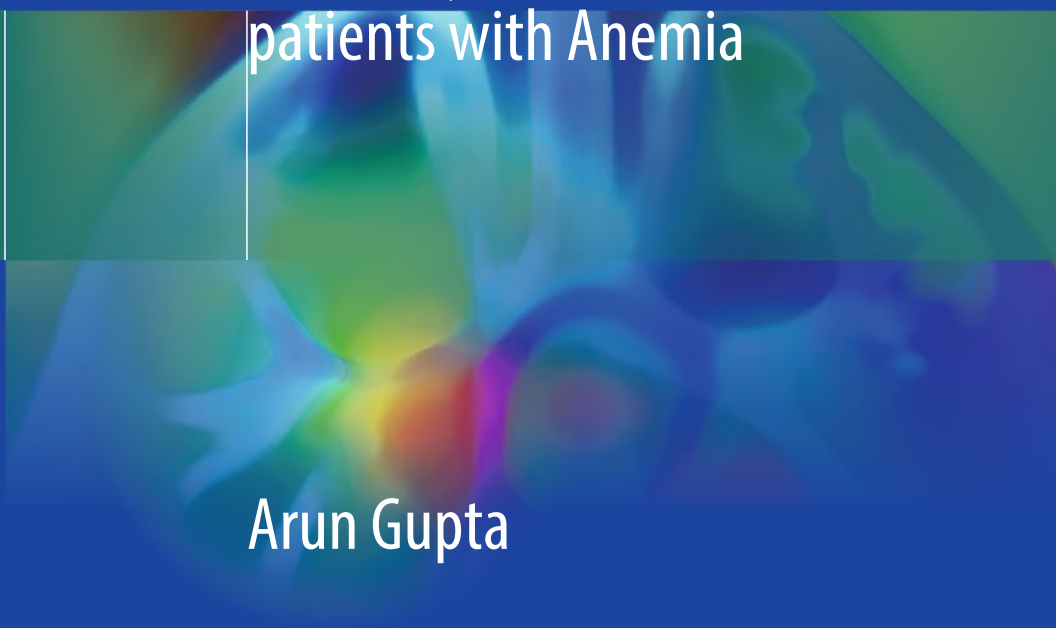
Decision Making Through Problem Based Learning in Hematology

A Step-by-Step Approach in patients with Anemia



Arun Gupta

Springer

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A Step-by-Step Approach in patients with Anemia

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Foreword 1

It is a great pleasure to write a brief foreword for this excellent hematology book written by Dr. Arun Gupta. Hematology was being practiced by both physicians and pathologists differently in different parts of the world until its recognition as a separate medical specialty. Long back, Dr. Arun Gupta started his professional career in hematology as a hematopathologist. Thus, his knowledge and expertise in laboratory hematology are immensely sound. Presently, practicing as a consultant and teacher in clinical hematology, his expertise in the correlation of patients' clinical presentation with precisely chosen laboratory investigations is of unique advantage. Now is the era of bedside teaching, interactive group discussions, and literature search for accurate information and its translation into diagnostic and management practices in patient care. His book is most appropriately titled "Decision Making Through Problem Based Learning (PBL) in Hematology—a Step-by-Step Approach." This book is what it really states. His description of 25 cases with step-by-step resolution of the patient's problems in a unique sequential manner is exemplary.

About the book itself: Apart from the wonderful layout of the patients' clinical presentation followed by step-by-step description of relevant laboratory investigations leading to firm diagnostic information, I consider two more features that attract appreciation and special mention. These include (a) the wonderful photographs, particularly of the microscopic pictures along with intelligent graphic illustrations, and (b) inclusion of some cases of not-so-common types of anemia such as cold agglutinin disease, paroxysmal cold hemoglobinuria, and anemia related to copper deficiency.

To happily mention, last but not least is that I feel immensely happy and privileged that Dr. Arun Gupta has been one of my favorite students and then after, a highly dedicated and committed colleague. Fortunate is the teacher whose student excels him like a father whose son beats him in reaching higher professional standing.

Professor and Consultant in Hematology,
Kuwait (Retired)

Ramesh Arya

Foreword 2

Hematology, the study of blood and blood-related disorders, demands not only a deep understanding of the science but also the ability to apply that knowledge in real-world scenarios.

This book introduces a dynamic approach. It transcends traditional didactics, emphasizing hands-on problem-solving. It offers a comprehensive and innovative guide to navigating the complex world of hematology, with a specific focus on anemia patients. Problem-based learning (PBL) empowers learners to actively engage with and solve actual clinical challenges.

This invaluable resource reflects the transformative power of problem-based learning. Whether you are a seasoned healthcare professional seeking to enhance your skills or a student embarking on a journey in hematology, it equips you with the tools necessary to make sound decisions, ultimately leading to improved patient outcomes.

Welcome to a new approach to hematology education and practice.

Professor Kuwait University,
Safat, Kuwait

Rajaa Marouf

Foreword 3

Dr. Arun Gupta has written a unique textbook of anemias that will have a useful role for medical students and even for postgraduate students in the early phase of their training. The case-based approach to anemias is an innovative and effective way of teaching medical students the fundamentals of the pathophysiology and pathology of anemias. The approach and framing of the questions are logical and follow a stepwise rational approach. Dr. Gupta's description and delivery are unique and provide a valuable resource for students on anemias. Case scenarios on anemias are well written and adopt a problem-oriented approach and provide the framework on which students can build.

