

PERSPECTIVE ARTICLE

Colorectal carcinoma-induced iron deficiency anemia: A literature review and a case scenario

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Abstract

Colorectal carcinoma (CRC) is among the leading cancers worldwide and a major cause of cancer-related mortality. Iron deficiency anemia (IDA), resulting from inadequate iron for hemoglobin production, has been increasingly linked to CRC, often leading to misdiagnosis. This study reviews the clinicopathological associations of IDA in the context of colorectal cancer, using the medical records of a septuagenarian diagnosed with both conditions as a case study. Employing the Problem-Intervention-Comparison-Outcome model, we searched for “colorectal carcinoma” and “iron deficiency anemia” as keywords. CRC ranks among the top five cancers of global health importance, with socioeconomic factors, sedentary lifestyles, and dietary choices significantly influencing both conditions. Notably, IDA is particularly associated with the right-sided CRC in individuals over 40. Upregulation of interleukin-6 in CRC cells stimulates hepcidin release, which mediates anemia of chronic disorders and IDA. The case revealed right-sided signet ring cell CRC, microcytic hypochromic anemia, bone marrow metastasis, and low serum iron and ferritin levels. This study highlights the need for increased suspicion of CRC in middle-aged and elderly patients presenting with recurrent IDA. Regular screening is essential for the early detection and improved treatment outcomes. While colonoscopy is the gold standard for prevention, its effectiveness in detecting early molecular links between neoplasia and chronic inflammation is limited. There is also no consensus on surveillance protocols, and many gastroenterologists do not adhere to recommended biopsy sampling practices. In conclusion, this study advocates for including complete blood count and iron studies as essential tests in guidelines for screening and diagnosis for CRC-related IDA to enhance diagnostic practices.

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1. Introduction

Iron deficiency anemia (IDA) is the most prevalent curable anemia worldwide.¹⁻³ It is caused by a deficiency of elemental iron, which is essential for the synthesis of the heme component of hemoglobin.⁴ While iron is one of the most abundant elements in the Earth's crust, hemoglobin stands as the most abundant iron-carrying protein in humans.^{1,5} Despite this, IDA constitutes 30 – 50% of anemia cases globally in both children and adults, with low-income countries disproportionately affected.⁵⁻⁷ The diagnosis of IDA relies on a combination of clinical and laboratory findings. Clinical indicators such as glossitis, dysphagia (Plummer-Vinson syndrome), koilonychia, and angular stomatitis should raise suspicion. Laboratory indicators include a hypochromic or normochromic microcytic profile with increased red blood cell distribution width in normal or low hemoglobin values (<12.5 g/dL for adult males and non-gravid women).^{8,9} Additional diagnostic criteria encompass reduced serum iron levels (<10 µmol/L), serum ferritin levels below the gender-specific normal ranges (40 – 340 µg/L for males and 14 – 150 µg/L for females), and elevated total iron-binding capacity (TIBC; >75 µmol/L or <10% iron saturation). Mathematically, TIBC is defined as the sum of serum iron and unbound iron-binding capacity (UIBC) ($TIBC = \text{Serum iron} + \text{UIBC}$), and serum iron percentage saturation is the ratio of serum iron to TIBC multiplied by 100 ($\% \text{ saturation} = \text{Serum iron} / TIBC \times 100\%$). A saturation value below 10% is typically indicative of IDA.^{5,10,11}

Colorectal carcinoma (CRC) is a malignant tumor affecting the large intestine, comprising the colon and rectum. It ranks as the third most common cancer worldwide and the fourth most prevalent cancer in Nigeria among both sexes.¹²⁻¹⁴ Although the incidence of CRC is rising in transitioning countries, early detection remains poor, particularly in low-middle-income countries (LMICs), due to the absence of organized cancer screening systems.¹⁴⁻²² In sub-Saharan Africa, the crude incidence of CRC is estimated at 4.04/100,000 (4.38 for men and 3.69 for women).¹⁶ In Nigeria, CRC presents a diagnostic challenge due to limited awareness and inadequate screening facilities.¹⁵ The effectiveness of fecal-based immunochemical screening tests for the early detection of CRC is uncertain, complicating the estimation of CRC's burden in Nigeria.¹⁷ Consequently, many diagnoses are made at advanced stages, resulting in poor prognoses and high mortality rates, particularly in LMICs. CRC is the second leading cause of cancer-related deaths worldwide and ranks third in the United States.¹⁴ Histological subtypes of CRC include adenocarcinoma (AC), mucinous AC, signet ring cell carcinoma (SRCC), and other

variants.²³ Both hereditary and environmental factors contribute to CRC, with environmental factors playing a more prominent role in developing countries. Risk factors for CRC include age, gender, diet, lifestyle, and genetics. Recent statistics indicate that the mean age of CRC onset in Nigeria is 41 years, with CRC being the second most common cancer in men and the third most common in women.²⁴

IDA and CRC share common characteristics as environmentally modifiable non-communicable diseases linked to unhealthy lifestyle choices, such as diets high in animal fat and protein (e.g., *suya*), low-fiber intake, alcohol consumption, tobacco use, obesity, and physical inactivity.²⁵⁻²⁸ IDA is often a result of dietary deficiencies, particularly in economically disadvantaged populations. In addition, socioeconomic disadvantage, sedentary lifestyles, and poor dietary habits are significant risk factors for CRC. Approximately 6% of CRC cases present with IDA, particularly when the tumor is located on the right side of the colon.^{29,30} As such, IDA, particularly in advanced CRC, may sometimes be the sole indicator for diagnosis.

