Case Report

When Iron Deficiency Is Not the Whole Story: Unicentric Castleman Disease Presenting as Persistent Microcytic Anemia in a Child

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ABSTRACT

Introduction: Iron deficiency anemia (IDA) is the most common cause of microcytic anemia in children and generally responds well to oral iron therapy. If the therapy fails, alternative causes need to be determined. Unicentric Castleman disease (UCD), a rare lymphoproliferative disorder, can mimic chronic inflammatory microcytic anemia. It is typically asymptomatic but smaller subsets will present localized mass, microcytic anemia and significant growth failure.

Aim: We highlight diagnostic anchoring on IDA, that delayed the diagnosis of inflammatory lymphoproliferative disease in a child with refractory microcytic anemia.

Case Presentation: A 7-year-old boy presented with symptomatic anemia (Hb 5.7 g/dL) and biochemical presumptive of IDA. Despite compliance with iron supplementation and nutritional intervention, hemoglobin levels remained low (6–7.6 g/dL) with microcytic, hypochromic features. Growth assessment demonstrated persistent below fifth centile. Further investigations revealed a state of chronic systemic inflammation, characterized by ESR >120 mm/h, CRP >100 mg/L and persistent thrombocytosis. Other blood investigations are not suggestive of chronic inflammation, connective tissue disease, and malignancy. Furthermore, abdominal mass was identified clinically, and it was confirmed with abdominal imaging revealed a 4.9x3.7x5.6cm, well-defined, homogenous enhancing mass in the left iliac fossa with associated satellite nodules. Subsequently, the patient underwent complete surgical excision of the 60g mass. Histopathological examination confirmed unicentric Castleman disease, revealing the pathognomonic "lollipop follicle" appearance: atretic germinal centers with prominent hyalinized postcapillary venules.

Conclusion: UCD is an important differential diagnosis in children with refractory microcytic anemia. Repeated physical examination, particularly abdominal assessment, may reveal occult masses, enabling timely diagnosis and curative excision.

Keywords: Iron Deficiency Anemia, Inflammatory Microcytic Anemia, Unicentric Castleman Disease

INTRODUCTION

According to World Health Organization, anemia remains a major global health burden where approximately 1.8 billion people worldwide affected notably children under five years being among the most vulnerable populations.[1,2] Nutritional causes especially iron deficiency associated with majority of anemia cases in children and commonly presents as microcytic hypochromic anemia.[2] The frequent association between

microcytic anemia and iron deficiency may lead to an initial therapeutic trial of iron supplementation However, failure of hemoglobin recovery despite adequate treatment should prompt re-evaluation, as persistent anemia may indicate either there is poor absorption, ongoing blood loss, haemoglobinopathy, chronic infection, inflammatory disease, or malignancy. In addition, anemia of chronic inflammation may also mimic iron deficiency which creates an important diagnostic challenge.[3]

Castleman disease is an uncommon non-clonal lymphoproliferative disorder associated with lymph node hyperplasia and dysregulated cytokine activity, particularly interleukin-6. It can be classified into two main groups, Unicentric and Multicentric Castleman Disease. Unicentric Castleman disease(UCD) often presents with localized lymphadenopathy or an incidental mass and it prognostically curable with complete surgical excision.[8,10] Diagnosis may be delayed especially in children due to their subtle or non-specific clinical features.[10, 11] We report a child with initial presumptive IDA whose persistent anemia, subsequently evolving inflammatory profile and eventually led to the diagnosis of UCD, highlighting the importance of avoiding diagnostic anchoring in common pediatric conditions.