Emeritus Professor of Medicine,
East TN State University,
Johnson City, TN, USA

K. Krishnan

Foreword 4

I am delighted to introduce this book, "Decision Making Through Problem Based Learning in Hematology: A Step-by-Step Approach in Patients with Anemia," by Dr. Arun Gupta. This book is a valuable resource for those who want to learn more about the diagnosis and management of anemia, a common and often complex hematological condition. The book covers various aspects of anemia, from its pathophysiology and symptoms to its evidence-based management. The book adopts a problem-based learning approach, which encourages the reader to apply their knowledge and skills to real-life scenarios and cases. The book also provides key points and summaries for each chapter, as well as a unique question–answer format that facilitates comprehension and retention. The book is suitable for students, teachers, clinicians, and researchers who are interested in hematology and anemia. It is also a useful reference for exam preparation and clinical practice. I congratulate Dr. Gupta for his excellent work and contribution to the field of hematology. I hope that you will enjoy reading this book and find it informative and helpful.

Faisal A. Alsayegh
Consultant Hematologist Associate Professor,
College of Medicine, Kuwait University,
Hawally, Kuwait

Foreword 5

ले जनरल नरेन्द्र कोतवाल, एस एम, वी एस एम
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FOREWORD

1. Hematology is a link between numerous subspecialities of medicine. Since ages, this has been an inseparable and indispensable branch of medical science. Almost everyone suffers from anemia once in their lifetime, be it a young or old.

2. The new system of medical training makes it mandatory for trainees to learn interpretation of laboratory data as soon as they enter second year of their training. At that time a book which provides information in simplified way is of much help to students. The postgraduates who specialize in hematology need in depth understanding of diseases and since anemia is the most common of all hematological diseases, this book will be of immense help to both postgraduates as well as physicians interested in managing patients of anemia.

3. I am very happy that Dr Arun Gupta who is my colleague and friend from our days together as undergraduate students has come up with such wonderful piece of work. Dr Arun Gupta pursued his postgraduate qualification from PGIMER Chandigarh, India and has acquired distinction of being certified as Diplomate National Board from National Board Pathology, India. He has acquired proficiency in hematology while working as member of faculty in Medical College Srinagar, India and as a Consultant Haematologist in middle east.

4. With his experience of over 25 years of working as a Consultant and teacher in hematology, he has acquired immense experience in both laboratory and clinical hematology and his experience, which is reflected in this book, will be of utmost benefit to readers. This book titled 'Problem based learning in Hematology-a step-by-step approach in patients with Anemia' covers wide range of topics on anemia from common types to rare ones, written in easy to recall question-answer format with excellent images and supportive graphic illustrations. I am sure this book will become a single compiled source of information for all readers as it has been written with incredible depth and breadth of knowledge, as well as with clarity and eloquence of expression.

5. I congratulate Dr Arun Gupta for bringing up such brilliant and original contribution to the field of Hematology and wish him good luck for all future endeavors.

Place: Pune

Date: 30 Sep 2023

AFMC,
Pune, India

(Narendra Kotwal)
Lt Gen
Director & Commandant
Lt Gen Narendra Kotwal

Foreword 6

It is indeed a privilege to write a foreword for a book being authored by a colleague who has been a close associate right from the undergraduate days to the postgraduate journey together.

Dr. Arun Gupta, an alumni of Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, has been an acclaimed clinical hematologist and hematopathologist for the past more than 20 years working in different capacities in Kuwait.

A very avid postgraduate and undergraduate teacher, he has been a keen researcher as well and has to his credit many international publications of high impact.

This book mainly lays stress on different types of anemias, their pathophysiology, and laboratory workup. The focus laid down in the problem-based learning (PBL) in each type of anemia is noteworthy. It is going to be of immense help not only for pathology residents but for clinical residents as well.

Dr. Arun Gupta has put in lots of hard work in making things look so simplified, especially the elaborate account of 25 cases of anemia with a stepwise approach for their evaluation and diagnosis.

The quality of photomicrographs has been excellent and so is their graphic description.

I wish Dr. Arun Gupta a huge success for his editorial venture.

Professor Pathology Medical College,
Jammu, India

Subhash Bhardwaj

Preface

This is an era of evolving teaching methods for medical students. The scenario is drifting away from traditional classroom teaching. Now, medical students are exposed to patients in clinics and wards as early as in the second year of their training, and a problem-based learning (PBL) has been advocated to impart more analytical power to students. PBL fosters critical thinking, clinical reasoning, and teamwork skills. PBL also helps to integrate basic science and clinical knowledge in a meaningful way. Unfortunately, students at that stage of training do not have the acumen to do concise literature search, have few or no comprehensive sources of information, and need guidance to access the wealth of knowledge available for programmed hematology training. This is time consuming and frustrating for many.

This book is written with an aim to bridge the gap in acquiring information, which can be transformed into clinical practice in a simple straightforward manner. It is based on problem-based learning in patients with anemia and will provide all relevant information at one platform. In this book, you will find 25 case scenarios that cover various aspects of anemia, followed by step-by-step investigations and their interpretation, trigger questions, key concepts, and references. Each case emphasizes a systematic approach for the analysis of laboratory information to exclude possible differential diagnoses and how to correlate results of tests done with final diagnosis.

The evaluation of each case is discussed in a question–answer format, as is expected in exams. Presentation is in the form of tables, diagrams, microscopic images including morphology, flow cytometry results, and molecular defects. An important aspect of the book is the explanation of each answer based on evidence from literature.

A brief description of the disease on its pathophysiology, clinical symptoms, and signs and most recent information is included in each chapter in a question–answer format followed by helpful points for quick reference for practicing clinicians and students in wards, clinics, and emergencies.

This book will be most useful for undergraduate medical students during hematopathology training and introductory phase in clinical medicine and hematology, postgraduate residents in hematology and medicine, and undergraduate and

postgraduate allied health students who want to enhance their knowledge and skills in diagnosing anemia using PBL. This will also be quite resourceful for practicing hematologists and teachers in medical and paramedical institutions and will benefit immensely in translating diagnostic proficiency into management practice in patient care.

