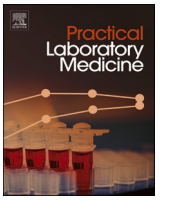
Practical Laboratory Medicine 45 (2025) e00459

Contents lists available at ScienceDirect

Practical Laboratory Medicine

journal homepage: www.elsevier.com/locate/plabm



A 9-year-old child presenting with anemia accompanied by abnormal red blood cell morphology

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ARTICLE INFO

Keywords:
Anemia
Abnormal erythrocyte morphology
Sideroblastic anemia
Children

ABSTRACT

Cases of anemia presenting with abnormal erythrocyte morphology often pose diagnostic challenges, particularly in patients with refractory anemia. Here, we present the case of a 9-year-old male patient under investigation for anemia, who had a history of anemia and received a blood transfusion at birth. Despite the absence of obvious clinical manifestations related to anemia thereafter, his condition was not given due consideration. The patient experienced a sudden onset of illness and was initially suspected to have thalassemia. However, subsequent pertinent examinations, notably bone marrow aspiration and genetic testing, led to the diagnosis of hereditary sideroblastic anemia alongside chronic atrophic gastritis. This case illustrates the diagnostic journey of anemia characterized by abnormal red blood cell morphology, aiming to facilitate early and accurate diagnosis, as well as prompt treatment, for such patients in clinical practice.

1. Introduction

In clinical practice, the observation of anemia in a patient, coupled with a microscopic examination of a blood smear revealing a significant presence of erythrocytes with aberrant morphology, demands serious attention. Such anomalies in erythrocyte morphology can serve as indicators of various underlying conditions, encompassing autoimmune hemolytic anemia (AIHA), microvascular hemolytic anemia (MAHA), and hemoglobinopathies [1]. These deviations often signify shared pathways in disease mechanisms, encompassing erythrocyte destruction, altered functionality and structure, and irregular metabolic processes [2]. Additionally, beyond hemolytic disorders, aberrant erythrocyte morphology is also observed in conditions such as megaloblastic anemia (MA) [3], myelodysplastic syndromes (MDS) [4], severe iron-deficiency anemia (IDA) [5], and metastatic cancers. Although the final diagnosis in the case report referenced herein was sideroblastic anemia (SA), further comprehensive evaluation and diagnostic procedures are imperative to elucidate the etiology and formulate an appropriate treatment strategy.

Sideroblastic anemia (SA) represents a rare hematologic disorder categorized into two distinct types: acquired SA and hereditary SA [6], with acquired SA exhibiting a higher prevalence. Acquired SA typically stems from bone marrow irregularities, exposure to toxins, or nutritional deficiencies, predominantly affecting elderly individuals. Conversely, hereditary SA manifests more frequently in children and necessitates meticulous morphological and cytogenetic assessment for diagnosis. The hereditary form often arises from a missense mutation in the ALAS-2 gene located on the X chromosome, leading to a predisposition to iron overload [7]. Treatment modalities necessitate a personalized approach. For acquired SA, therapeutic interventions encompass blood transfusions, pyridoxine

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https://doi.org/10.1016/j.plabm.2025.e00459
Received 25 September 2024; Accepted 26 February 2025
Available online 20 March 2025
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supplementation, iron overload correction, and genetic counseling [8].

Hence, in our clinical practice, prompt and precise diagnosis, and treatment are imperative upon encountering abnormal erythrocyte morphology in peripheral blood. Such measures are pivotal for enhancing patient survival and quality of life.

