



Sideroblastic Anemia: Laboratory Evaluation, Diagnostic Challenges, and Clinical Correlation

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Abstract

Background: Sideroblastic anemia (SA) is a heterogeneous group of disorders unified by the pathological hallmark of ring sideroblasts—erythroid precursors with perinuclear mitochondrial iron accumulation visible on Prussian blue-stained bone marrow aspirates. This results from defective heme synthesis, leading to ineffective erythropoiesis and a characteristic paradox of systemic iron overload concurrent with anemia.

Aim: This article provides a comprehensive review of the laboratory evaluation, diagnostic challenges, and clinical management of sideroblastic anemia. It aims to delineate the pathophysiologic pathways, categorize the diverse etiologies, and correlate diagnostic findings with appropriate therapeutic strategies.

Methods: A detailed analysis of the etiology, pathophysiology, and histopathology of SA is presented. The diagnostic approach integrates complete blood count, iron studies, peripheral smear for siderocytes, and definitive bone marrow examination. Further classification relies on genetic testing for hereditary forms and molecular analysis (e.g., for SF3B1 mutations) for acquired, clonal variants like myelodysplastic syndromes with ring sideroblasts (MDS-RS).

Results: Management is etiology-driven. Hereditary forms, often involving ALAS2 mutations, may respond to pyridoxine (Vitamin B6). Acquired, reversible causes (e.g., copper deficiency, alcohol, drugs) require removal of the insult. Clonal MDS-RS variants are managed with erythropoiesis-stimulating agents, luspatercept, or hypomethylating agents. Iron overload, a universal complication, necessitates vigilant monitoring and chelation or phlebotomy to prevent end-organ damage.

Conclusion: Accurate diagnosis of SA hinges on marrow morphology and systematic evaluation to distinguish between congenital, acquired, and clonal causes, which is crucial for implementing targeted therapy and managing iron overload to improve patient outcomes.

Keywords: Sideroblastic Anemia, Ring Sideroblasts, Heme Synthesis, Iron Overload, Myelodysplastic Syndromes, SF3B1 Mutation, Pyridoxine.

Introduction

Sideroblastic anemia is a heterogeneous group of disorders unified by a common cellular phenotype: ineffective erythropoiesis with pathologic mitochondrial iron deposition in erythroid precursors. The central defect is abnormal utilization of iron during hemoglobin synthesis, such that iron delivery to mitochondria is preserved or even increased, yet incorporation into protoporphyrin IX to form heme is impaired. The morphologic hallmark is the ring sideroblast—an erythroblast in which non-heme iron accumulates within perinuclear mitochondria to create a circumferential “ring” encasing at least one-third of the nuclear rim, demonstrable by Prussian blue staining on bone marrow aspirates [1][2]. Recognition

of this feature is essential because it defines the diagnosis across otherwise diverse etiologies and directly links clinical anemia to a mitochondrial iron–heme metabolic bottleneck. Understanding the heme moiety clarifies why derangements in its biosynthesis so profoundly disrupt erythropoiesis. Heme is the iron-protoporphyrin prosthetic group that enables hemoglobin to bind and transport oxygen efficiently to peripheral tissues. Structurally, it comprises a planar porphyrin macrocycle—four pyrrole rings interconnected by methine bridges at the α positions—with a centrally chelated ferrous iron atom that coordinates oxygen reversibly [3]. Beyond hemoglobin, heme participates broadly in cellular physiology, acting in gas sensing, signal transduction,

circadian clock regulation, and microRNA processing; thus, deficits in heme biogenesis reverberate beyond red cells to systemic homeostasis [4]. In erythropoiesis, heme production is particularly intense: approximately 85% of total heme synthesis occurs within erythroblasts, relying on a coordinated cytoplasmic–mitochondrial choreography, while the liver contributes the remainder primarily for cytochrome and detoxification pathways [3].

At the biochemical level, the Shemin (heme biosynthesis) pathway proceeds through eight sequential enzymes: δ -aminolevulinic acid (ALA) synthase, uroporphobilinogen synthase, uroporphobilinogen decarboxylase, uroporphyrinogen decarboxylase, coproporphyrinogen oxidase, protoporphyrinogen oxidase, and ferrochelatase [3]. Disruption at any step—in substrate provision, enzymatic activity, mitochondrial import, or iron insertion—can uncouple iron delivery from heme assembly. The consequence in erythroid precursors is mitochondrial iron sequestration with inadequate heme availability, which in turn impairs hemoglobinization, reduces red cell survival, and triggers compensatory yet ineffective erythroid hyperplasia. Clinically, this manifests as anemia with variably increased iron indices despite marrow iron overload, a paradox that distinguishes sideroblastic anemia from classic iron-deficiency states. Two broad etiologic categories are recognized: hereditary and acquired sideroblastic anemias. Hereditary forms most often produce a microcytic anemia owing to primary defects in heme synthesis, though some genotypes present with normocytic—and rarely macrocytic—indices, reflecting the complex interplay between globin production, erythroid maturation, and mitochondrial function [5]. Unlike iron deficiency anemia, in which total body iron is depleted and ferritin is low, patients with sideroblastic anemia typically exhibit normal or elevated iron stores and transferrin saturation, underscoring that the core problem is misallocation rather than scarcity of iron. In the differential diagnosis of microcytosis, sideroblastic anemia must therefore be considered alongside thalassemia syndromes and chronic anemia, each of which has distinct pathobiology, laboratory signatures, and therapeutic implications [6].

Acquired sideroblastic anemia spans a spectrum from reversible toxic-metabolic insults to clonal marrow disorders. A prototypical clonal entity is refractory anemia with ring sideroblasts (RARS), classified within the myelodysplastic syndromes (MDS). RARS is characterized by anemia and $\geq 15\%$ ring sideroblasts in bone marrow, reflecting a persistent defect in erythroid maturation despite hyperplastic marrow activity [7][8].