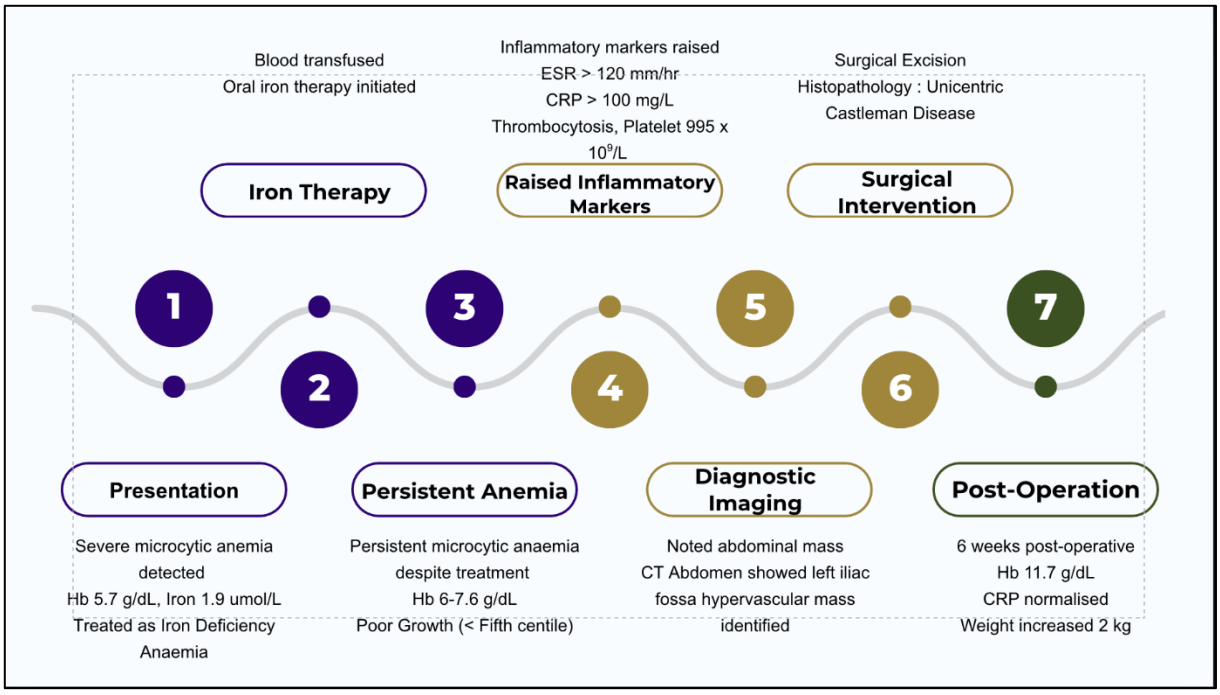
History

A 7-year-old boy presented with history of pale for several days and his blood parameters showed severe microcytic hypochromic anemia [hemoglobin level of 5.7 g/dL, mean corpuscular volume (MCV) of 36 fL, and mean corpuscular hemoglobin concentration (MCHC) of 30.8 g/dL]. Otherwise, he had no history of overt blood loss, tea-colored urine, bone pain, recurrent fever, or any constitutional symptoms. Furthermore, no significant history of malignancy or haemoglobinopathy is running in his family. His dietary history revealed selective eating behavior with suboptimal intake of iron-rich foods, supporting the initial diagnosis of nutritional iron deficiency anemia. His growth assessment showed both weight and height were below the 5th centile for age (Table 1). Clinically, he was markedly pallor, but no jaundice, abdominal mass, hepatosplenomegaly, or peripheral lymphadenopathy. Post-transfusion hemoglobin increased to 9.6 g/dL after he received packed red blood cell transfusion. Peripheral blood film demonstrated microcytosis, hypochromia with teardrop, target and cigar cells while serum iron was 1.9 umol/L, therefore a presumptive diagnosis of iron deficiency anemia was made. He commenced on oral iron supplementation together with nutritional intervention following packed red blood cell transfusion.