This article aims to elucidate the clinicopathological associations of IDA and CRC, and explore how IDA can facilitate the diagnosis of CRC through an index case scenario.

2. Methodology

This methodology involved a literature review of previous studies on CRC-induced IDA, as well as a description of a clinical case scenario involving a patient managed for CRC-induced IDA at a private medical center. The rationale for focusing on this case is the rare histologic variant of CRC, SRCC, and the unique circumstances surrounding its diagnosis, as the condition initially presented as a hematological disorder.

2.1. Literature review

This literature review examines the clinicopathological correlations of CRC-induced IDA, drawing on previous studies and medical records of a septuagenarian diagnosed with CRC-induced IDA and treated at the Federal Medical Center, Umuahia. The Problem-Intervention-Comparison-Outcome (PICO) model guided the literature review process,^{31,32} consisting of four strategic steps: problem identification, interventions, comparison, and expected outcomes (Figure 1). The problem statement addresses how CRC can lead to IDA, while the intervention pertains to conventional and investigational diagnostic approaches for CRC-induced IDA. The comparison involves evaluating evidence-based studies on CRC-induced IDA alongside clinicopathological findings from the case scenario. The

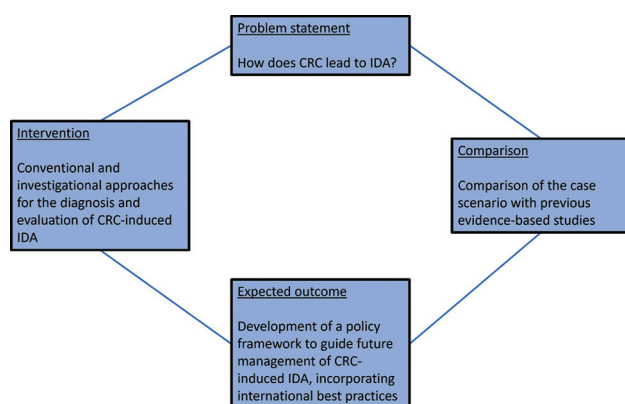


Figure 1. Problem-intervention-comparison-outcome model for the research question

outcome centers on developing policy statements to enhance future management of CRC-induced IDA in line with international best practices. The medical subject headings “colorectal carcinoma” and “iron deficiency anemia” were used as keywords for the PICO-based search strategy.

Google Scholar, African Journal Online, PubMed, Cumulative Index to Nursing and Allied Health Literature, Cochrane, and Medline were the databases used in this literature review. The search for relevant evidence-based studies yielded 100 articles that met the inclusion criteria for the research question. Additional references, manually selected for their relevance, were also included in the bibliography. The inclusion criteria consisted of full-text reports, web pages, and peer-reviewed articles published between 1980 and 2023, focusing on the clinicopathological correlation and management of CRC-induced IDA. This paper synthesizes the reviewed articles and discusses possible interventions for CRC control. A discussion on the clinicopathological correlation between CRC and IDA, in comparison with the clinical-laboratory findings from the case scenario, is highlighted.

2.2. Case scenario

A septuagenarian male university teacher presented with recurrent anemia over 2 months. He also experienced bilateral leg swelling, more pronounced in the right leg. Three weeks before consulting a hematologist, who was referred by his primary physician, the patient had received three units of packed red blood cells. On clinical examination, significant findings included bilateral inguinal lymphadenopathy and non-pitting pedal edema, most prominent in the right lower limb. A complete blood count, iron studies (serum iron assay, serum ferritin assay, serum transferrin test, and TIBC), and a bone marrow study were conducted to establish an initial diagnosis of