2. Case presentation

The patient, a 9-year-old male, presented with pre-admission hemorrhagic pallor, malaise, poor concentration, and loss of appetite. He was born prematurely at 32 + 4 weeks and was previously admitted to a local hospital for "anemia" shortly after birth, where he received two blood transfusions before discharge. The parents reported good health with no history of hereditary diseases, and no other family members were known to have any related conditions. The results of routine blood tests conducted at our hospital are summarized in Table 1. The patient exhibited decreased levels of RBC, HB, MCV, and RDW-SD. Microscopic examination of the blood smear revealed irregularities in the size of mature erythrocytes, including elliptical, tear-drop, and target forms, along with a noticeable increase in erythrocyte fragments (Fig. 1). The lobular erythrocyte ratio was 10.6 %.Due to the patient's low hemoglobin levels upon admission, he received 1.0 unit of A type Rh-positive irradiated suspended erythrocytes. The transfusion process proceeded smoothly, and the child did not experience fever, chills, rash, nausea, or other discomforts. Urine analysis, liver and kidney function tests, coagulation studies, and CRP levels were all within normal ranges. Abdominal ultrasound revealed hepatosplenomegaly. The preliminary diagnosis of the child was hemolytic anemia (HA).

Continuing with further refinement of relevant tests: the reticulocyte cell count measured at 1.17 %. Erythrocyte and leukocyte CD55 and CD59 levels were all within the normal range. Hemoglobin electrophoresis revealed no significant abnormalities. The Coombs test also showed no significant abnormalities. Additionally, the thalassemia gene test yielded normal results. Serum iron levels were measured at 59.2 μmol/L, with unsaturated iron binding capacity at 4.9 μmol/L, and total serum iron binding capacity at 64.1 μmol/L, resulting in a transferrin saturation of 92.4 %. Glucose 6-phosphate dehydrogenase activity was determined to be 4556 U/L, thus ruling out hemolytic anemia. Although the child did not present with black or bloody stools, a stool monoclonal antibody occult blood test returned weakly positive results. Given the possibility of occult hemorrhage, vigilance for Meckel diverticulum is warranted. Further imaging to assess ectopic gastric mucosa is recommended to assist in diagnosis. Gastroscopy findings indicated chronic atrophic gastritis (Fig. 2), while no signs of Meckel's diverticulum were observed.

To further investigate the cause of anemia, we conducted repeated routine blood tests following the child's admission. These tests revealed a significant decrease in the peripheral blood red cell count, while the granulocyte and megakaryocyte lineages remained relatively unaffected. This prompted consideration of pure erythrocyte aplastic anemia and early-stage myelofibrosis. Further diagnostic refinement was achieved through bone marrow aspirate smears. Analysis of the bone marrow image indicated an increased proportion of ring-shaped iron granulocytes (Fig. 3), with iron staining revealing external iron: 2+, and internal iron accounting for 96 % of iron granulocytes (of which ring-shaped iron granulocytes constituted 22 %). Additionally, abnormal red blood cells were observed in the smear. Considering these findings alongside the patient's clinical history, a diagnosis of ferrocytic anemia was made. Ferrocytic anemia, classified into hereditary and acquired types, prompted additional investigations including trace element analysis, whole exome sequencing, and genetic abnormality testing (using fluorescence in situ hybridization (FISH)). Trace element levels (lead, thallium, mercury, cadmium, arsenic) were found to be within normal range. The genetic examination of the child revealed X-linked recessive inheritance, with the identified genetic marker being ALAS2 (located at Xp11.21). Further analysis of MDS chromosomes and genes via fluorescence in situ hybridization (FISH) showed no significant abnormalities. Ultimately, the patient received a diagnosis of hereditary ferrocytic anemia alongside chronic atrophic gastritis. Treatment comprised intravenous infusion of vitamin B6, rehydration, and other symptomatic supportive therapies. The child's clinical symptoms have since improved, with a rebound in hemoglobin levels and stable condition. Consequently, medication is being continued, with regular reviews and monitoring in place.

Table 1
Report of routine blood tests for this child.