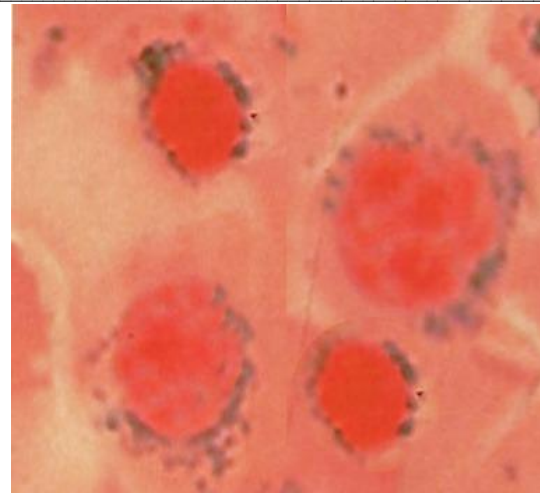


Fig. 1: Sideroblastic Anemia.

Patients commonly present with normochromic, normocytic anemia—although a dimorphic picture with concurrent hypochromic and normochromic populations may be seen—because the marrow’s attempt to compensate for ineffective erythropoiesis does not translate into durable, functional erythrocytes. Erythroid precursors may display dyserythropoietic changes with occasional megaloblastoid features, consistent with disordered nuclear–cytoplasmic maturation. In contrast, granulopoiesis and megakaryocytopoiesis are typically preserved morphologically, and platelet and neutrophil counts are often normal or mildly increased, reinforcing the erythroid-predominant nature of the defect [7][8]. Hemoglobin concentrations frequently lie in the 9 to 12 g/dL range at diagnosis, though more profound anemia can occur depending on disease burden and comorbidities. From a diagnostic perspective, the integration of marrow morphology with iron studies and red cell indices is pivotal. The presence of ring sideroblasts anchors the diagnosis, but it is the broader clinical context—hereditary history, exposure risks, comorbid conditions, and the pattern of cytopenias—that directs classification and management. In hereditary disease, identifying the specific biosynthetic or mitochondrial lesion refines prognosis and guides supportive strategies. In acquired cases, distinguishing primary clonal disorders such as RARS from secondary, potentially reversible causes is crucial to avoid overtreatment or missed opportunities for correction. Across forms, the unifying concept remains the same: sideroblastic anemia is a disorder in which iron is available but not effectively harnessed for heme, producing a characteristic marrow iron ring around the nucleus of erythroid precursors and a systemic phenotype of anemia despite iron excess [1][2][3][4][5][6][7][8].

Etiology

Sideroblastic anemia encompasses a diverse group of disorders unified by defective heme synthesis in developing erythroblasts, resulting in abnormal mitochondrial iron accumulation. Its etiology can be

broadly divided into hereditary (congenital) and acquired forms, each involving distinct molecular, genetic, and environmental mechanisms. Understanding these causes is crucial because the underlying pathophysiology directly influences the clinical presentation, laboratory findings, and therapeutic approach. The hereditary form of sideroblastic anemia results primarily from genetic mutations that impair enzymes or transporters involved in heme biosynthesis, iron-sulfur (Fe-S) cluster formation, or mitochondrial metabolism [7][9][10]. The most common hereditary type is the X-linked form, caused by mutations in the *aminolevulinic acid synthase 2 (ALAS2)* gene, which encodes the rate-limiting mitochondrial enzyme in erythroid heme biosynthesis. This enzyme catalyzes the condensation of glycine and succinyl-CoA to form aminolevulinic acid (ALA), the first step in the heme synthesis pathway. Mutations in *ALAS2* disrupt ALA production, leading to reduced heme availability and consequent mitochondrial iron overload [10]. In addition to *ALAS2*, other gene mutations are implicated in congenital sideroblastic anemia. Mutations in *ABCB7* and *GLRX5*, both located on the X chromosome, interfere with the formation or export of mitochondrial iron-sulfur clusters that are essential for iron homeostasis and heme synthesis. Defects in these genes lead to intramitochondrial iron accumulation and ineffective erythropoiesis [7][9]. Similarly, mutations in *SLC25A38*, a mitochondrial transporter gene, cause severe, early-onset sideroblastic anemia by disrupting glycine import into mitochondria—a critical step for ALA formation. Other rare mutations affect genes encoding enzymes or transporters critical for mitochondrial function, such as *SLC19A2* (thiamine transporter), *PUS1* (pseudouridine synthase involved in tRNA modification), and *YARS2* (mitochondrial tyrosyl-tRNA synthetase) [11].

Hereditary sideroblastic anemias can be classified further based on the nature of the mutation and resulting red cell morphology. Mutations in *ALAS2*, *SLC25A38*, *GLRX5*, *HSPA9*, and *ABCB7* generally produce microcytic anemia, reflecting defective heme synthesis with preserved globin production. In contrast, mutations involving mitochondrial genes such as *SLC19A2*, *PUS1*, *YARS2*, and *TRNT1* may cause macrocytic anemia, likely due to broader mitochondrial dysfunction affecting DNA replication and ribosomal activity [12]. In general, X-linked mutations are associated with microcytic anemia, whereas mitochondrial deletions and nuclear-mitochondrial interaction defects may produce normocytic or macrocytic variants [9]. The acquired forms of sideroblastic anemia are more common in adults and are typically divided into primary (clonal) and secondary (reversible) categories. Primary acquired sideroblastic anemia arises from bone marrow stem cell disorders, particularly

myelodysplastic syndromes (MDS) or myelodysplastic/myeloproliferative neoplasms (MDS/MPN) [1]. Classic refractory anemia with ring sideroblasts (RARS), now termed *MDS with ring sideroblasts (MDS-RS)*, represents a clonal stem cell disorder characterized by ineffective erythropoiesis and dysplastic changes restricted largely to the erythroid lineage. Another related entity, *MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)*, features both erythroid dysplasia and increased platelet production due to concomitant mutations such as *SF3B1* and *JAK2* [13].