I have written this book with my experience of more than 25 years of teaching undergraduate and postgraduate medical students in hematology and practice in clinical and laboratory hematology. I hope that this book will help you improve your analytical skills and enhance confidence in diagnosing anemia in your patients. I welcome your feedback and suggestions for improvement. Please contact me at drarun1962@yahoo.com with your comments.

Hawally, Kuwait Arun Gupta

Acknowledgments

I would like to express my deepest gratitude to the following people who have supported me throughout the journey of writing this book:

First and foremost, I want to thank my wife, Dr. Geeta, who has always encouraged me to pursue my passion for writing. I could not have done this without her love and support.

I have to give credit to my children, Sheena and Anshul, who helped me a lot in shaping the book structure and initial formatting. They were quite excited about the book and challenged me to think deeper.

I am indebted to Dr. Ramesh Arya, Dr. Rajaa Marouf, and late Professor KC Das, whose immense experience as a teacher and colleague taught me in depth hematology, which inspired me to translate my knowledge into writing this book.

I wish to thank all doctors working with me, Dr. Eman Kamal, Dr. Rasha Joudah, Dr. Mona Mahmoud, and Dr. Sarah Sayed, who provided assistance in procuring the best set of slides for photography at every step.

I am grateful to all friends, colleagues, and well-wishers who spared their precious time to write a note of Foreword for this book.

Last but not least, I am thankful to the editors and publishers who have worked hard in a very professional way to give perfect look to this book and provided invaluable feedback and suggestions that made a considerable improvement in this piece of work.

Hawally, Kuwait Arun Gupta

Contents

Chapter 1
Iron Deficiency Anemia

A 38-year-old lady reports to the hematology clinic with complaints of tiredness, dizziness, easy fatigability, and mild dyspnea on exertion of 1-month duration. She also gave history of menorrhagia during the preceding 3 months. Recently, she had been diagnosed to have type-2 diabetes mellitus and mild hypertension, for which she is receiving antidiabetic and antihypertensive medications. Physical examination showed pallor. There is no jaundice or palpable organomegaly. Table 1.1 shows result of CBC done at presentation:

Table 1.1 CBC

CBC parameter	Patient's result	Reference range
WBC	5.9	3.7–10 × 10^9/L
RBC	3.39	4.5–5.4 × 10^{12}/L
HB	85	130–170 g/L
Hct	0.27	0.36–0.46 L/L
MCV	73	83–101 fL
MCH	22	27–32 pg
MCHC	302	315–345 g/L
RDW	19	11.6–14.6%
PLT	500	130–430 × 10^9/L
MPV	8	7–11 fL
Poly #	3.5	1.7–6 × 10^9/L
Lymp#	1.9	1–3 × 10^9/L
Mono#	0.3	0.2–1.0 × 10^9/L
EO#	0.2	0.02–0.5 × 10^9/L
BASO#	0	0.02–0.1 × 10^9/L
RETIC%	0.6	0.5–1.5%

A. Gupta, *Decision Making Through Problem Based Learning in Hematology*,
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1.1 Questions

Q1. Interpret the CBC result given above and suggest investigations for further evaluation in such case**.**

Answer: The CBC result shows low values for red cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, and reticulocyte count. Values for red cell distribution width (RDW) and platelet count are high. These findings suggest microcytic hypochromic anemia with reticulocytopenia.

Most common causes of microcytic hypochromic anemia include [1]:

1. Iron deficiency anemia (IDA)
2. Thalassemia
3. Sideroblastic anemia
4. Anemia of chronic disorders (ACD)
5. Lead poisoning

The next best line of investigations should include examination of peripheral blood film, estimation of serum levels of iron, ferritin, transferrin and transferrin saturation, and CRP. Baseline investigations for functions of liver, kidney, thyroid, pancreas, and bone are also required to exclude chronic pathology.

Q2. Given are images from peripheral blood film (Figs. 1.1, 1.2, 1.3, 1.4), serum levels of iron, ferritin, transferrin and transferrin saturation, and CRP (Table 1.2). Baseline investigations for functions of liver, kidney, thyroid, pancreas, and bone are also presented (Table 1.3). Interpret these results and suggest provisional diagnosis?