During outpatient follow-up, treatment compliance was reported to be satisfactory. However, his serial hemoglobin measurements remained persistently low, ranging between 6.0 and 7.6 g/dL, with ongoing microcytic hypochromic indices. His serial iron is still low 2.2 umol/L, ferritin (62.2 ng/ml) and transferrin (3.1 g/L) levels remain normal. On further history clarification, there was no chronic bleeding tendencies, recurrent vomiting, loss of appetite, night sweats or recurrent fever. Serial growth assessment demonstrated minimal interval weight gain and his height velocity was at 5cm per year. Clinically, noted a firm left iliac fossa mass measuring approximately

5×5 cm, with no palpable of peripheral lymphadenopathies. The chronological evolution of clinical, laboratory, and diagnostic findings is summarized in Figure 1

Figure 1. Diagnostic timeline of evolving iron deficiency and inflammatory anemia



Despite prolonged iron therapy, his serial laboratory results demonstrated persistent anemia, accompanied by thrombocytosis and progressively rising inflammatory markers [erythrocyte sedimentation rate (ESR) persistently above 120 mm/hr and C-reactive protein (CRP) exceeding 100 mg/L.]. The trend in hematologic and inflammatory parameters is summarized in Table 1.

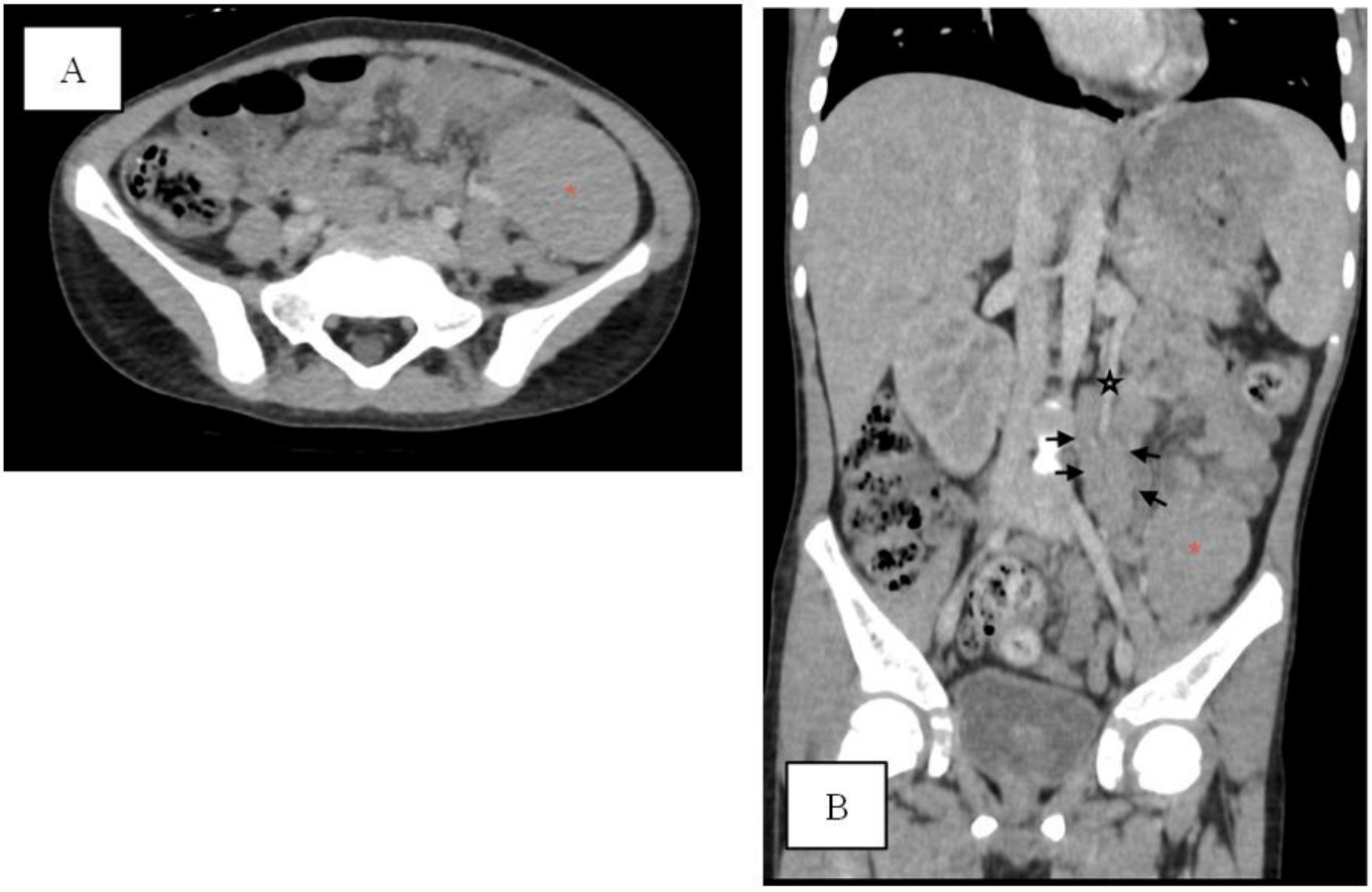
Table 1. Evolution of haematologic and inflammatory parameters during diagnostic workup