The morphology observed in these clonal disorders is diagnostically significant and prognostically informative. Bone marrow examination typically reveals erythroid hyperplasia with $\geq 15\%$ ring sideroblasts, dyserythropoiesis, and often normocytic or dimorphic anemia. Most RARS cases remain stable and indolent for years, categorized as low-risk MDS with near-normal life expectancy. However, approximately 7–10% of cases evolve into higher-grade MDS or transform into acute myeloid leukemia (AML), particularly when additional cytogenetic abnormalities develop [1][13]. Secondary (reversible) acquired sideroblastic anemias arise from environmental or metabolic disturbances that interfere with mitochondrial heme synthesis or iron utilization. Common causes include copper deficiency, zinc toxicity, drug-induced mitochondrial dysfunction, and chronic alcohol abuse [14][15]. Copper is essential for the activity of mitochondrial cytochrome c oxidase and for mobilizing iron from stores; its deficiency, often due to excessive zinc intake or malabsorption, leads to defective iron incorporation into heme and subsequent ring sideroblast formation. Certain medications, including *isoniazid*, *chloramphenicol*, and *linezolid*, inhibit mitochondrial protein synthesis or heme enzyme function, causing reversible sideroblastic anemia upon withdrawal. *Isoniazid* disrupts pyridoxine (vitamin B6) metabolism, which is a cofactor for *ALAS2*, thus impeding ALA synthesis. Likewise, chronic alcohol consumption impairs mitochondrial metabolism, interferes with pyridoxine utilization, and promotes iron accumulation. The hallmark of these secondary forms is reversibility: once the offending agent or deficiency is corrected, erythropoiesis normalizes and ring sideroblasts disappear. For instance, discontinuation of the causative drug, cessation of alcohol use, or supplementation with pyridoxine or copper can lead to full hematologic recovery [14][15]. In summary, the etiology of sideroblastic anemia reflects a convergence of genetic, metabolic, and toxic mechanisms that all compromise mitochondrial heme synthesis. Hereditary variants stem from gene mutations affecting heme biosynthetic enzymes or mitochondrial iron metabolism, while acquired forms emerge from clonal bone marrow disorders or external insults disrupting cellular metabolism. Recognizing

the underlying cause is essential not only for classification and prognosis but also because many acquired forms are potentially reversible, contrasting with the lifelong yet often manageable nature of congenital sideroblastic anemias [7][9][10][11][12][13][14][15].

Epidemiology

Sideroblastic anemia is classified as a rare disorder, and in the United States the “rare disease” designation applies to conditions affecting fewer than 200,000 people, underscoring the inherent challenges of generating robust incidence and prevalence estimates [7]. The overall epidemiology is therefore imprecise, with most knowledge derived from case series, tertiary-center registries, and extrapolation from specific subtypes rather than population-level surveillance. This rarity is compounded by clinical heterogeneity—spanning hereditary forms with early onset to acquired variants linked to clonal marrow disorders or reversible toxic-metabolic causes—which leads to underrecognition in general practice and variable coding in administrative datasets [7]. The condition spans a wide age distribution, occurring in infants and children with congenital forms and in middle-aged and older adults with acquired disease, including myelodysplastic syndromes with ring sideroblasts (MDS-RS) [16]. In pediatric cohorts, hereditary mutations often predominate, whereas in adults, acquired etiologies—including clonal hematopoiesis and drug-, alcohol-, or deficiency-related mechanisms—are more frequently identified. Geographic and environmental factors, local patterns of medication use, and nutritional deficiencies (e.g., copper deficiency due to excess zinc intake) likely modulate regional prevalence, but definitive comparative data remain limited given the low case numbers and diagnostic variability [16]. Overall, the epidemiologic picture is one of rarity coupled with broad age penetrance and etiologic diversity, necessitating high clinical suspicion, appropriate marrow evaluation for ring sideroblasts, and thoughtful integration of genetic, exposure, and hematologic data to avoid misclassification and to inform accurate reporting and counseling [7][16].

Pathophysiology

Sideroblastic anemia is fundamentally a disorder of heme insufficiency within erythroid precursors, despite adequate or even excessive iron availability. The core lesion resides at the interface of mitochondrial metabolism and iron handling: iron is delivered to the mitochondrion and accumulates there, but incorporation into protoporphyrin IX to form heme is impaired. The result is pathognomonic ring sideroblasts—erythroblasts with perinuclear aggregates of iron-laden mitochondria—reflecting a failure of coordinated heme biosynthesis and iron-sulfur (Fe-S) cluster-dependent processes that normally sustain erythroid hemoglobinization [1][2]. Understanding how specific enzymatic steps, transport systems, and mitochondrial maintenance pathways

intersect explains both the morphologic phenotype and the laboratory paradox of anemia with normal-to-high body iron stores. The heme biosynthetic sequence begins with a substrate choreography that places glycine and succinyl-coenzyme A within the mitochondrial matrix. Glycine entry is mediated by the inner-membrane carrier SLC25A38; once present, glycine condenses with succinyl-CoA to generate δ -aminolevulinic acid (ALA) in a reaction catalyzed by the erythroid isoform of ALA synthase, ALAS2 [3]. This step is rate-limiting in red cells and exquisitely cofactor- and substrate-dependent. When SLC25A38 is dysfunctional, mitochondrial glycine supply becomes limiting, strangling ALA production at its source. When ALAS2 is mutated, catalytic throughput itself falls, directly curtailing ALA formation. In either case, heme output drops, starving the developing erythroblast of the prosthetic group essential for globin assembly and normal hemoglobinization; mitochondrial iron, delivered via dedicated import machinery, has nowhere to go, and accumulates in a peri-nuclear distribution that defines ring sideroblasts [3]. After ALA generation, the traffic intermediates to the cytosol for porphyrin assembly and then return to mitochondria for the terminal insertion of ferrous iron by ferrochelatase. Thus, even defects that are “upstream” at the level of ALA provision ramify through the entire pathway, producing the convergent phenotype of mitochondrial iron sequestration.