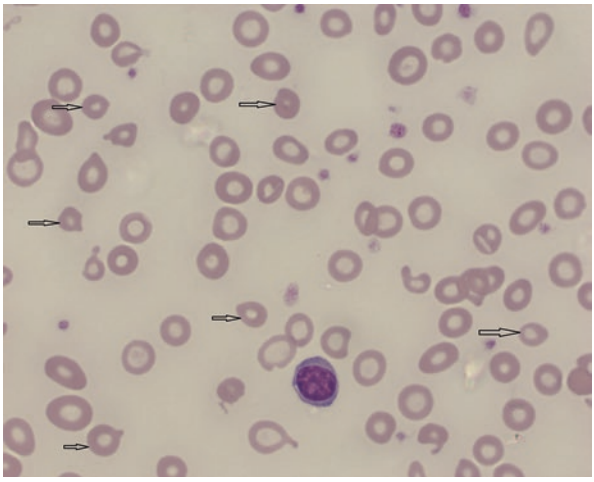

Fig. 1.1 PBF. Microcytes. Leishman stain ×100

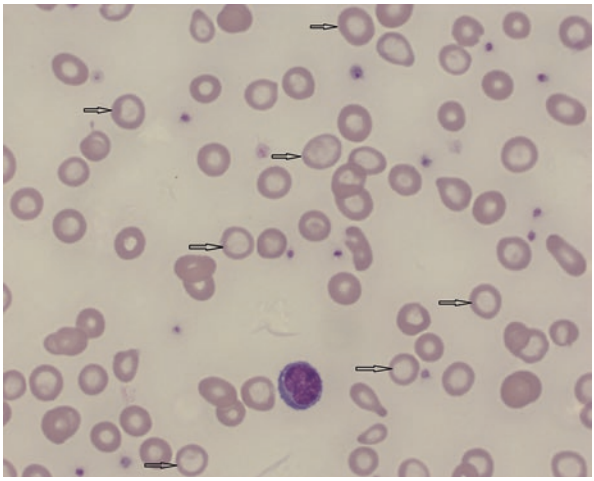

Fig. 1.2 PBF. Hypochromic cells. Leishman stain ×100

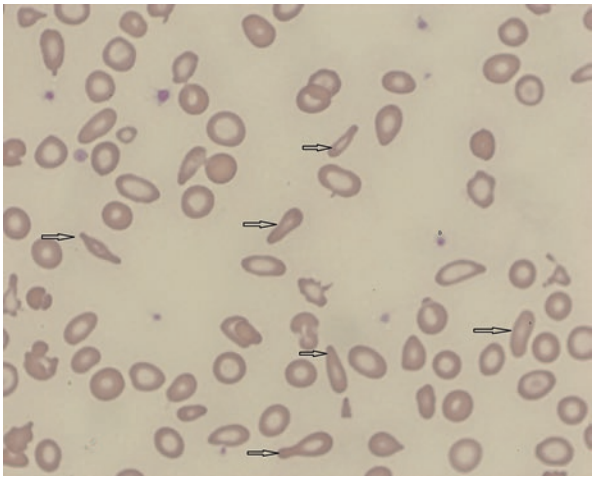

Fig. 1.3 PBF. Poikilocytes. Leishman stain ×100

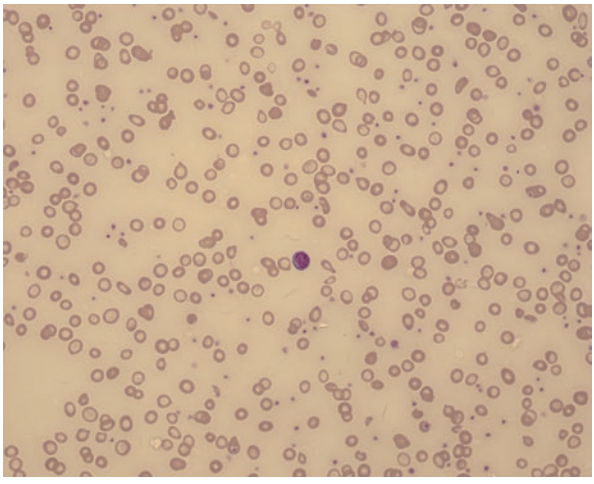

Fig. 1.4 PBF. Low density of red cells. Leishman stain ×40

Table 1.2 Serum iron profile, CRP and ESR

Test	Patient's result	Ref range
S. Iron	2.0	11–31 µmol/L
Transferrin	2.3	2.1–3.6 g/L
Trans. Sat% (TSAT)	3.0	20–40%
Ferritin	11.5	24–336 ng/mL
ESR	30	0–20 mm/h
CRP	2	0–10 mg/L

Table 1.3 Biochemical tests

Test	Patient's result	Ref range
Glu	6.0	3.9–6.1 mmol/L
Urea	2.9	2.5–6.6 mmol/L
Creat	90	60–120 µmol/L
Na^+	139	136–146 mmol/L
Ca^+	2.3	2.2–2.6 mmol/L
Mg^+	1.0	0.08–1.1 mmol/L
T. Prot	68	63–80 mmol/L
Alb	41	35–47 mmol/L
Choles	2.5	1.5–5.2 mmol/L
TG	0.9	0.4–1.7 mmol/L
Urates	370	150–400 mmol/L
T Bil	12	3–20 µmol/L
D. Bil	5	0–5 µmol/L
Alk Ph	41	26–88 IU/L
ALT	29	10–60 IU/L
AST	32	10–42 IU/L
GGT	20	7–64 IU/L
LDH	120	90–180 IU/L
Hapto	0.5	0.2–2.0 g/L
T4	10.6	7.8–16 pmol/L
TSH	3.99	0.27–4.2 ulU/ml

Answer: The blood films show reduced density of red cells. Smears show anisocytosis* with many microcytic** red cells. Few poikilocytes*** are also seen. There is mild to moderate hypochromia.**** Results of iron studies show low serum iron, transferrin saturation, and ferritin. Results of biochemical tests show values within normal range. Anemia due to infections/ inflammation is excluded as CRP is normal. Mild increase in ESR is due to anemia. Based on these results, provisional diagnosis of anemia secondary to iron deficiency is suggested.

However, other pathologies which can be associated with IDA need to be investigated under appropriate clinical setting. Further tests may be required to exclude dual deficiency (B12 + folic acid), hemoglobinopathies like thalassemia (hemo-

globin electrophoresis), and estimation of serum levels of lead. A bone marrow examination will be required to evaluate possibility of sideroblastic anemia and assess iron stores and for further evaluation in case patient does not respond to iron therapy.

**Anisocytosis: Variation in size of red cells.*

***Microcytes: Red cells smaller than 6 micron. Rough visual estimation is done by comparing size of red cells with size of nucleus of a resting lymphocyte.*

****Poikilocytosis: Variation in shape of red cells. These may include slightly oval/elongated, pencil shaped, elliptical shaped, and cells resembling tear drops.*

*****Hypochromia: Red cells that have greater central area of pallor (reduced hemoglobinization) It can be mild, moderate, or severe. Normal pallor is 30–33% of total diameter of cell.*

Q3. Given are results of serum B12, folic acid, red cell folate, serum lead levels (Table 1.4), result of HPLC (Fig. 1.5), and images from bone marrow aspirate (Figs. 1.6 and 1.7). Interpret these results and suggest final diagnosis.