IDA. The complete blood count revealed severe anemia, as evidenced by low red blood count (RBC; $2.2 \times 10^{12}/L$), low hemoglobin concentration (4.8 g/dL), low hematocrit (HCT; 15.2), low mean corpuscular volume (69.4 fl), low mean corpuscular hemoglobin (22 pg), and a microcytic hypochromic erythrocyte pattern (Table 1). The iron studies confirmed IDA, showing a low serum iron level (3.8 $\mu\text{mol}/L$), low serum ferritin level (20.8 ng/mL), low serum iron saturation (7.7%), and high/normal serum transferrin (24.6 $\mu\text{mol}/L$) (Table 1). A subsequent bone marrow study revealed features suggestive of tumor metastasis (Table 1). With the diagnosis of tumor metastasis alongside a background IDA, CRC was not initially suspected. Angiography and prostatic surface antigen tests were conducted, but the findings were inconclusive. However, an abdominal computed tomography (CT) scan with contrast revealed circumferential thickening of a short segment of the right colon (about 7 cm), involving the hepatic flexure and proximal transverse colon, with marked irregular luminal narrowing. In addition, multiple hypo-dense, non-enhancing lesions were identified in both liver lobes, the largest measuring 1.32×1.06 cm in segment VIII, with local nodal involvement (Table 2). A lymph node biopsy, colonoscopy, and colorectal tissue biopsy were subsequently performed, leading to the diagnosis of SRCC (Table 3).

This article is divided into several sections: the epidemiology of CRC and IDA, how CRC leads to IDA, the interleukin-6 (IL-6)-induced hepcidin theory, the expression of hepcidin mRNA and its upregulation by CRC tissues, the pathogenesis of IDA in CRC, and the challenges of managing CRC in underserved settings.

3. Results

This section presents the laboratory hematological parameters (Table 1), imaging results (abdominal CT scan and colonoscopy) (Table 2), histology (lymph node and colonic tissue biopsies) (Table 3), and biochemical analytes, including liver transaminase enzymes (Table 4) of the case subject. A comparison between the clinicopathological findings of the case subject and those from previous evidence-based studies is also provided (Table 5). The hematological results showed severe anemia, evidenced by a low RBC, hemoglobin concentration (4.8 g/dL), and HCT level (15.2%). In addition, laboratory evidence of IDA was confirmed by the presence of hypochromic microcytic red blood cells in the peripheral blood smear. Iron study assays further supported the diagnosis of IDA, as evidenced by low serum iron, low serum ferritin, and low transferrin levels (Table 1).

Problem statement

How does colorectal carcinoma cause IDA? ^[1-82]

- CRC is the third most common cancer and 2nd most common cause of cancer-related death worldwide.
- 1 in every 20 IDA (6%) in the adult population could be attributable to CRC.
- Diagnostic dilemma due to poor screening system in LMICs.
- CRC-induced IDA is more common with right-sided colon cancer.
- High expression of Interleukin-6 cytokines by CRC cells linked to intrinsic release of Hepcidin which mediates AOCD and IDA.
- Hepcidin increases ICC iron accumulation which triggers the Wnt/ β -catenin oncogenic signalling pathway that leads to colorectal carcinogenesis.

Interventions

Conventional and investigational approaches to diagnosis and treatment of CRC-induced IDA ^[29-77, 89-100]

- Hepcidin –a putative iron regulatory hormone, a proto-oncogenic factor, and a useful marker for diagnosing CRC-induced IDA. Its antidote, ihepcidin could be a proposed inhibitor of the Wnt/ β -catenin oncogenic pathway.
- BRAF oncogene-BRAFV600E can induce colon tumorigenesis. This biomarker is useful in molecular diagnosis of CRC-induced IDA and decision-making regarding therapy (e.g., Vemurafenib is an iBRAF).
- Anatomic position of CRC- a right-sided CRC is predictive position CRC-induced-IDA.
- HER2 biomarker for metastatic CRC whose inhibitor (anti-HER2 agents such as Tucatinib and Trastuzumab) could be effective against HER2-positive CRC.
- PD-L1 Monoclonal Antibody Therapy- a novel therapy of choice for treating dMMR/MSI-H CRC.
- Conventional therapies such as 5-fluoropyrimidine (5-FU)- based therapy with oral capecitabine could be effective for MSS and stage III MSI primary SRCC

Comparison

Evidence-based studies ^[23-100]

- SRCC is a rare histological form of CRC with 0-12% 5-year survival interval. ^[23]
- It occurs predominantly in the young female gender.
- Usually right-sided colon cancer (especially of the appendix) is diagnosed at an advanced stage.
- Chronic anemia evidenced by the recurrence could be the clinical presentation.
- Early detection/screening tests could delay complications, and improve mOS
- Diagnosis made by histology/IHC of biopsied colonic tissues and lymph nodes.
- Cytogenetic and molecular tests for tumor markers could contribute to diagnosis and tailored treatment

Case scenario

- Index case was an SRCC with <2 years survival interval.
- The index case was an elderly male gender, unlike the prediction of previous studies.
- Diagnosed at an advanced stage (unresectable metastatic right-sided colon cancer).
- The patient presented with recurrent anemia refractory to blood transfusion with right leg swelling.
- No previous screening tests (i.e., FOB, colonoscopy)
- Abdominal CT scan with radio-contrast and histology of colonic/LN tissues contributed to diagnosis.
- The patient could not access molecular and cytogenetic tests to establish the tumor pattern

Expected outcomes

Policy formulations and operable framework for CRC ^[15,17,24-25,34-50,60,78-79,83,84,108,109]

Useful policies that will improve the diagnosis and treatment of CRC.