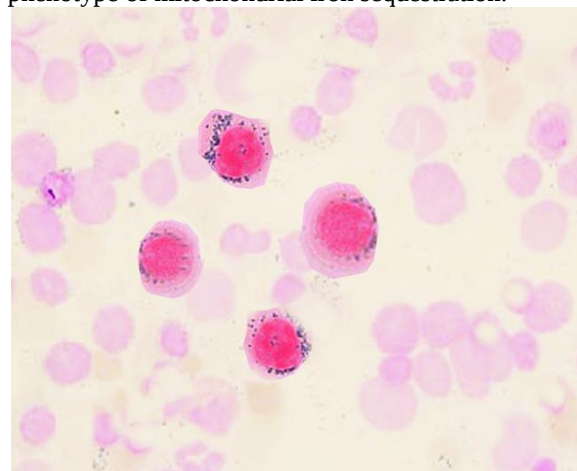


Fig. 2: Sideroblastic Anemia.

Not all genetic lesions act by throttling ALAS2 or glycine supply. Mutations in ABCB7 and GLRX5 impair Fe-S cluster biogenesis and export, processes that are indispensable for multiple mitochondrial and cytosolic enzymes, including those that control iron allocation and heme synthesis [2]. GLRX5 participates in the production of Fe-S clusters within mitochondria; its deficiency deranges the iron regulatory protein/iron responsive element (IRP/IRE) axis, inappropriately signaling cellular iron starvation despite mitochondrial overload. The paradoxical result is enhanced iron uptake and delivery to the very organelle that cannot utilize it efficiently, further intensifying mitochondrial iron deposition. ABCB7, a

half-transporter in the inner mitochondrial membrane, is required for exporting Fe–S cluster precursors to the cytosol; its loss cripples cytosolic Fe–S enzymes and perturbs iron sensing, again favoring iron misallocation into mitochondria where it aggregates as inert ferritin–mineral complexes rather than being mobilized for ferrochelatase. In both scenarios, heme deficiency is mechanistically downstream of Fe–S cluster failure, linking iron handling and porphyrin biochemistry into a single vulnerable node [2][3].

These molecular lesions map clinically onto two broad categories of hereditary sideroblastic anemia—non-syndromic and syndromic—defined by whether the defect predominantly affects erythropoiesis or manifests as a multi-system mitochondrial disease [1][12]. Non-syndromic disease is typified by X-linked sideroblastic anemia due to *ALAS2* mutations (historically designated SIDBA1), where missense, nonsense, or regulatory variants diminish erythroid ALA production and yield a primarily microcytic anemia with iron overload [17]. Although X-linked, symptomatic females occur due to skewed lyonization, producing functional mosaicism with sufficient erythroid clones carrying the mutant allele to express disease [12]. Mutations of *SLC25A38* (SIDBA2) interrupt glycine transport into mitochondria; multiple variant classes (nonsense, frameshift, missense) have been described and often present in infancy with severe microcytosis and transfusion dependence because the very first step toward ALA is substrate-starved [18]. *GLRX5* mutations (SIDBA3) are rare—reported in only a few families—but mechanistically instructive: splicing defects reduce *GLRX5* function, collapsing Fe–S cluster availability, distorting iron sensing, and producing the striking sideroblastic phenotype via the iron misallocation mechanism noted above [12]. Mutations in *HSPA9* (SIDBA4), encoding a mitochondrial chaperone (mortalin/GRP75), impair protein import and folding; in erythroid cells, its absence blocks terminal differentiation and contributes to ineffective erythropoiesis with ring sideroblast formation, again via a mitochondria-centric failure that converges on heme deficiency.

Syndromic forms broaden the physiologic footprint beyond erythroid cells and illustrate how defects in mitochondrial proteostasis and genome integrity derail heme production indirectly. X-linked sideroblastic anemia with ataxia arises from *ABCB7* mutations; beyond anemia, patients manifest cerebellar dysfunction because neuronal cells are also dependent on intact Fe–S cluster biogenesis, and the shared bottleneck in Fe–S handling produces combined neurologic-hematologic disease [12]. Pearson marrow–pancreas syndrome exemplifies the impact of large-scale mitochondrial DNA deletions: by disabling multiple components of the respiratory chain, global mitochondrial ATP production falls, undermining energy-intensive pathways such as heme

synthesis in erythroblasts and exocrine secretion in the pancreas, producing refractory sideroblastic anemia with pancreatic insufficiency [19][20]. In thiamine-responsive megaloblastic anemia due to *SLC19A2* mutations, defective thiamine transport deprives the cell of a cofactor necessary for pyruvate dehydrogenase and α -ketoglutarate dehydrogenase, indirectly reducing succinyl-CoA availability; with less succinyl-CoA, ALA synthesis falters and sideroblastic anemia coexists with diabetes and deafness [12]. Mutations of *PUS1* (pseudouridine synthase) and *YARS2* (mitochondrial tyrosyl-tRNA synthetase) disrupt mitochondrial translation broadly; although the precise link to ring sideroblast formation is incompletely defined, the prevailing model is that impaired respiratory chain assembly creates an energetic bottleneck and redox stress that secondarily sabotages heme biosynthesis in erythroblasts [12]. Likewise, *TRNT1* mutations (CCA-adding tRNA nucleotidyltransferase) compromise mitochondrial tRNA maturation, provoking multi-system dysfunction with immunodeficiency, fevers, developmental delay, and sideroblastic anemia; again, erythroid heme insufficiency likely reflects downstream effects of stalled mitochondrial protein synthesis and ATP deficit [12]. *NDUFB11* deficiency, due to an in-frame deletion in a complex I subunit, underscores that even narrowly targeted defects in oxidative phosphorylation can yield normocytic sideroblastic anemia with lactic acidosis, highlighting the sensitivity of erythroid heme synthesis to mitochondrial bioenergetic integrity [21].