Parameter	At Presentation	After A Year of Iron Therapy	Post Excision (After 6 weeks)
Hemoglobin (g/dL)	5.7	7.6	11.7
Iron (umol/L)	1.9	2.2	-
Ferritin (ng/mL)	25	62.2	-
Platelet (x109/L)	762	995	369
ESR (mm/hr)	-	>120	3
CRP (mg/L)	-	>100	<0.5
Weight (kg)	16.2 (Less than fifth percentile)	16.3 (Less than fifth percentile)	18kg (Increased 2kg)
Height (cm)	112 (Less than fifth percentile)	117 (Less than fifth percentile)	125 (Less than fifth percentile)

At this point as shown in Table 1, the combination of persistent anemia, thrombocytosis, elevated inflammatory markers, and discordant iron studies raised suspicion of an alternative inflammatory process or neoplastic process rather than nutritional iron deficiency. Moreover, with newly detected left iliac fossa mass on examination, abdominal ultrasonography was performed to evaluate for an underlying inflammatory, infectious, or neoplastic

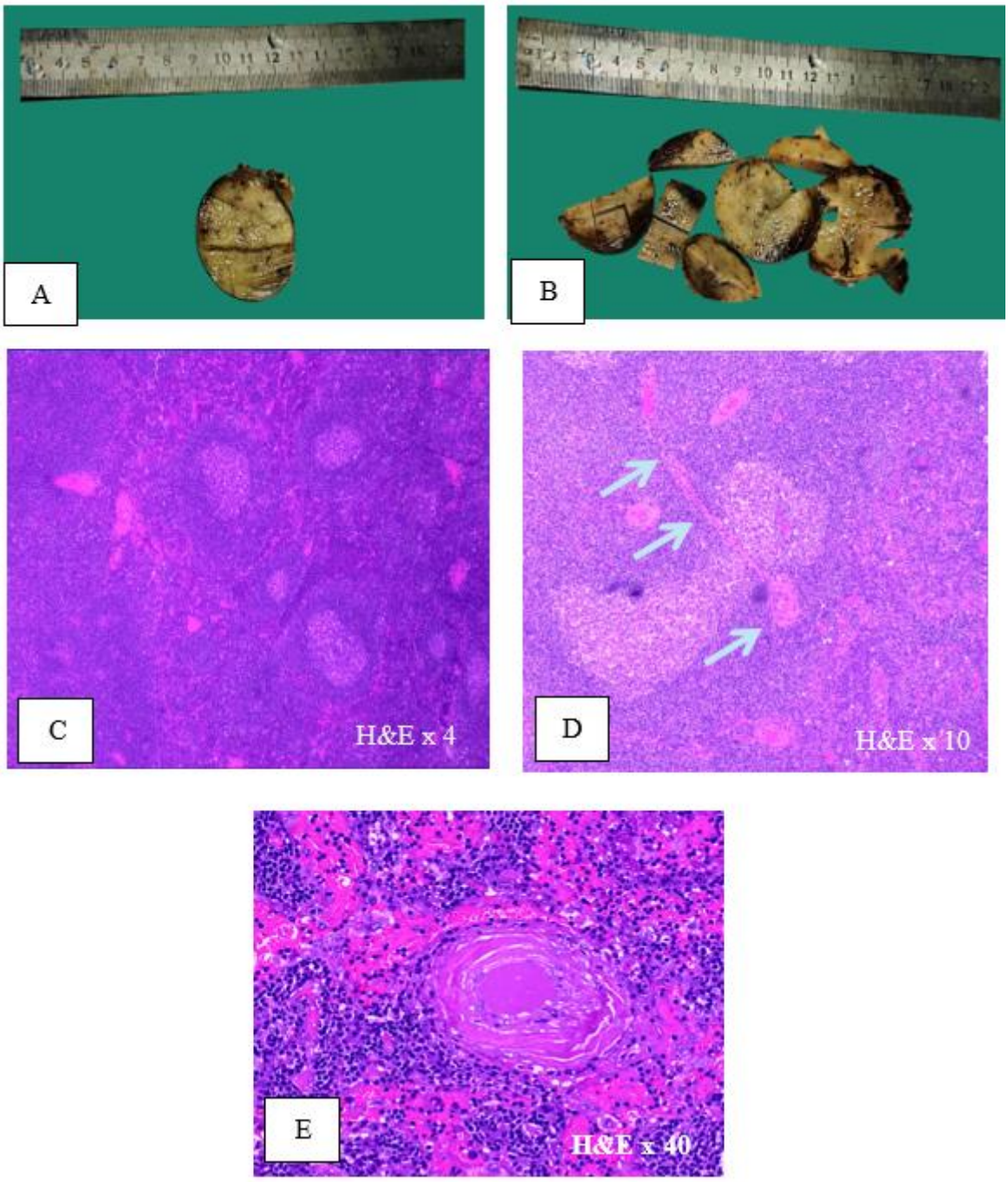
process. His abdominal ultrasound shows a well-defined mass at the left iliac fossa with internal vascularity. Thereby proceeded with contrasted CT Abdomen and reveals an oval shaped well circumscribed mass with homogeneous enhancement. Abnormally enlarged and matted nodes seen surrounding the left gonadal vein. Radiologic findings are illustrated in Figure 2.

Figure 2. Axial contrast-enhanced CT image (A) shows a well-defined homogenous enhancing mass at left iliac fossa about 4.9 x 3.7 x 5.6cm in size (* in A) centered at the left iliac fossa which does not appear to invade adjacent structures. Coronal CT image (B) shows that the mass (* in B) with multiple enlarged nodes (black arrows) surrounding the left gonadal vein (☆ in B)



Based on the radiologic findings, differential diagnoses included lymphoma, germ cell tumor, and other lymphoproliferative disorders. His autoimmune, tumor markers and connective tissue screening was unremarkable. Consequently, he underwent complete surgical excision of the lesion. Gross examination of the lesion demonstrated a well-circumscribed nodular mass measuring approximately 65×45×35mm and weight 60grams. Histopathological examination showed preserved nodal architecture with regressed germinal centers penetrated by hyalinized vessels, producing the characteristic "lollipop follicle" appearance, consistent with unicentric hyaline vascular Castleman disease. Gross and histopathological findings are shown in Figure 3

Figure 3. Gross specimen and microscopic features of Unicentric Castleman Disease**.** (A and B) Gross specimen showed a well-circumscribed nodular mass measuring approximately 6.5×4.5×3.5 cm and weight 60 grams**.** (C) Histopathological section demonstrates intact nodal architecture containing multiple lymphoid follicles of various sizes with prominent germinal centers. (D) The characteristic "lollipop follicle" appearance with hyalinized penetrating vessels, diagnostic of unicentric hyaline vascular Castleman disease. (E) Prominent hyalinization of postcapillary venule.