- Education- public health awareness campaign on CRC. Sensitization of the target population on risk factors (i.e., inactive physical activities, unhealthy diets, smoking, increased body mass index, etc) and preventive approaches such as engaging in healthy living lifestyle variables and access to quality healthcare.
- Institutionalize screening/early detection tests for CRC in the target population in health institutions. This includes but is not limited to:
 - Fecal Occult Blood Test (FOB)
 - FIT or HS-gFOBT
 - Complete Blood Count and Iron Study Tests
 - Investigational (molecular) tests for tumor markers such as (Hepcidin, IL-6, BRAF mutations, dMMR/MSI-H, HERS, PD-L1)
 - Colonoscopy
- Increase representation in clinical trials- therapeutic trials
- Early Treatment -using conventional and novel therapeutic interventions
- Surveillance- monitoring, and evaluation of CRC registry, case ascertainment, QALYs, DALYs, MMRs, mOS and LE of people living with CRC.

Figure 2. Summary flow chart of the problem statement, interventions, comparison, and expected study outcomes

Abbreviations: AOCD: Anemia of chronic disorder; CRC: Colorectal cancer; CT: Computed tomography; dMMR/MSI-H: Deficient mismatch repair and high microsatellite instability; FIT: Fecal immunochemical test; FOB: Fecal occult blood test; HS-gFOBT: High-sensitivity guaiac fecal occult blood test; ICC: Intracellular colonocyte; IDA: Iron deficiency anemia; IHC: Immunohistochemistry; LE: Life expectancy; LMIC: Low- and middle-income country; LN: Lymph node; MMRs: Morbidity and mortality rates; mOS: mean overall survival; MSS: Microsatellite-stable; QALY: Quality-adjusted life-year; SRCC: Signet ring cell carcinoma.

Table 1. Hematological findings in the case subject

Classifications	Investigation	Findings	Remarks
Hematologic investigations	Complete blood count		
	Red blood cell	2.2 (4.5 – 5.5)×10 ⁹ /L	L
	Hemoglobin concentration	4.8 (13–18) g/dL	L
	Hematocrit (%)	15.2 (40 – 52)	L
	Mean corpuscular volume	69.4 (73 – 96) fl	L; microcytosis
	Mean corpuscular hemoglobin	22.0 (27 – 36) pg	L
	Mean corpuscular hemoglobin concentration	31.7 (31 – 36) g/dL	N
	White blood cell	5.3 (4.0 – 10.8)	N
	Neutrophil	77% (40 – 77)	N
	Lymphocyte	18.1% (20 – 45)	L
	Monocyte	4.8% (2 – 10)	N
	Eosinophil	0.0% (1 – 5)	L
	Basophil	0.1% (<1)	N
	Platelet	378 (140 – 400)	N
Iron study			
	Serum iron	3.8 (11.6 – 31.3) µmol/L	L
	Serum ferritin	20.8 (34 – 310) ng/mL	L
	Transferrin	24.6 (20.2 – 44.8) µmol/L	N
	% Saturation	7.7 (20.2 – 55.0)	L
	Peripheral blood report (post-transfusion)	Rouleaux formation, a dimorphic spectrum of normocytic Myeloproliferative disorder; normochromic and microcytic hypochromic red cells. Leuco-distant metastatic tumor with erythroblastosis. Normal white blood cells. Neutrophil-to-background iron deficiency lymphocyte ratio of 1:1. Platelets are adequate in number and appearance anemia	
	Bone marrow study	Hypercellular marrow with a 3:1 myeloid-to-erythroid ratio. Lymphoproliferative disorder/ Normoblastic erythropoiesis with decreased erythroid activity. plasma cell dyscrasia: *SPE Normal granulopoiesis with sequential myeloid maturation and advised; metastatic tumor: **LNB mild eosinophilia. Increased lymphopoiesis with predominant and ***IHC advised small-matured-looking lymphocytes. Normal megakaryopoiesis with active budding pattern. Presence of few plasmacytoid cells with atypical mononuclear cell infiltrations into the bone marrow microenvironment	

Notes: Iron deficiency anemia: Low serum iron+low serum ferritin+low serum iron saturation and high/normal serum transferrin; Severe anemia: Low red blood cells+low hemoglobin concentration+low hematocrit.

Abbreviations: *SPE: Serum protein electrophoresis; **LNB: Lymph node biopsy; ***IHC: Immunohistochemistry; L: Low; N: Normal; H: High.