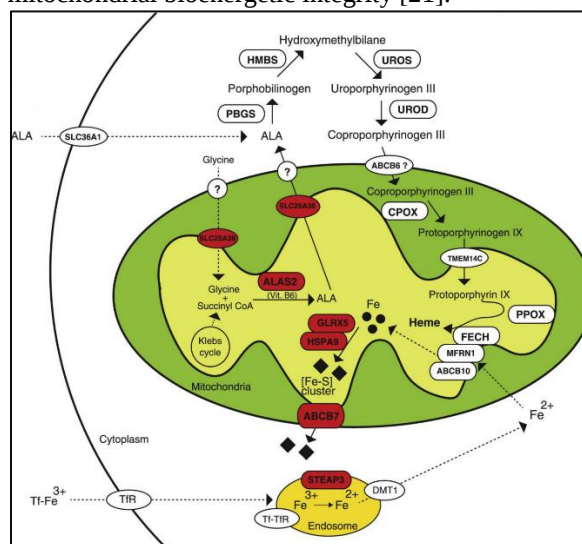


Fig. 3: Pathophysiology of Congenital Sideroblastic Anemia.

At the cellular systems level, these diverse lesions converge on a common maladaptation: ineffective erythropoiesis. In the erythroid marrow, EPO-driven proliferation and differentiation are robust, but hemoglobinization lags because heme availability is inadequate. The heme-regulated inhibitor (HRI) kinase senses heme scarcity and

phosphorylates eIF2 α , dampening global translation while permitting stress-adaptive transcripts; this translational brake contributes to microcytosis and hypochromia in many non-syndromic forms and to megaloblastoid dyspoiesis in syndromic variants where mitochondrial translation is globally perturbed. Meanwhile, iron regulatory proteins (IRP1/2), deprived of Fe–S clusters, bind IREs in target mRNAs, increasing transferrin receptor expression and decreasing ferritin translation, an adjustment that paradoxically heightens iron ingress into a cell already burdened with mitochondrial iron. The result is a feed-forward loop: more iron enters, more is shunted into dysfunctional mitochondria, reactive oxygen species (ROS) increase, mitochondrial membranes are damaged, and ring sideroblasts become more conspicuous as iron-granule-laden organelles coalesce around the nucleus. This sustained ineffective erythropoiesis drives increased intestinal iron absorption via hepcidin suppression and fosters systemic iron overload, compounding organ injury independent of transfusional iron.

Acquired sideroblastic anemias share this mitochondrial final common pathway but arise from clonal and reversible causes. The most clinically prevalent clonal causes are the myelodysplastic and myelodysplastic/myeloproliferative neoplasms with ring sideroblasts—entities now codified as MDS with ring sideroblasts and single-lineage dysplasia (MDS-RS-SLD), MDS with ring sideroblasts and multilineage dysplasia (MDS-RS-MLD), and MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) [22]. Here, the genetic signature is dominated by acquired missense mutations in *SF3B1*, a core component of the U2 small nuclear ribonucleoprotein (snRNP) within the spliceosome; these mutations are detected in up to ~85% of such cases and are strongly associated with the ring sideroblast phenotype [23]. Mechanistically, *SF3B1* mutations alter branch-point recognition and 3' splice site selection, promoting use of cryptic splice sites and generating aberrantly spliced transcripts. A growing catalogue of mis-spliced targets includes genes pivotal for mitochondrial iron handling and heme biosynthesis, providing a molecular bridge from splicing dysregulation to iron misallocation and mitochondrial iron deposition. Structurally, *SF3B1* participates in assembly of the pre-splicing complex that positions U2 snRNP on pre-mRNA; it also helps stabilize an intermolecular helix between U2 and U6 snRNAs during catalysis, functions perturbed by pathogenic variants [14]. Clinically, detecting *SF3B1* mutations corroborates the diagnosis of an MDS/MPN ring-sideroblast variant, conveys a relatively favorable prognosis compared with other MDS genotypes, and, in women, argues against an X-linked *ALAS2* etiology when genetic ambiguity exists [24].

The reverberations of these clonal lesions within the marrow mirror those of congenital forms: erythroid hyperplasia with ineffective maturation,

increased apoptosis of late erythroblasts, and accumulation of iron-engorged mitochondria. However, unlike purely metabolic congenital defects, the neoplastic context adds dysplastic morphology in one or more lineages and a risk of progression. Nevertheless, the sideroblastic signature— $\geq 15\%$ ring sideroblasts—remains the morphologic anchor, and the mitochondrial iron phenotype remains the pathophysiologic endpoint shared with hereditary disease [22][23]. Reversible acquired sideroblastic anemias illustrate targeted insults that pinch critical nodes in the same pathway. Copper deficiency, sometimes driven by zinc excess or malabsorption, diminishes activity of copper-dependent oxidases (e.g., cytochrome c oxidase) integral to mitochondrial respiration and iron mobilization, uncoupling iron delivery from heme assembly and producing ring sideroblasts that vanish with copper repletion. Several drugs inhibit mitochondrial translation or heme enzyme function: linezolid and chloramphenicol suppress mitochondrial ribosomes; isoniazid depletes pyridoxal-5'-phosphate, the cofactor for ALAS2, throttling ALA synthesis; alcohol impairs pyridoxine utilization and mitochondrial metabolism. Removal of the offending agent or repletion of the missing cofactor reverses the sideroblastic phenotype because the mitochondrial block is relieved and heme throughput resumes [1][14][15]. These vignettes underscore that sideroblastic anemia is not a single enzymopathy but a syndrome emergent from multiple inputs that converge on mitochondrial heme insufficiency and iron misallocation. At the ultrastructural level, the ring of iron that stains with Prussian blue reflects both ferritin mineral cores and damaged mitochondrial matrices physically arrayed around the nucleus, a configuration influenced by the cytoskeletal architecture of maturing erythroblasts. Mitochondrial biogenesis normally ramps during hemoglobinization; when porphyrin synthesis or Fe–S cluster assembly fails, the expanded mitochondrial network becomes a sink for iron and a source of ROS. This oxidative milieu damages mitochondrial DNA and proteins further, worsening respiratory chain function and reducing ATP supply for heme synthesis and iron–sulfur assembly—a vicious circle that sustains ineffective erythropoiesis. The heme deficit, by activating HRI, also reprograms translation in a manner that attempts to ration resources but at the cost of red cell size and hemoglobin content, explaining the microcytosis of many non-syndromic forms and the macrocytosis of syndromic variants where mitochondrial translation defects slow nuclear–cytoplasmic maturation.