Eventually, following complete excision, he demonstrated rapid clinical and hematologic recovery. Six weeks post-operative, hemoglobin improved from 7.6g/dL to 11.7g/dL, with normalization of inflammatory markers (platelet count reduced from $762x10^9$/L to $369x10^9$/L, ESR normalized from >120 mm/hr to 3 mm/hr and CRP normalized from >100mg/L to < 0.5mg/L) and significant weight gaining (increased 2 kg). Moreover, his follow up ultrasound abdomen two months post-operation showed no residual mass detected.

DISCUSSION

Microcytic anemia is a hematological condition characterized by reduced mean corpuscular volume (MCV), commonly resulting from impaired hemoglobin synthesis. Iron deficiency anemia (IDA) is a leading cause of microcytic anemia in children worldwide. [1,2] As iron deficiency is a prevalent cause of microcytic anemia in children, a presumptive diagnosis of IDA may lead to the initiation of oral iron therapy. An adequate response to treatment is typically characterized by reticulocytosis within approximately one week, followed by an increase in hemoglobin of approximately 1–2 g/dL within four weeks.[4] Normalization of red cell indices and replenishment of iron stores occur more gradually over subsequent weeks to months.[4,5]

This case highlights the diagnostic challenge of persistent microcytic anemia initially attributed to iron deficiency but inadequately responsive to iron and nutritional therapy. At presentation, the child had severe microcytic anemia with markedly reduced serum iron and normal ferritin, prompting a presumptive diagnosis of IDA. Oral iron supplementation was initiated following packed red blood cell transfusion. However, despite prolonged treatment and reported adherence, hemoglobin recovery remained suboptimal during serial follow-up. As illustrated in Figure 1, persistent anemia was subsequently accompanied by poor growth, thrombocytosis, and markedly elevated inflammatory markers. This evolving clinical and laboratory profile suggested that nutritional iron deficiency alone could not adequately explain the persistent hematologic abnormalities and warranted further investigation for an underlying inflammatory disorder.

In addition, serial laboratory investigations provided important diagnostic clues. As shown in Table 1, serum iron was markedly reduced at initial presentation despite normal ferritin, prompting a presumptive diagnosis of IDA. However, microcytic anemia persisted despite subsequent normalization of serum iron, while thrombocytosis and markedly elevated ESR and CRP became increasingly apparent. This evolving biochemical profile raised the possibility that an underlying inflammatory process contributed to persistent anemia, rather than nutritional iron deficiency alone. One proposed mechanism is inflammation-mediated functional iron restriction, in which iron availability for erythropoiesis is reduced despite preserved iron stores.[6] In Castleman disease, increased production of inflammatory cytokines, particularly interleukin-6, may stimulate hepatic hepcidin synthesis. Hepcidin subsequently reduces intestinal iron absorption and inhibits iron release from macrophages, potentially limiting iron availability for erythropoiesis.[7] Although IL-6 and hepcidin levels were not measured in our patient, this proposed mechanism may explain the persistent anemia in the presence of systemic inflammation and its subsequent improvement following surgical excision. Consequently, serum iron and ferritin must be interpreted alongside inflammatory markers, as neither parameter in isolation reliably distinguishes absolute iron deficiency from inflammation-mediated iron restriction. [6]

The persistent inflammatory profile raised the need to identify an underlying source of inflammation. Subsequent identification of an occult intra-abdominal mass broadened the differential diagnosis to include chronic inflammatory, infectious, and neoplastic conditions. Histopathological examination ultimately established

the diagnosis of unicentric Castleman disease. Castleman disease is an uncommon non-clonal lymphoproliferative disorder associated with dysregulated cytokine production, particularly interleukin-6, which may contribute to anemia, thrombocytosis, and systemic inflammatory manifestations.[8,9] The clinical findings are often subtle or non-specific in children causing delayed diagnosis in this group.[10,11] De Heer-Groen et. al. describleed a 13-year-old girl with two years of iron-resistant microcytic anemia, fatigue, poor growth, elevated inflammatory markers, and normal ferritin, in whom repeated abdominal imaging eventually identified a mesenteric Castleman lesion. Complete surgical excision resulted in normalization of hematologic parameters and catch-up growth.[12] Chandrakasan et. al. later reported two additional children presenting with chronic iron-refractory microcytic anemia, growth failure, elevated inflammatory markers, and occult intra-abdominal UCD, both of whom demonstrated rapid hematologic recovery after surgery.[9] More recently, Okeleji et. al. described a 12-year-old boy with short stature, poor weight gain, abdominal pain, thrombocytosis, elevated ESR and CRP, normal ferritin, and retroperitoneal unicentric Castleman disease, with normalization of hemoglobin and inflammatory markers following complete excision.[13]