4. Discussion

Colorectal cancer ranks among the top five cancers with the highest global burden. In 2020, CRC accounted for 1.93 million of the 19.3 million newly diagnosed cancer cases.¹² It is the second most common cause of cancer-related death worldwide. According to the International Agency for Research on Cancer, there were 10 million cancer-related deaths in 2020, of which 915,880 were attributed to CRC. Colon and rectal cancers comprised

63% and 37% of these deaths, respectively.^{12,33} One in every three cancer-related deaths can be linked to unhealthy lifestyle behaviors, including physical inactivity, tobacco use, excessive alcohol consumption, increased body mass index, dietary factors such as low fiber diet, high consumption of animal fats, and inadequate consumption of fruits, vegetables, vitamins, and antioxidants. In addition, the lack of periodic screening contributes to CRC development.^{34,35} These unhealthy lifestyle

Table 2. Imaging (abdominal computed tomography and colonoscopy) results of the case subject

Test	Findings	Remarks
Abdominal computed tomography	- A circumferential thickening of a short segment (approximately 7 cm) of the colon involving the hepatic flexure and proximal transverse colon, with marked irregular luminal narrowing and paracolic fat stranding. - Multiple non-enhancing hypodense lesions in both liver lobes, the largest measuring 1.32×1.06 cm in segment VIII, which was suggestive of a hepatic cyst or tumor metastasis.	- Thickened colonic wall with luminal narrowing - Colonic tumor with possible hepatic metastasis
Colonoscopy	Colonic thickening with areas of hemorrhage.	Colonic neoplasm

Table 3. Histological results of lymph node and colonic tissue biopsies of the case subject

Test	Findings	Remarks
Lymph node biopsy	Effaced architecture due to invasive sheets, nests, and cords of malignant epithelial cells. Hyperchromic, irregular, pleomorphic nuclei with indistinct nucleoli. Extravascular tissue invasion with areas of hemorrhage.	Metastatic adenocarcinoma (Primary origin: Lung, gastrointestinal tract, or urogenital). An immunohistochemistry was recommended.
Colonic tissue biopsy	Histologic sections show a lesion composed of cells with signet ring-shaped nuclei and mucinous cytoplasmic inclusion. These cells are seen in clusters invading the muscularis mucosa.	Signet-ring cell colorectal carcinoma confirmed.

behaviors have been consistently linked to CRC in the literature.^{25-28,34-49}

SRCC is a histological subtype of CRC characterized by distinct molecular and tumor biology.⁵⁰⁻⁵² Although rare compared to AC, the most common CRC subtype, SRCC exhibits specific features. Primary SRCC is more often associated with female gender, younger age (<40 years), and molecular characteristics such as microsatellite instability (MSI) and activating *BRAF* mutations.^{50,51} The prognosis for SRCC is often poor, as most cases are diagnosed at an advanced stage.^{50,53-55} While primary SRCC is most commonly found in the stomach (96%), it can also occur in the colon, rectum, gallbladder, pancreas, urinary bladder, and breast.^{50,51,56}

In the case scenario discussed, the patient was a 77-year-old man who presented with recurrent IDA and bilateral leg swellings. He was diagnosed with primary SRCC of

Table 4. Clinical biochemistry results of case subject

Test	Findings	Remarks
Serum electrolyte urea creatinine		
Sodium	134.0 (135 – 145) mmol/L	L
Potassium	3.6 (3.5 – 5.0) mmol/L	N
Bicarbonate	26 (20 – 31) mmol/L	N
Chloride	100.5 (97 – 107) mmol/L	N
Calcium	2.22 (2.3 – 2.7) mmol/L	L
Urea	6.39 (1.7 – 9.1) mmol/L	N
Creatinine	115.36 (53 – 124) μ mol/L	N
Liver function test		
Total protein	68.3 (63 – 84) g/L	N
Albumin	36.72 (35 – 50) g/L	N
Total bilirubin	7.66 (0 – 17) μ mol/L	N
Conjugated bilirubin	2.5 (0 – 8.5) μ mol/L	N
Serum glutamic-pyruvic transaminase (alanine aminotransferase)	3.13 (0 – 37) U/L	N
Serum glutamic-pyruvic transaminase (alanine aminotransferase)	6.08 (0 – 39) U/L	N
Alkaline phosphatase	389.4 (64 – 306) U/L	H
Vitamin B12	251 (133 – 675) μ mol/L	N

Abbreviations: L: Low; N: Normal; H: High.

the colon (right-sided). Notably, increased age and male gender are not typically risk factors for SRCC. However, in this case, further investigations and palliative surgical resection were not feasible due to the patient's significantly deteriorating functional and clinical conditions. Unfortunately, the patient was lost to follow-up.

The critical issue in this case scenario is the relationship between IDA and CRC.