Systemically, ineffective erythropoiesis depresses hepatic hepcidin via erythroferrone and other mediators, unlocking duodenal iron absorption and macrophage iron release. In the absence of an effective mitochondrial “sink-to-heme,” this extra iron worsens tissue siderosis—liver, endocrine organs, myocardium—independent of transfusions. Thus, a

disorder that begins as a failure to use iron ends as one of iron excess. This pathophysiologic arc justifies therapeutic strategies that either bypass the bottleneck (e.g., pyridoxine supplementation in *ALAS2*-deficient states) or mitigate the iron overload that is a predictable downstream consequence of the marrow's futile attempt to make heme. In summary, sideroblastic anemia arises when mitochondrial and cytosolic programs required for heme construction fall out of register: substrates are misplaced or insufficient (*SLC25A38*, thiamine pathways), catalytic capacity is curtailed (*ALAS2*), Fe-S cluster biology misguides iron traffic (*GLRX5*, *ABCB7*), mitochondrial proteostasis and genome integrity are compromised (*HSPA9*, mitochondrial DNA deletions, *PUS1*, *YARS2*, *TRNT1*, *NDUFB11*), or splicing derangements distort expression of critical iron-heme genes (*SF3B1*) [1][2][3][12][19][20][21][22][23][14][24]. Whatever the proximal lesion, the distal phenotype is consistent: heme-starved erythroblasts laden with iron-rich mitochondria that form a ring around the nucleus, ineffective erythropoiesis yielding anemia, and systemic iron overload driven by maladapted iron homeostasis. Appreciating this integrated pathophysiology is not merely academic—it directly informs diagnosis (marrow morphology plus genetic testing), risk stratification (e.g., *SF3B1* status in MDS-RS), and therapy (cofactor repletion, drug withdrawal, transfusion and iron chelation, or disease-modifying approaches in clonal marrow disease).

Histopathology

On peripheral blood smear, siderocytes are highly characteristic of sideroblastic anemia and serve as a peripheral correlate of the bone-marrow lesion. These erythrocytes are typically hypochromic and display coarse, punctate basophilic granules on Wright-Giemsa staining; the granules represent iron-laden, degenerating mitochondria that persist into the mature red cell and are termed Pappenheimer bodies. Their detection suggests disordered mitochondrial iron handling and ineffective erythropoiesis, and, while not pathognomonic, the presence of numerous siderocytes in the appropriate clinical context is strongly supportive of a sideroblastic process. Functionally, siderocytes constitute the circulating, enucleated counterpart to the ring sideroblasts identified in marrow, underscoring the continuity between intramedullary mitochondrial iron sequestration and peripheral red-cell morphology [25]. Bone marrow evaluation is often pursued for worsening anemia, emerging cytopenias—particularly neutropenia—or unexplained microcytosis with elevated iron indices. Marrow findings vary with etiology: hypocellularity with dysplastic changes may be seen in clonal forms, whereas erythroid hyperplasia reflecting ineffective erythropoiesis is common across categories [26]. The diagnostic anchor is iron staining of the aspirate smear with Prussian blue (Perls reaction), which highlights perinuclear aggregates of iron-laden mitochondria

encircling the nucleus in erythroblasts. By convention, a ring sideroblast is defined when at least five distinct iron granules are present and occupy at least one-third of the nuclear circumference, a quantitative criterion that improves interobserver agreement and diagnostic specificity [14]. In addition to ring sideroblasts, iron staining frequently reveals abundant iron-loaded macrophages within the marrow stroma, a feature that may be inconspicuous on routine Romanowsky stains but becomes evident with dedicated iron histochemistry.

Granulopoiesis in sideroblastic anemia is often left-shifted yet typically culminates in complete maturation, distinguishing it from high-grade myelodysplasia with maturation arrest. Dyserythropoietic features, including a left shift in erythroid precursors, megaloblastoid changes, and binuclearity, are commonly encountered in myelodysplastic syndrome (MDS) variants with ring sideroblasts and provide morphologic evidence of a clonal hematopoietic disorder; these abnormalities are less prominent in non-clonal or reversible sideroblastic states such as those induced by drugs, toxins, or nutritional deficiencies [27]. Certain secondary causes, notably copper deficiency, produce additional histopathologic signatures: vacuolization of early erythroid and myeloid precursors is frequently observed, and a relative hyperplasia of lymphoid precursors may be present, findings that, when integrated with clinical and biochemical data, help differentiate copper-deficiency-related sideroblastic anemia from clonal MDS mimics [28]. Altogether, a synthesis of peripheral smear morphology, iron histochemistry, and lineage-specific maturation patterns yields a robust histopathologic framework for diagnosing and classifying sideroblastic anemia, guiding subsequent genetic testing and therapeutic decisions.

History and Physical

Patients with sideroblastic anemia most often present with nonspecific symptoms attributable to reduced oxygen-carrying capacity: progressive fatigue, malaise, exertional dyspnea, palpitations, reduced exercise tolerance, lightheadedness, and headaches. Symptom tempo varies by etiology—congenital forms may manifest in infancy or childhood with feeding difficulty, growth delay, or school fatigue, whereas acquired forms, including myelodysplastic variants, typically emerge in mid-to-late adulthood with insidious decline. A meticulous history is essential to uncover reversible precipitants and distinguish clonal from nonclonal disease. Key elements include alcohol intake (quantity, pattern, and duration), medication exposures (isoniazid, linezolid, chloramphenicol, chemotherapeutics), and occupational or environmental risk for heavy metals such as lead. Nutritional history should probe for malabsorption or restricted diets; prior gastrointestinal surgery (e.g., gastrectomy, bariatric procedures), long-

term enteral/parenteral nutrition without trace-element supplementation, or excessive zinc use raise suspicion for copper deficiency. Elicit transfusion history, prior iron studies, and any chelation therapy, as well as symptoms of iron overload (arthralgias, fatigue out of proportion to anemia, hypogonadal symptoms, glucose intolerance). A family history of anemia, early transfusion dependence, mitochondrial disorders, or hematologic malignancy supports hereditary or clonal causes. Finally, screen for constitutional symptoms (fevers, night sweats, weight loss) suggestive of marrow disorders, and for neurologic features—ataxia, peripheral neuropathy, hearing difficulties—or endocrine comorbidities (diabetes), which may point toward syndromic hereditary forms such as thiamine-responsive megaloblastic anemia.