Table 1.4 Serum B12, folate, and lead levels

Test	Patient's result	Reference range
S. B12	565	150–700 pmol/L
S. Folate	31.7	10–42 nmol/L
RBC folate	2554	1187–2854 nmol/L
Lead	0	0–10 mcg/L

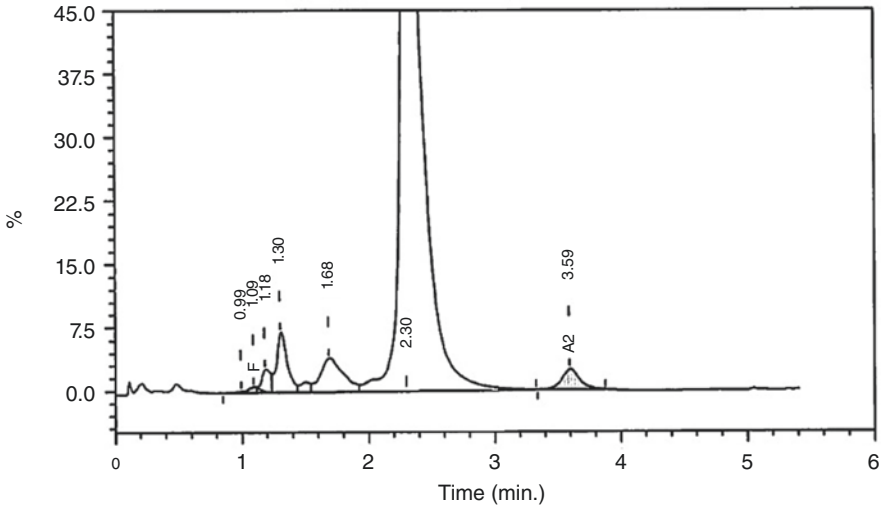

Fig. 1.5 Respresentative HPLC. Hb A: 96.5%, HbA2: 2.5%

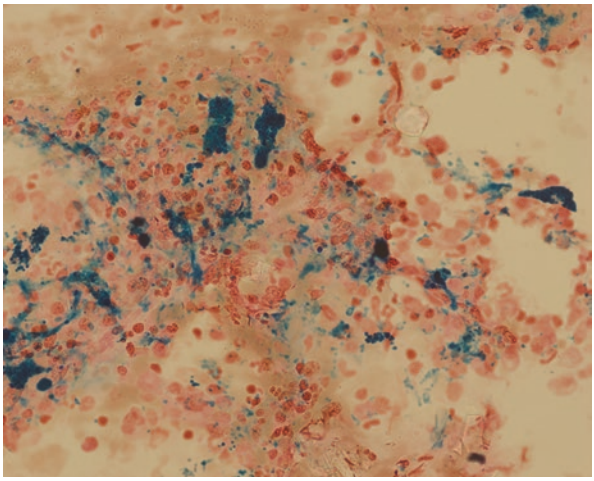

Fig. 1.6 BM aspirate (control). Normal iron stores. Prussian blue stain ×40

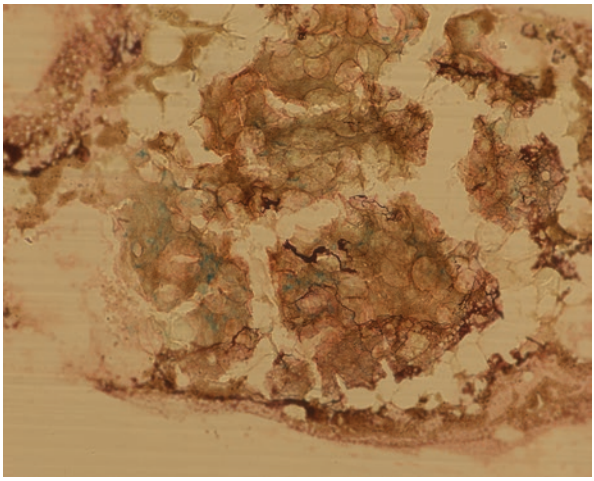

Fig. 1.7 BM aspirate (Patient) Markedly reduced iron stores. Prussian blue stain ×40

Answer: The results of serum B12, folic acid, RBC folate, and lead are within normal reference range, thus excluding the posssibilies of dual deficiency anemia and anemia due to lead toxicity. The HPLC shows normal percentage of HbA and Hb A2, thus eliminating thalassemia as an etiology.The bone marrow iron stores as shown by Prussian blue stain are markedly reduced, thus substantiating iron deficiency as a cause of anemia in this case. As no sideroblasts are seen, the possibility of sideroblastic anemia is also ruled out.

Thus microcytic hypochromic anemia along with reduced serum iron, transferrin saturation, and iron stores (ferritin and hemosiderin) confirms diagnosis of iron deficiency anemia in this case.

Once diagnosis of IDA is established, next investigations are done to evaluate the cause of iron deficiency.

Q4. What are the major causes of IDA and what specialized tests may be required to establish iron deficiency as a cause of anemia?

Answer: Some of the common causes of IDA are [2, 3]:

1. Blood loss. In males, it is from the gastrointestinal system (ulcers in the stomach/ duodenum, prolonged ingestion of medications like aspirin, hemorrhoids, polyps, occult malignancies, etc.). In females, the most common cause is menorrhagia.
2. Worm infestation as hookworm.
3. Bleeding from the kidney or into the lungs can also produce iron deficiency.
4. Other causes include reduced intake as in malnutrition, conditions that interfere with the absorption of iron as achlorhydria, long-term use of antacids, excessive intake of tea/ coffee, H. pylori-associated gastritis, gastrectomy, and intestinal conditions which result in poor absorption such as following gastric bypass surgery, celiac disease, Whipple's disease, and Crohn's disease.
5. Iron deficiency can occur in pregnancy and during growth in the adolescent period.
6. Diseases such as thalassemia, sideroblastic anemia, and chronic inflammations/infections result in ineffective utilization of iron.
7. Rare causes include regular dialysis and repeated phlebotomies.