4.1. CRC and its association with IDA?

Studies have shown that about 6% of adults with IDA have underlying CRC, and this association is more common with the right-sided lesions than with the left-sided CRC.^{29,30} The proposed mechanism involves chronic occult blood loss (fecal occult blood), frequently observed in right-sided colon cancer. Unlike the overt bleeding often seen with left-sided CRC, occult blood loss in right-sided lesions is less easily detected, leading to delayed diagnosis.³⁰

4.1.1. IL-6-induced hepcidin theory

Colorectal cancer cells upregulate the cytokine IL-6, which stimulates the release of hepcidin.^{57,58} There is a direct correlation between IL-6 expression and the

Table 5. Comparison of clinicopathological findings of the case subject with previous evidence-based studies

Serial No	Clinic-biologic characteristics	Evidence-based studies	Case subject
1.	Age predilection	Predominantly affects young females.	The index case was an elderly male, which contrasts with the prediction of previous studies.
2.	Anatomical location	Right-sided colon cancer (especially of the appendix) is usually diagnosed at an advanced stage.	The diagnosis was made at an advanced stage (unresectable metastatic right-sided colon cancer).
3.	Pattern of anemia	Recurrent chronic anemia, typically with low serum ferritin, could be the clinical presentation.	The patient presented with chronic recurrent anemia refractory to blood transfusion, with right leg swelling. The red cells were microcytic with all the classical features of iron deficiency anemia.
4.	Screening tests	Early detection or screening tests can delay complications and improve overall survival.	No previous screening tests were performed on the index case. A colonoscopy and abdominal CT scan were performed at a late stage of the disease.
5.	Diagnostic histologic findings	SRCC is a rare histological form of CRC with a 0 – 12% 5-year survival rate.	The index case was diagnosed with SRCC and had a survival interval of <2 years.
6.	IHC	Histological diagnosis is common, but IHC of biopsied colonic tissues and lymph nodes provides more detailed immunologic information for novel therapies.	The diagnosis was made via histology and abdominal CT scan with radioactive contrast.
7.	Molecular biology/ cytogenetics	Cytogenetic and molecular tests for tumor markers, such as increased expression of IL-6 and hepcidin peptides, can aid in diagnosis and personalized treatment.	The patient did not have access to molecular and cytogenetic tests to determine the tumor characteristics.

Abbreviations: CRC: Colorectal cancer; CT: Computed tomography; IHC: Immunohistochemistry; SRCC: Signet ring cell carcinoma.

tumor-nodal-metastasis (TNM) stage, with higher IL-6 expression found in poorly differentiated tumor cells.⁵⁷ IL-6 is a pro-inflammatory cytokine,⁵⁹ while hepcidin, a type-2 acute-phase protein and antimicrobial peptide, regulates iron homeostasis by inhibiting both intestinal iron absorption and iron release from macrophages in the reticuloendothelial system.^{50,60-62} Hepcidin is a putative mediator of anemia of inflammation, including anemia of chronic disorder (AOCD) and IDA in CRC. It exerts its effect by downregulating ferroportin (iron-transport channel in duodenal enterocytes), leading to decreased iron absorption into circulation.⁶³ This inhibition occurs through the internalization and degradation of ferroportin, which blocks ferrous iron (Fe²⁺) export.^{50,62-64} This process results in an increase in cellular iron import proteins, such as transferrin receptor 1 and divalent metal transporter protein 1.⁶⁵ The hallmark is the accumulation of iron in the ferroportin, which leads to elevated intracellular iron levels in colonocytes – a condition that triggers activation of the Wnt oncogenic signaling pathway, a crucial factor in colorectal carcinogenesis.^{66,67} Increased intracellular iron levels in colonocytes, particularly in the context of adenomatous polyposis coli or beta-catenin mutations, result in the activation of the Wnt/ β -catenin oncogenic signaling pathway. This pathway plays an integral role in embryogenesis and adult tissue homeostasis, but its aberrant activation is linked to growth-associated diseases and cancers, especially in the initiation and progression of colorectal neoplasm.⁶⁸ Given its role in linking Wnt

oncogenic signaling with CRC, hepcidin is considered a proto-oncogenic factor. Its circulating levels may serve as a useful marker for CRC diagnosis. In addition, IL-6, which induces hepcidin, is associated with increased systemic hepcidin levels, which is positively associated with CRC progression.⁶⁹⁻⁷¹

4.1.2. Expression of hepcidin mRNA and its upregulators in colorectal cancer tissues

Colonic epithelial cells in CRC acquire the ability to express hepcidin, a protein physiologically produced by the liver. It has been shown that about 33% of CRC tissues express hepcidin mRNA.⁷¹ Further studies have demonstrated the overexpression of hepcidin upregulators, such as *TFR2*, *BMP4*, *STAT3*, *SMAD4*, *IL6*, and *p53*, in CRC tissues.^{69,70,72-74}

These findings suggest that hepcidin expression in CRC tissues may represent a novel oncogenic signaling mechanism, with its link to IL-6 offering a potential therapeutic target for CRC management.