Several similarities exist between these published reports and our patients, including persistent microcytic anemia, growth impairment, elevated inflammatory markers, and occult intra-abdominal masses requiring imaging for diagnosis. Complete surgical excision was followed by hematologic and clinical improvement.

Beyond these similarities, our case highlights the importance of recognizing evolving clinical red flags during longitudinal follow-up. Although the initial presentation of severe microcytic anemia with markedly reduced serum iron (2.2 μmol/L) prompted a presumptive diagnosis of iron IDA, persistent anemia despite prolonged iron supplementation and reported treatment adherence warranted reassessment of the working diagnosis. The subsequent recognition of poor growth, thrombocytosis, markedly elevated inflammatory markers, and normalization of serum iron without corresponding hematologic recovery further suggested that nutritional iron deficiency alone could not explain the clinical course. These findings emphasize that follow-up should extend beyond monitoring hemoglobin and iron indices to include repeated clinical assessment and comprehensive physical examination. In particular, careful abdominal examination may reveal a previously undetected mass, provide an important localizing clue and prompting timely imaging for an underlying inflammatory or lymphoproliferative disorder.

Retrospectively, this case also illustrates the potential impact of diagnostic anchoring bias in pediatric practice. Continued attribution of persistent microcytic anemia to nutritional iron deficiency may delay recognition of an evolving underlying pathology, particularly when the initial diagnosis appears plausible. Earlier reconsideration of the diagnosis may have been warranted when hemoglobin recovery remained inadequate despite reported adherence to treatment. Rather than continuing iron supplementation under the initial diagnostic assumption, clinicians should reassess the clinical history, treatment response, growth trajectory, laboratory trends, and physical findings. The coexistence of refractory anemia, growth impairment, thrombocytosis, and systemic inflammation

should prompt investigation beyond nutritional deficiency, including consideration of occult inflammatory, infectious, and neoplastic conditions.

Conclusion

This case highlights the diagnostic complexity of persistent microcytic anemia in children and the importance of reconsidering an initial diagnosis when the clinical course is inconsistent with the expected treatment response. Although severe microcytic anemia and markedly reduced serum iron initially suggested iron deficiency anemia, persistent anemia despite iron supplementation, poor growth, thrombocytosis, and markedly elevated inflammatory markers prompted further investigation, ultimately leading to the diagnosis of unicentric Castleman disease. Complete surgical excision was followed by rapid hematologic and clinical recovery. Clinicians should recognize evolving red flags, reassess the working diagnosis, and perform repeated comprehensive physical examinations, particularly when presumed iron deficiency anemia fails to respond as expected. Early recognition of discordant clinical and laboratory findings may facilitate timely imaging, reduce diagnostic delay, and identify potentially curable underlying conditions.

Learning Points

1. Persistent microcytic anemia despite adequate iron therapy and nutritional intervention should prompt reassessment of the diagnosis and investigation for alternative etiologies.

2. Poor growth, thrombocytosis, elevated inflammatory markers, and discordance between iron studies and hematologic recovery are important to evolving red flags. Repeated comprehensive physical examination, particularly abdominal examination, may reveal previously undetected pathology.

3. UCD should be considered as a potential underlying cause of refractory microcytic anemia with systemic inflammation, particularly when an intra-abdominal mass is identified, as complete surgical excision may be curative.

Consent for publication

Written informed consent for publication of this case report and accompanying images was obtained from the patient's parent/legal guardian.

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