So if the cause of iron deficiency is not clear from history, a battery of investigations will be required. These include

1. Stool examination for ova/cysts and occult blood
2. Upper and lower gastrointestinal endoscopy and biopsy (H. pylori)
3. Urine examination for hematuria
4. Serological tests for celiac disease, autoimmune atrophic gastritis, and H. pylori
5. Rarely radiological investigations for intra-abdominal and pelvic pathologies

Q5. A summary of additional tests done to evaluate bleeding and celiac disease in this patient is presented (Table 1.5). Interpret the results and suggest cause of IDA in this patient.

Table 1.5 Results of additional tests

Test	Result
Stool examination for ova/cysts and occult blood	Negative
Upper and lower GI endoscopy	Normal
Urine routine examination	Normal
Serological tests for celiac disease, autoimmune diseases, and H. pylori	Normal
Ultrasound abdomen and pelvis	Uterine fibroids

Answer: The test results show uterine fibroids by pelvic ultrasound. All other tests are normal. This patient has history of menorrhagia. So a final diagnosis of IDA secondary to menorrhagia due to uterine fibroids is confirmed.

Q6. Some specialized tests are also performed in evaluation of microcytic hypochromic anemia. What is the role of red cell ferritin, serum transferrin receptors (STRf), red cell zinc protoporphyrin/heme ratio, and free erythrocyte porphyrin (FEP) in differentiating various causes of microcytic hypochromic anemia?

Answer: When hemoglobin synthesis is impaired, red cell ferritin increases, e.g., thalassemia [1] or sideroblastic anemia. This excess of iron will appear as siderotic granules. These are known as Pappenheimer bodies. They stain purplish blue with Leishman and blue with Prussian blue [5].

In IDA, the number of serum transferrin receptors (STfR) increases. In fact, any condition in which there is hyperplasia of erythroid precursors such as iron deficiency anemia and thalassemia will show an increased number of STfR**.** These can be identified with anti-CD71 antibodies. Serum transferrin receptors are normal in anemia due to chronic inflammation. It is of immense value in distinguishing iron deficiency from anemia of chronic disease [2, 3, 8].

In IDA, zinc substitutes for iron in protoporphyrin IX, and the concentration of zinc protoporphyrin relative to heme increases. So Zn-protoporphyrin/heme ratio increases. This test is more sensitive than ferritin level and is not altered in chronic inflammation/ infections [7, 9].

Free erythrocyte protoporphyrin (FEP) is raised in iron deficiency anemia but not in thalassemia. Other conditions in which it is raised include lead poisoning, chronic infection, and rarely in dyserythropoietic and sideroblastic anemias [10–12].

Q7. What is the role of hepcidin, ferroportin-1, and hephaestin in pathophysiology of IDA?

Answer: In IDA, hepcidin levels are decreased. Normally hepcidin reduces release of iron from intestinal epithelial cells to plasma and also inhibits release of iron from macrophages. It probably acts by binding to ferroportin and enhances its destruction. In anemia due to inflammation, hepcidin production is increased many folds, and this results in sequestration of iron into macrophages and inhibition of release of iron from intestinal epithelial cells into circulation [13, 14].

Ferroportin1 helps in transport of iron across the cell membrane. Hephaestin is present in villous cells of small intestine. It is involved in conversion of Fe^{2+} to Fe^{3+} [15, 16].

Q8. What are the pathophysiological effects of IDA?

Answer: Iron is an essential component of hemoglobin and myoglobin. It has important role in many enzymatic reactions involving peroxidase, mitochondrial dehydrogenase, monoamine oxidase, etc. In IDA, heme production is decreased, there is ineffective erythropoiesis, and the red cell rigidity and auto hemolysis are increased. There is overall decreased red cell survival [17].

1.2 Correlation of Results of Investigations with Symptoms and Signs in Iron Deficiency Anemia

Q9. What are the common symptoms of IDA and how do these correlate with diagnosis in this patient?

Answer: Common symptoms in IDA are easy fatiguability, weakness, pale skin, dizziness, cravings for clay, brittle nails, hair loss, poor appetite, frequent infections, etc. [18, 19].

Long standing deficiency produces cheilitis, atrophic glossitis, Plummer-Vinson pharyngeal webs [20, 21].

This patient has tiredness, dizziness, easy fatigability, and mild dyspnea on exertion. These symptoms are due to decreased oxygen carrying capacity of hemoglobin. When oxygen supply is reduced, the muscles depend on anaerobic respiration also. So capacity to perform normal day-to-day activity decreases. The body tries to acquire more oxygen through respiratory effort, and patient becomes dyspnea on exertion.

Q10. How do the CBC parameters correlate with diagnosis of IDA in this patient and how do they help in differentiating IDA from thalassemia?

Answer: In IDA, low hemoglobin correlates with low values for red cell count, MCV, MCH, and MCHC. The RDW is high. Platelets may be normal or increased (reactive increase). Our patient has all these findings which correlate well with the diagnosis. In thalassemia, red cell number is disproportionately high in relation to decreased hemoglobin. MCV and MCH are low but MCHC and RDW are usually normal. Platelet count remains within normal range [22].

Q11. How is mild, moderate, and severe hypochromia assessed on blood film?