4.2. IDA versus anemia of chronic disorder

4.2.1. Hepcidin's effect on erythropoiesis

In chronic inflammatory diseases, including malignancies such as cancers, AOCD is one of the most common forms of anemia, frequently mediated by hepcidin.⁷⁵ Hepcidin is regulated by iron availability, erythropoietic activity, and inflammation. Recent advances have enabled the measurement of hepcidin levels, offering

diagnostic potential.⁷⁶ Elevated hepcidin levels reduce iron absorption, promote ferroportin degradation, enhance iron storage, and lead to iron sequestration and restricted erythropoiesis.⁷⁵ The hallmark of IDA is the production of microcytic hypochromic erythrocytes, which is pathognomonic of the condition.⁷⁷ Although severe AOCD may present a similar morphological pattern to IDA, iron studies are usually used to confirm the diagnosis.⁵

4.2.2. Iron study findings

Iron studies serve as confirmatory tests for IDA, AOCD, acute iron poisoning, and iron overload. Three major laboratory parameters are required to differentiate IDA from AOCD: serum iron levels, TIBC, and serum ferritin levels. In IDA, serum iron and ferritin are low, while TIBC is high due to elevated UIBC. In contrast, AOCD presents with high serum ferritin, with serum iron and TIBC being normal or low. This pattern differs from iron overload, in which both serum iron and ferritin are abnormally elevated.^{5,77} In the presented case scenario, the patient's serum iron level was significantly low (3.8 $\mu\text{mol/L}$), with a serum iron saturation percentage of 7.7% (<10%) and serum ferritin lower than the reference range, confirming a diagnosis of IDA. If the patient had AOCD, serum ferritin levels would have been elevated. Although TIBC and UIBC were not provided, the serum iron level and percentage saturation were available. TIBC can be derived from UIBC and serum iron, following established formulas. IDA can also be defined by a serum iron-to-UIBC ratio of $\leq 1:10$ or a serum iron saturation percentage below 10%.⁵

4.2.3. Anatomical location of the primary tumor (right-sided colorectal cancer)

The anatomical location of the primary tumor in the presented case scenario is another factor supporting the diagnosis. The tumor was located on the right side of the colon, near the appendix and right hepatic flexure, an area commonly associated with chronic occult blood loss, as shown in prior studies of the right-sided CRC.^{30,51} A high index of suspicion for colon cancer is warranted in at-risk sub-populations presenting with IDA, as IDA serves as the only significant predictor of right-sided CRC, unlike other diagnostic pathways such as the Bowel Cancer Screening Program (BCSP) and the Symptomatic Pathway.⁷⁸ Furthermore, research shows an increased risk of delayed CRC diagnosis in populations lacking routine complete blood counts.⁷⁹

4.3. Challenges in the management of colorectal cancer

Management of CRC in low-income countries faces two major public health challenges: inadequate awareness

campaigns and insufficient health protection for affected populations.¹⁴⁻²² Disparities in CRC outcomes between low- and high-income countries can be attributed to limited healthcare access, delayed diagnoses, higher rates of late-stage complications, increased morbidity, underrepresentation in clinical trials, reduced use of novel therapies, and, ultimately, increased mortality.^{12,80-82} A systematic review and meta-analysis identified a correlation between pre-operative anemia in CRC patients and poorer prognostic outcomes, including reduced overall survival and shorter disease-free survival intervals.⁸³⁻⁸⁵ Therefore, periodic screening of average-risk populations (40 years and above) for colorectal neoplasms using clinical and laboratory interventions such as colonoscopy, fecal immunochemical test, high-sensitivity guaiac fecal occult blood testing, and carcinoembryonic antigen assays, can enhance early detection and improve survival rates.^{35,85} In this case, it took 3 months to confirm the diagnosis due to poor health literacy (awareness) and insufficient facilities for the early CRC detection. Early diagnosis is key to timely therapeutic intervention, reducing disability-adjusted years, and improving CRC survival outcomes. Health policies that support public education and targeted screening programs are strongly recommended to improve case detection and survival outcomes for colorectal neoplasm.^{85,86}

A colonoscopy, a procedure in which a physician examines the rectum and colon with a colonoscope,^{87,88} allows for the detection of irritated bowel, swelling, ulcer craters, polyps, hemorrhoids, masses, and tumors. This procedure is the gold-standard screening test for colorectal neoplasms.⁸⁸ However, in developing countries such as Nigeria, the average cost of a colonoscopy is approximately 1000 USD (about 750,000 NGN), and the colonoscopy rate is estimated at 1 per 600,000 people in Nigerian urban areas, with even lower access in rural communities.⁸⁸⁻⁹² This limited availability results in low colonoscopy utilization and suboptimal practice quality in Nigeria. A previous study showed that only 4.3% of the average-risk population in Nigeria undergoes periodic colonoscopy screening.⁸⁵ The most common indication for colonoscopy in Nigeria is unspecified gastrointestinal symptoms (47%), followed by lower gastrointestinal bleeding (24.2%). In this case, abnormal thickening of the right colon is observed in an abdominal CT scan, suggesting that early abdominal CT scans may serve as a cost-effective alternative to periodic screening colonoscopy.^{88,90} However, biopsy and histological examination of colonic tissue obtained during colonoscopy remain essential for confirming CRC diagnosis.⁹²