The physical examination should be comprehensive and hypothesis-driven. Vital signs may show tachycardia or wide pulse pressure in severe anemia. General inspection often reveals pallor of the skin and conjunctivae; some patients exhibit bronze or slate-gray skin hyperpigmentation consistent with iron overload. Head-and-neck assessment may demonstrate glossitis, angular cheilitis, or scleral icterus if hemolysis coexists. Cardiopulmonary examination may show a soft systolic flow murmur and, in chronic severe anemia, signs of high-output physiology. Abdominal examination should assess for hepatosplenomegaly—mild enlargement can occur in long-standing disease or myelodysplastic syndromes due to extramedullary hematopoiesis. Stigmata of chronic liver disease (palmar erythema, spider angiomas, gynecomastia) raise concern for alcohol-related pathology and secondary iron overload. Extremity and skin evaluation may reveal easy bruising or petechiae if thrombocytopenia is present (as in MDS), or koilonychia-like nail changes that, while classically linked to iron deficiency, can be mimicked by chronic anemia. A careful neurologic examination is crucial: gait testing and Romberg for sensory ataxia (copper deficiency), cerebellar signs (ABCB7-related ataxia), and peripheral neuropathy screening (vibration/proprioception) help identify syndromic variants. Ophthalmologic and auditory screening may detect sensorineural hearing loss in thiamine-responsive syndromes. Age and context provide important clues: hereditary forms more often affect younger patients—and sometimes females through skewed lyonization—while acquired sideroblastic anemia predominates in older adults and may accompany myelodysplastic syndromes, presenting with pallor, bruising, recurrent infections, or macro-/dimorphic indices. Integrating exposure history, family pedigree, syndromic features, and signs of iron overload or marrow failure at the bedside guides targeted testing (iron studies, trace elements, marrow evaluation, and molecular assays) and accelerates distinction between reversible causes and clonal hematopoiesis requiring disease-modifying strategies.

Evaluation

Sideroblastic anemia is fundamentally a laboratory diagnosis, and the evaluative workflow should be structured to confirm the morphologic hallmark, characterize red cell indices, identify iron overload, and delineate clonal versus secondary or congenital etiologies. Initial testing includes a complete blood count with differential, reticulocyte count, peripheral smear, and a chemistry profile that screens for end-organ effects of iron overload and concomitant deficiencies. Assessment of vitamin B12, folate, and copper is essential, given the frequency with which deficiency states—especially copper deficiency related to malabsorption or excess zinc—can mimic or precipitate sideroblastic changes and are readily reversible with repletion [25]. The mean corpuscular volume (MCV) provides a helpful orienting signal: most congenital forms present with microcytosis, whereas nearly all acquired etiologies—including myelodysplastic syndromes (MDS), copper deficiency, and many medication-induced cases—are normocytic to macrocytic, reflecting broader disturbances in erythroid maturation beyond isolated heme synthetic blockade [25][29]. The reticulocyte count is typically low or inappropriately normal, consistent with ineffective erythropoiesis. Iron studies are central for both diagnosis and longitudinal management. Serum ferritin, transferrin saturation, and serum iron are usually elevated, distinguishing sideroblastic anemia from iron deficiency and signaling a propensity to systemic siderosis. When laboratory evidence confirms iron overload, noninvasive organ quantification by magnetic resonance imaging—particularly liver iron concentration—offers accurate staging and follow-up; in select scenarios, liver biopsy remains the reference to define architectural injury and iron distribution patterns that guide chelation or phlebotomy decisions [29]. On the peripheral smear, red cells containing coarse, basophilic iron inclusions (Pappenheimer bodies) are termed siderocytes and reinforce the suspicion of a sideroblastic process, but definitive diagnosis rests on bone marrow examination [2].

Bone marrow aspirate with Prussian blue (Perls) staining is diagnostic when ring sideroblasts are demonstrated—classically, erythroblasts with at least five iron granules encircling one-third or more of the nuclear circumference. Once ring sideroblasts are confirmed, the marrow should be scrutinized for dysplasia across lineages and evaluated for *SF3B1* mutations; the presence of dysplasia with *SF3B1* mutation strongly favors a clonal hematologic disorder within the MDS/MPN spectrum, which carries distinct prognostic and therapeutic implications [2]. In the absence of clonal markers and with no evident secondary cause, targeted genetic testing for congenital sideroblastic anemia genes is appropriate, particularly in younger patients, those with compatible family histories, or individuals with long-standing microcytosis and elevated iron indices [2][25]. This

tiered approach—CBC and nutrient assays, iron studies, marrow morphology with iron histochemistry, clonal genetics, and finally hereditary panels when indicated—ensures accurate classification, reveals reversible etiologies, and informs decisions regarding chelation, phlebotomy, vitamin/cofactor supplementation, or disease-modifying therapy in clonal disease [29].

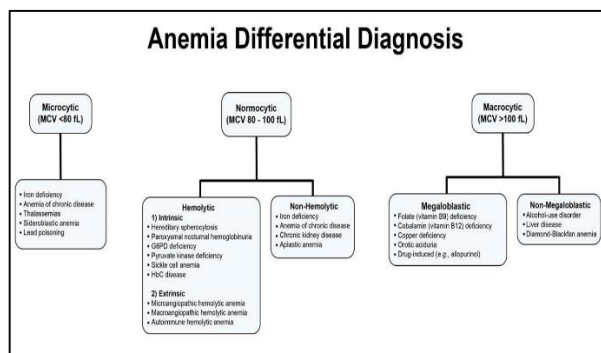


Fig. 4: Diagnosis of Anemia.