Answer: There are no clear guidelines for such assessment. However, a rough visual estimation is done by looking at the hemoglobinized (colored) part of the red cell. In normal red cells, the central pallor is not more than one-third (30–33%) of the total diameter of the cell. In mild deficiency, the pale part is little more than one-third. In severe hypochromia, only a thin rim of hemoglobinized part is seen. A moderate hypochromia is considered if pale area is seen covering red cell between mild and severe hypochromia [23].

Q12. This patient has high red cell distribution width (RDW). What is the significance of RDW in IDA?

Answer: Red cell distribution width reflects variation in size of red cells in blood. More the variation, higher the value for RDW. In IDA, as there is variation in size and shape of red cells, the RDW is higher than normal. This helps in differentiating it from thalassemia minor and anemia of chronic disease, where RDW is usually normal.

Q13. How are reticulocyte count and reticulocyte hemoglobin helpful in diagnosis and management of IDA?

Answer: In mild iron deficiency, reticulocyte count is usually normal or on lower side, but in severe deficiency, it may be lower than normal. Also it is helpful in assessing the response of bone marrow when a patient of IDA is treated with iron. The reticulocyte count should start increasing within 5 to 10 days of beginning of iron therapy, and the hemoglobin should increase by about 2 g/dL within 3 to 4 weeks. Anemia is considered refractory if the response is not satisfactory [24]. A new additional parameter, reticulocyte hemoglobin content, has come up which is helpful in identifying iron deficient erythropoiesis. It is especially helpful when the traditional biochemical parameters are noninformative [25, 26]. Reticulocyte hemoglobin content is not influenced by other factors such as inflammation, infection and malignancy etc. It indicates the amount of iron available to the newly formed red cells in bone marrow.

Q14. This patient has a high platelet count. What is the cause of thrombocytosis in IDA?

Answer: Platelets are derived from megakaryocytes. Iron deficiency increases the megakaryopoietic differentiation. A possibility of cytokine-mediated increase in megakaryopoiesis has been proposed [27].

Q15. How are CRP, ESR, and biochemical tests helpful in evaluation of microcytic hypochromic anemia and differentiating it from ACD?

Answer: CRP is produced in liver. Its level will increase in response to inflammation (acute phase reactant). ESR is an indirect measure of acute phase reactants and is also a positive inflammatory marker. Both are raised in anemia due to chronic inflammation and normal in other conditions [28].

The biochemical tests for liver, kidney, thyroid, pancreas, and bone are helpful if a patient is suffering from chronic inflammation/ infections of these organs.

Q16. This patient has deranged iron profile. What is the role of transferrin, transferrin saturation, and ferritin in evaluation and differential diagnosis of microcytic hypochromic anemia?

Answer: Transferrin is a glycoprotein produced from liver and is responsible for transport of iron to various organs like liver, spleen, and bone marrow. It binds to transferrin receptors on target cells and delivers iron to them. Its synthesis is decreased in ACD but increased in iron deficiency. Values are usually normal in thalassemia. Its saturation is decreased in iron deficiency [7, 26].

Ferritin is storage form of iron in circulation (blood). It is water soluble and is composed of apoprotein enclosing iron molecules. It is a marker of total iron store in body. Liver, spleen, muscles, reticuloendothelial cells, and bone marrow have highest concentration. Low ferritin is a sensitive marker for diagnosis of early IDA. It is also an acute phase reactant with increased levels seen in chronic inflammations and infections [29].

Q17. How is hemosiderin different from ferritin and what is its significance?

Answer: Hemosiderin is composed of partially degraded ferritin molecules, proteins, and lipids. It contains ferric iron. Major site of storage is macrophages in bone marrow, reticuloendothelial cells of liver, spleen, etc. Prussian blue stain on bone marrow smears shows a blue colored pigment in macrophages and erythroid precursors. This pigment is ferri-ferrocyanide formed by combination of acidic ferrocyanide with ferric ions [30].

In normal bone marrow, siderotic granules are seen in erythroid precursors. Their number is usually less than 15 per cell and are randomly distributed. No ring sideroblasts are seen. However, they are either absent or their number is significantly reduced in IDA depending on severity. In case of sideroblastic anemia, increased number of granules are seen and these are arranged in form of ring around the nucleus [31]. In ACD, increased hemosiderin is noted in macrophages. ([32] Given below are representative images of iron in normal bone marrow (Fig. 1.8), iron overload anemia (Fig. 1.9), anemia of chronic disorder (Fig. 1.10), and sideroblastic anemia (Fig. 1.11).