SRCC is a subtype of *BRAF*-mutated CRC characterized by a high prevalence of *BRAF* mutations, a low prevalence

of *KRAS* mutations, and an absence of E-cadherin expression, in contrast with AC of the colon.^{93,94} *BRAF*, a serine/threonine protein kinase, is involved in the mitogen-activated protein kinase signaling cascade, promoting cell proliferation, differentiation, migration, survival, and angiogenesis.⁹³ *BRAF*-mutated CRCs are usually right-sided, advanced-stage cancers associated with female patients, mucinous histology, and resistance to standard chemotherapies, with a mean overall survival of approximately 12 months.⁹⁴ These tumors also frequently exhibit deficient mismatch repair and high MSI (dMMR/MSI-H), imparting aggressive, high-grade, and stem cell-like properties.^{95,96} Notably, dMMR/H-MSI CRCs, which account for 5% – 15% of cases, show increased susceptibility to immunotherapy.^{97,98} At present, human epidermal growth factor receptor 2 (HER2) is emerging as a biomarker for metastatic CRC and other cancers, including gastroesophageal and breast cancers, providing an additional therapeutic target in CRC management.⁹⁹ Inhibitors of *BRAF* and *HER2* have demonstrated efficacy in modern therapeutic interventions for CRC.^{100,101}

The TNM staging and histological grade are critical factors in determining the overall prognosis of SRCC. Tumor staging is the most reliable predictor of SRCC prognosis, with higher tumor stages associated with poorer outcomes. The 5-year survival rate for SRCC ranges from 0% to 12%, and there is a significant risk of disease recurrence.¹⁰²⁻¹⁰⁴ A lower TNM stage, characterized by the absence of lymphovascular invasion and lymph node metastasis, generally indicates a more favorable prognosis and improved survival outcomes for SRCC patients.¹⁰³ For early-stage microsatellite-stable SRCC, the recommended treatment is adjuvant fluoropyrimidine (5-FU)-based therapy, commonly administered as oral capecitabine. Interestingly, a study demonstrated that stage III MSI-H primary SRCC responded more favorably to single-agent 5-FU adjuvant therapy compared to stage II disease.¹⁰⁴ Tucatinib (Tukysa) and trastuzumab (Herceptin) are newly approved monoclonal antibody therapies by the United States Food and Drug Administration for treating HER2-positive metastatic CRC.^{101,105} Their accelerated approval was granted after clinical trials showed that 40% of participants experienced tumor shrinkage following the combination therapy. Pembrolizumab, an anti-PD-L1 monoclonal antibody, has also proven effective in treating various solid tumors, especially in patients with unresectable or metastatic dMMR/MSI-H and high-tumor-mutational *RAS* wild-type CRC that has progressed following prior treatments without satisfactory alternatives.¹⁰⁶ Tumor cells expressing PD-L1 often evade the immune system through adaptive immune resistance mechanisms, including immune escape, MSI, cytotoxic

infiltrating lymphocytes, and medullary morphology. However, these tumors are more responsive to PD-1/PD-L1 inhibitors, such as pembrolizumab.¹⁰⁷

In the presented case scenario, the patient was diagnosed with advanced-stage (unresectable) primary SRCC of the right colon, with evidence of distant metastasis and local nodal involvement. Unfortunately, the patient was unable to undergo molecular testing or access the novel therapeutic options mentioned above before being lost to follow-up. It is clear that early detection and treatment could have significantly improved the patient's survival interval. The late diagnosis was partly due to the limitations of detecting CRC through the IDA pathway.¹⁰⁸ Early intervention might have better controlled the IDA if the CRC had been identified at an earlier stage, allowing for pre-operative management.¹⁰⁹

5. Conclusion

CRC should be considered a potential diagnosis in average-risk target populations (40 years and above) who present with chronic anemia or IDA. Therefore, periodic screening tests (such as fecal immunochemical test, high-sensitivity guaiac fecal occult blood test, carcinoembryonic antigen tumor marker assay, colonoscopy, and abdominal CT) are essential for early detection, timely treatment, and improved survival outcomes in this population. Hematological tests such as complete blood count, peripheral blood smear, and iron studies are the recommended diagnostic tools for CRC-induced IDA, according to consensus guidelines. In addition, the oncogenic signaling mechanism involving the IL-6-hepcidin pathway may provide a novel therapeutic strategy for CRC management. Evaluating serum levels of hepcidin and IL-6 could provide valuable insights for potential therapeutic interventions. Future research should explore anti-hepcidin and anti-IL-6 therapeutic strategies, which could not only ameliorate the severity of chronic IDA but also act as negative feedback mechanisms for the Wnt/ β -catenin oncogenic signaling pathway, which is involved in CRC progression. This article can be summarized with the flowchart in [Figure 2](#).

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

This is a perspective study with retrospective case scenario. The patient was lost at follow-up (demise). Therefore, it was not possible to obtain his consent.

Availability of data

The data supporting the results are available, and the authors are willing to share the same on request.

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