Variable Blood (abbreviation)	Reference Range	Day 1	Day 2	Day 4	Day 5	Day 8	2 weeks post-discharge
WBC (10^9/L)	4.30–11.30	6.20	6.19	4.79	4.34	5.68	5.52
NEUT (%)	31.0–70.0	56.0	51.0	47.0	55.1	47.1	40.6
LYMPH (%)	23.0–59.0	37.8	38.8	44.7	37.6	46.6	50.9
MONO (%)	2.0–11.0	4.8	6.0	5.8	4.6	5.5	5.3
EOS (%)	0.0–9.0	0.9	2.2	2.0	0.9	0.7	2.6
BASO (%)	0.0–1.0	0.5	0.2	0.5	0.8	0.1	0.6
RBC (10^{12}/L)	4.20–5.70	3.83	4.47	3.89	3.63	4.18	4.81
HBG (g/L)	118–156	64	83	71	68	82	95
HCT (%)	36.0–46.0	22.1	27.2	23.8	22.3	25.9	32.1
MCV (fL)	77.0–92.0	57.7	60.8	61.3	61.3	62.0	66.8
MCH (pg)	25.0–34.0	16.7	18.6	18.3	18.6	18.7	19.7
MCHC (g/L)	310–355	290	305	298	305	301	296
RDW-SD (fl)	38.4–47.8	102.7	108.6	115.2	108.1	116.6	101.2
PLT (10^9/L)	167–453	452	438	524	556	561	458
Ret (%)	1.06–3.00	1.78	–	0.43	0.25	–	–

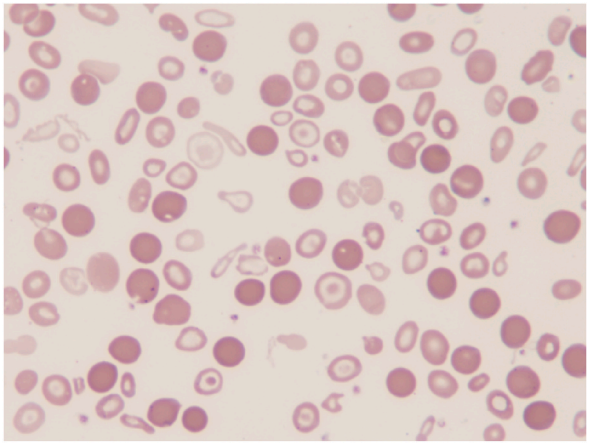

Fig. 1. Peripheral Blood Smear (Magnification X1000): Oval-shaped erythrocytes, teardrop-shaped erythrocytes, target-shaped erythrocytes, and erythrocyte fragments are prominently visible.

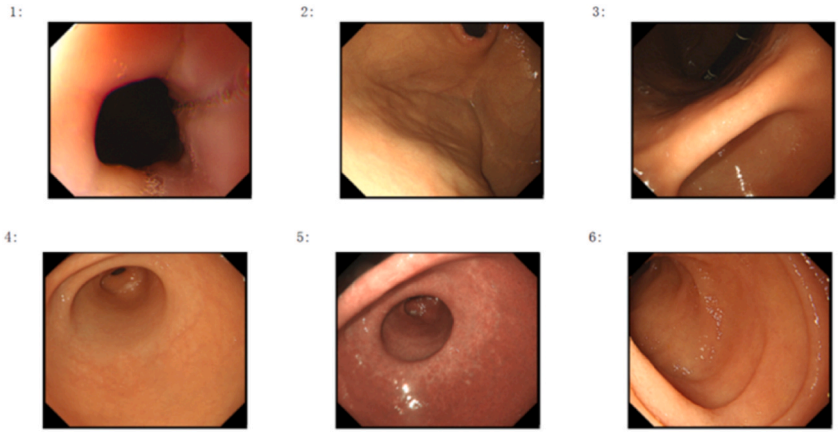

Fig. 2. Gastroenteroscopic images of the child.