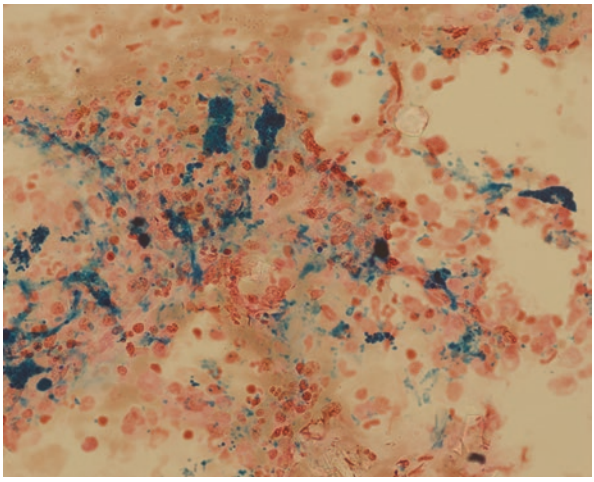

Fig. 1.8 BM aspirate. Normal iron stores. Prussian blue stain ×40

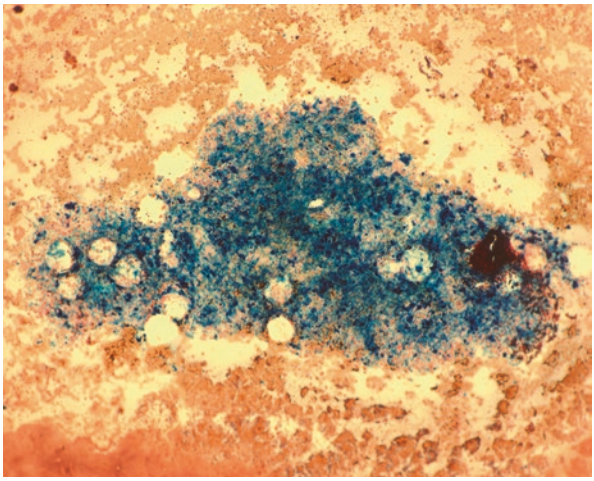

Fig. 1.9 BM aspirate. Markedly increased iron stores (iron overload anemia). Prussian blue stain ×40

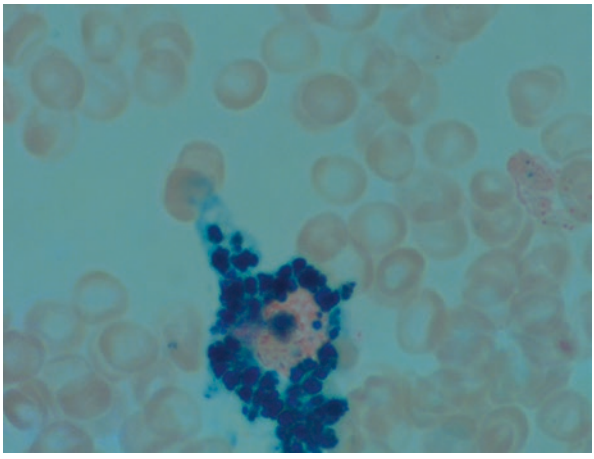

Fig. 1.10 BM aspirate. A macrophage loaded with iron (ACD) Prussian blue stain ×100

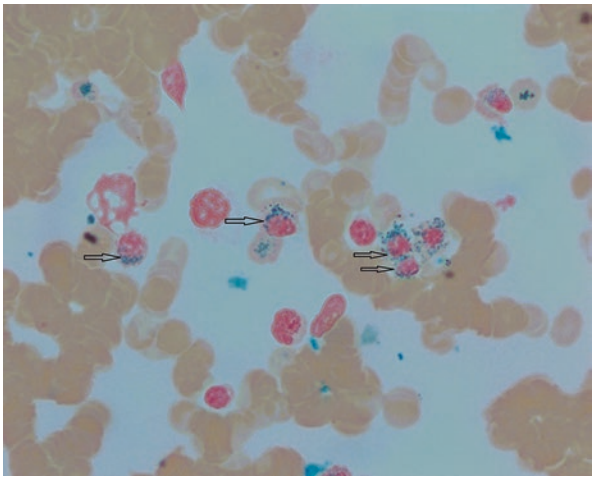

Fig. 1.11 BM aspirate. Ring sideroblasts (sideroblastic anemia) Prussian blue stain ×100

Q18. How is bone marrow graded for iron status?

Answer: A fairly used system of grading iron status in bone marrow has been in practice for a long time. It is graded from zero (0) to 6+ based on the size and quantity of iron granules. For practical purposes, content less than 2+ is considered a deficient state. More details are in reference [33].

Q19. Which foods are rich in iron?

Answer: Foods which are rich in iron include chicken, turkey, duck meat, pork, lamb, beef, fish, green leafy vegetables such as broccoli, kale, legumes, pasta, etc.

Q20. What is the mechanism of absorption of iron.

Answer: Food contains two forms of iron—one is heme and the other nonheme. Heme iron is present in products of animal origin such as fish, meat, and poultry. The nonheme iron is found in vegetables, fruits, nuts, beans, grains, and meat [34]. In intestine, the heme iron has better absorption than nonheme iron [35]. Iron absorption occurs mainly in the duodenum and the proximal jejunum [36].

Most of the non-heme iron in the diet is in the ferric form. For its absorption, it needs to be reduced to Fe^{2+} form. This is achieved by the actions of the membrane bound duodenal cytochrome B, a ferric reductase enzyme expressed on brush border membrane of intestinal epithelial cells [37]. Ferrous iron moves across the apical membrane of enterocytes by a protein known as divalent metal transporter 1 (DMT1) [38].

To enter the systemic circulation from intestinal cells, iron has to cross the basolateral membrane of intestinal enterocytes. This is helped by another protein called ferroportin [39].

The release of ferrous iron into the blood by ferroportin is assisted by hephaestin. These enzymes oxidize Fe^{2+} to Fe^{3+} before the iron binds to the iron-transport protein transferrin in circulation [40].

Heme iron is more readily absorbed than non-heme iron derived from vegetables and grain. Most heme is absorbed in the proximal intestine, with absorptive capacity decreasing distally [40].

Q21. What are rare and refractory causes of IDA?

Answer: Refractoriness is considered when there is no response after the patient has received at least 100 mg of elemental iron per day for 4 to 6 weeks. There are numerous causes of iron deficiency anemia refractory to treatment. Among them are H. pylori infection, autoimmune gastritis, and celiac disease which will require additional specialized investigation [4]. Mutations in the TMPRSS6 gene have been identified as cause of iron-refractory iron deficiency anemia (IRIDA) [40]. Several other reasons can result in poor response to treatment with iron. Some of them are poor compliance, malabsorption, continuous bleeding, drug/food interaction, incorrect diagnosis, or more than one cause of anemia.

Some more rare causes include INH therapy, hereditary orotic aciduria, hypo- or atransferrinemia, nephritic syndrome, copper deficiency, and inborn errors of iron metabolism.