low ferritin levels despite iron supplementation.

Test	Initial result	After 2 months of medication
Serum iron	32 mcg/dL	Not repeated
Total iron binding capacity	349 mcg/dL	Not repeated
Transferrin saturation	9%	Not repeated
Ferritin	14 µg/L	17 µg/L
Occult blood (OB)	Not performed	Negative
White blood cell (WBC)	8.05×10^9/L	7.2×10^9/L
Neutrophils	57.6%	74.3%
Lymphocytes	37.3%	18.3%
Monocytes	4%	5.4%
Red blood cell (RBC)	4.85×10^{12}/L	4.68×10^{12}/L
Hemoglobin (HB)	13 g/dL	13.5 g/dL
Mean corpuscular volume (MCV)	82.7 fL	83.8 fL
Red cell distribution width (RDW)	14.1%	13.8%

The patient underwent an esophagogastroduodenoscopy (EGD) and colonoscopy to further investigate the anemia. The EGD was unremarkable; however, the colonoscopy revealed a 9 mm sessile polyp in the rectum (Figure 1). The polyp was removed during the colonoscopy, and multiple biopsies were taken and sent for pathology analysis.
The pathology report confirmed the presence of a well-differentiated neuroendocrine tumor (G2), classified as stage 1. Immunohistochemistry results showed positive synaptophysin and chromogranin markers along with a Ki67 index of 3%. The tumor had invaded the submucosa and demonstrated vascular invasion.

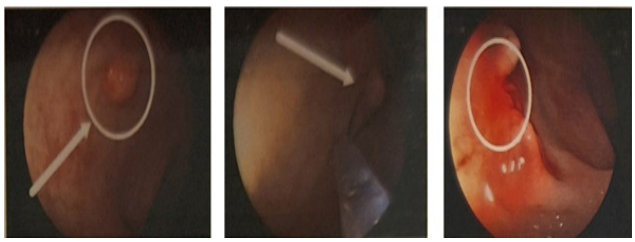

Figure 1. Colonoscopy revealing a 9 mm sessile rectal polyp

After being diagnosed with a tumor, the patient underwent a subsegmental resection of the affected area of the rectum. Tumor markers, including 5-Hydroxyindoleacetic Acid (5-HIAA) and morning cortisol levels, were within normal limits. Imaging studies, including a computed tomography (CT) of the chest, abdomen, and pelvis, showed no signs of metastatic disease.
She continued taking ferrous sulfate for two additional months, which proved effective as her ferritin levels improved to 55 ng/mL. Additionally, the sensation of pruritus was completely resolved.
A follow-up colonoscopy was performed two months after surgery to check for possible local recurrence. A biopsy sample taken from the previous tumor site was sent for pathological evaluation and showed no abnormalities.

DISCUSSION

Sometimes, the first indicator of an underlying malignancy is pruritus, which can result from either the tumor's direct effect on local tissues or a systemic response to the cancer. This systemic reaction is referred to as "paraneoplastic itch" related to paraneoplastic syndromes (PNSs) (11). These syndromes often present with hormonal or neurological symptoms. Advances in diagnostic tools, such as chromogranin A measurement, have significantly improved the detection of PNSs in affected patients (12).
IDWA is often underdiagnosed and inadequately treated. In addition to iron supplementation, it is crucial to thoroughly investigate the underlying causes of IDWA. For patients who do not fit typical risk groups for iron deficiency, the possibility of occult blood loss must always be considered. IDWA can be an early stage that may progress to severe ID, making a comprehensive GI work-up essential for identifying the cause (13). The diversity of patients with malignancies underscores the importance of addressing functional and absolute ID in individuals with all types of solid tumors (14). It is essential to consider NETs as part of the differential diagnosis when evaluating cases of ID and to implement evidence-based surveillance strategies as needed (15). Rectal NETs are rare but increasingly detected. This rise is likely due to advancements in endoscopic techniques and greater participation in colorectal screening programs rather than an actual increase in prevalence (16). Most rectal NETs are asymptomatic and discovered incidentally during colonoscopy as small, yellowish, submucosal lesions in the mid-rectum (4-8 cm from the anorectal junction). Approximately 80% are less than 10 mm in size and confined to the submucosal layer at diagnosis. Rectal NETs generally have a better prognosis compared with other GI neuroendocrine neoplasms, primarily because they are often detected incidentally at an early stage (17). Complete histological resection is considered curative in cases of localized NETs and offers an excellent prognosis, even for patients with potential remnant NET (18). Grade 1 or 2 rectal NETs smaller than 10 mm are associated with a low risk of recurrence and may be considered for discharge from surveillance after initial treatment (17). Additional endoscopic mucosal resection (EMR) or surgical intervention can provide effective outcomes if complete resection is not achieved. Precise pathological evaluation of resection margins and scheduled endoscopic follow-ups are crucial for detecting local recurrence and ensuring long-term success (18).

CONCLUSION

In conclusion, this case underscores the critical importance of recognizing ID and chronic itching (pruritus) as potential indicators of underlying systemic conditions, including serious diseases such as NETs. Persistent itching, often overlooked as a symptom, can serve as an early warning sign of significant health issues. It is essential to conduct comprehensive diagnostic evaluations for unexplained ID, particularly when it does not respond to treatment. This approach ensures timely identification and management of the underlying causes. Consequently, there is a need for increased clinical vigilance in similar presentations.
Informed Consent: Informed consent was obtained from the patient to publish this report.

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