3. Discussion

The present case report underscores the critical importance of promptly identifying aberrant red blood cell morphology in clinical practice, particularly in patients presenting with anemia, where keen observation is paramount. Such anomalies may signal various underlying conditions, including hemolytic anemia, megaloblastic anemia, severe iron deficiency anemia, sickle cell anemia, metastatic cancer, and bone marrow infiltrative diseases. The diagnostic approach employed in this cohort of cases is outlined in Fig. 4. These deviations in erythrocyte morphology often hint at shared pathogenic pathways, encompassing factors such as erythrocyte degradation, functional and structural changes, as well as anomalies in production and metabolism. Given the youth of the patient in this instance, considerations initially leaned towards thalassemic hemolytic anemia or occult hemorrhage stemming from Meckel's diverticulum. Subsequent to ruling out common maladies, a bone marrow aspiration was conducted. The bone marrow iron staining of the patient revealed a substantial presence of ring-shaped ferritic erythrocytes, prompting consideration of ferritic anemia or MDS-SF3B1. Thus, further genetic screening is imperative to validate this suspicion. Unfortunately, genetic testing was not performed on the patient's parents, as they did not report any symptoms.

In addition to congenital iron-granulocytic anemia, the patient in this case also presented with concurrent chronic atrophic gastritis, a condition characterized by prolonged inflammation and progressive atrophy of the gastric mucosa. We postulated that the interplay between these two conditions may involve disruptions in iron metabolism and nutrient provision to the gastric mucosa. Patients with congenital iron-granulocytic anemia often experience anemia due to impaired erythropoiesis. This anemia results in tissue hypoxia due to reduced oxygen supply, which can affect various organs, including the gastric mucosa. Consequently, vasculopathy and inadequate blood perfusion may ensue, predisposing to the development of chronic atrophic gastritis. Furthermore, individuals with congenital iron-granulocytic anemia may accumulate excessive iron due to multiple transfusion treatments, a known risk factor for chronic atrophic gastritis. Iron deposition in the stomach can induce cellular damage to the gastric mucosa, exacerbating the gastritis process.

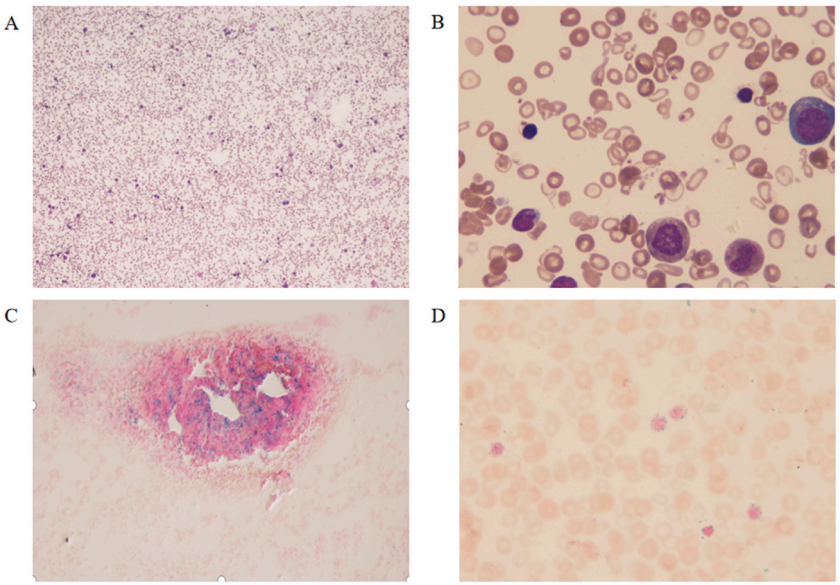

Fig. 3. Bone Marrow Smear with Iron Staining. (A) Bone Marrow Blood Smear (Magnification 100 X): Demonstrates active bone marrow proliferation. (B) Bone Marrow Blood Smear (Magnification 1000 X): Reveals a significant presence of mature erythrocytes exhibiting abnormal morphology, along with evident cytoplasmic empty halos in young erythrocytes. (C) Bone Marrow Iron Staining (Magnification 100 X): Indicates external iron deposition at 3+ intensity. (D) Bone Marrow Iron Staining (Magnification 1000 X, Oil Microscopy): Displays internal iron deposition, appearing as ring-shaped ferritin granules within young cells.

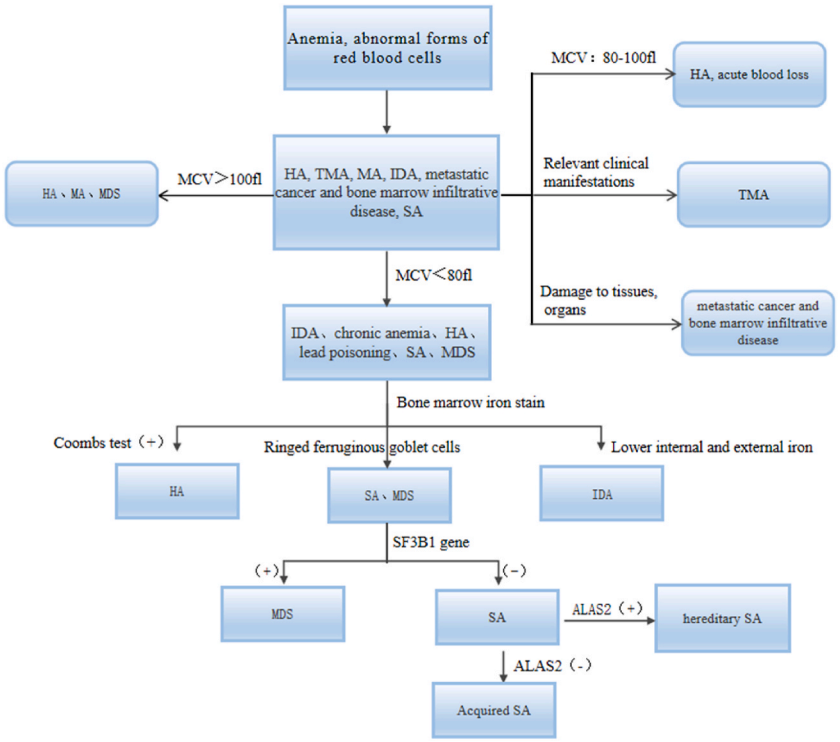

Fig. 4. Diagnostic process of anemia with abnormal red blood cell morphology.

4. Conclusion

In clinical practice, when managing children with refractory anemia, it is essential to consistently prioritize careful observation of their clinical manifestations and pertinent examination results, particularly screening for any abnormalities. Through offering early diagnosis and timely treatment to patients, we can significantly enhance the quality of their survival.

CRediT authorship contribution statement

Huijun Qin: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Yuan He:** Investigation, Software, Supervision, Validation. **Zaixiang Xie:** Funding acquisition, Methodology, Writing – review & editing.

Statement of ethics

I ensure that the work described has been carried out in accordance with *The International Code of Ethics of the World Medical Association*. This work has been conducted in accordance with ethical principles and guidelines. The research protocol and procedures involved in this study have been reviewed and approved by the appropriate Ethics Committee or Institutional Review Board.

All participants involved in this study were fully informed about the nature, purpose, and potential risks and benefits of their participation. They provided voluntary and informed consent to participate, and their confidentiality and privacy rights have been strictly protected throughout the study.

The ethical considerations guiding this work include.

1 Informed Consent: Participants were provided with comprehensive information about the study objectives, procedures, potential risks, benefits, and their rights as participants. They were given adequate time to ask questions and make an informed decision about their participation. Written informed consent was obtained from each participant prior to their involvement in the study.
2 Confidentiality: All personal and sensitive information obtained from participants has been treated with strict confidentiality. Data collected has been anonymized and stored securely to protect the privacy of participants.
3 Respect for Participants: The dignity, rights, and well-being of all participants have been upheld throughout the study. Participants were treated with respect, and their autonomy was respected in all aspects of the research process.
4 Ethical Conduct of Research: This study has been conducted with integrity, honesty, and transparency. Researchers have adhered to professional standards and ethical guidelines in all stages of the research, including data collection, analysis, and reporting.
5 Compliance with Regulations: This work complies with all relevant laws, regulations, and ethical standards governing research involving human participants. Any deviations from standard ethical procedures have been duly justified and documented.

This Statement of Ethics affirms our commitment to conducting research that upholds the highest ethical standards and ensures the well-being and rights of all participants involved.

Funding source

The project was carried out without any specific support.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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