Treatment / Management

Management of sideroblastic anemia is individualized to the disease category (hereditary, acquired non-clonal, or clonal MDS/MPN variants), the severity of anemia, iron burden, and the presence of syndromic features or reversible precipitants. The overarching goals are to restore effective erythropoiesis where possible, minimize transfusion requirements, prevent and treat iron overload, and address disease-specific drivers. Patients who are mildly anemic or asymptomatic can often be followed in the outpatient setting with periodic assessment of hemoglobin, reticulocyte indices, iron studies, and symptom-directed adjustments, whereas those with symptomatic or progressive anemia require disease-modifying pharmacotherapy, transfusion support, and iron management. A foundational early step is classification: ruling out secondary causes (medications, alcohol, copper deficiency), evaluating for clonal features (dysplasia and *SF3B1* mutation), and considering hereditary testing in appropriate clinical contexts, because subsequent therapy hinges on etiology [2][25][29]. For X-linked hereditary sideroblastic anemia due to *ALAS2* variants, pyridoxine (vitamin B6) is the principal disease-specific therapy. Doses of 50–100 mg/day can partially or completely correct anemia by restoring cofactor availability for *ALAS2* and improving *ALA* formation; responses range from transfusion independence to modest hemoglobin gains, and are best sustained when iron overload is simultaneously prevented or reversed [2]. In congenital forms characterized by profound ineffective erythropoiesis, luspatercept, an erythroid-maturation agent that traps select TGF- β superfamily ligands to enhance late-stage erythropoiesis, may be beneficial and has shown activity in settings of marked dyserythropoiesis [30][31]. Syndromic variants should be treated

according to their specific metabolic derangements—for example, thiamine repletion for thiamine-responsive megaloblastic anemia (due to *SLC19A2*), with careful glucose management in those who develop diabetes as part of the phenotype [12].

Supportive care remains central across categories. Patients who are not responsive to pyridoxine and who develop symptomatic or severe anemia should receive red blood cell transfusions, following institutional thresholds and clinical status [2]. Because repeated transfusions rapidly increase body iron stores, iron chelation therapy must be considered to prevent cardiomyopathy, endocrinopathies, hepatic injury, and infection susceptibility related to iron overload. A commonly used practice threshold is serum ferritin >1000 ng/L to initiate chelation with deferoxamine or an oral chelator, chosen according to comorbidities, adherence potential, and toxicity profile [32]. The importance of iron control is twofold: it prevents long-term organ damage and can enhance responsiveness to pyridoxine, as iron excess may blunt B6 efficacy and perpetuate oxidative injury within erythroid mitochondria. When hemoglobin normalizes on pyridoxine but iron stores remain high, therapeutic phlebotomy is recommended to reduce tissue siderosis; both chelation and phlebotomy have been associated with improvement in anemia and better pyridoxine responses when iron levels are lowered [32][33]. Meticulous management of secondary acquired sideroblastic anemia depends on the precipitant. For drug-induced cases (e.g., isoniazid, linezolid, chloramphenicol), the offending agent should be discontinued whenever feasible; the anemia often improves after withdrawal. Isoniazid-related sideroblastic changes typically reverse with high-dose pyridoxine, which replenishes the *ALAS2* cofactor pool and restores *ALA* synthesis [14][15]. In copper deficiency, whether due to malabsorption, prior gastrointestinal surgery, excess zinc ingestion, or prolonged parenteral nutrition without trace elements, copper repletion—initially parenteral in severe neurologic disease, then oral—leads to the disappearance of ring sideroblasts and normalization of erythropoiesis over weeks to months. Alcohol-associated sideroblastic anemia improves with alcohol cessation, nutritional rehabilitation, and targeted vitamin support. In syndromic congenital disease, concurrent conditions such as diabetes require rigorous glycemic control, and the risk of hypoglycemia should be mitigated with individualized nutrition plans; optimizing metabolic milieu can improve fatigue and functional status even when hematologic responses are partial.

When sideroblastic anemia arises within clonal hematologic disorders—specifically MDS with ring sideroblasts (MDS-RS) and MDS/MPN-RS-T—management parallels that for low-risk MDS, with tailoring to the ring sideroblast phenotype and

transfusion dependence. Erythropoiesis-stimulating agents (ESAs) are a reasonable first step in selected patients with low endogenous EPO levels; they may be combined with granulocyte colony-stimulating factor (G-CSF) in refractory anemia to enhance erythroid responses and reduce transfusion needs [34]. For patients with persistent transfusion dependence or ESA-refractory disease, hypomethylating agents such as azacitidine or decitabine are widely used disease-modifying options. A commonly employed regimen is azacitidine 75 mg/m² daily for 7 consecutive days every 28 days, administered subcutaneously or intravenously, which can improve cytopenias and decrease transfusion burden in appropriate candidates, including adults who meet criteria for RARS/MDS-RS with neutropenia ($<1 \times 10^9/L$) [34]. Some patients with indolent disease and minimal symptoms may be observed on a watch-and-wait strategy with close monitoring, but most require intervention once transfusion dependence or symptomatic anemia evolves. Luspatercept has emerged as an important therapy for low-risk MDS with ring sideroblasts, particularly in transfusion-dependent patients. In the randomized, double-blind MEDALIST trial, luspatercept significantly reduced transfusion requirements and improved hematologic endpoints versus placebo, supporting its use as first-line therapy in some patients or after ESA failure in others [35][36]. Dosing and interval adjustments are guided by hemoglobin response and transfusion needs, with attention to adverse effects such as fatigue, bone pain, and hypertension. Another newer option is imetelstat, a telomerase inhibitor that demonstrated clinically meaningful transfusion independence in the phase 3 IMerge trial and received approval in 2024 for transfusion-dependent low- to intermediate-risk MDS; imetelstat provides an additional pathway-distinct approach for patients refractory to ESAs [37]. In MDS/MPN-RS-T, where thrombocytosis coexists with ring sideroblasts, aspirin is recommended for thrombosis prevention when a JAK2V617F mutation is present, balancing bleeding risk against thrombotic risk at the individual level [14].

Across all forms, longitudinal iron management is integral. Ferritin trends, transferrin saturation, and periodic organ iron assessments (with MRI when available) inform chelation intensity and the consideration of phlebotomy in patients with adequate hemoglobin. Proactive iron control can reduce cardiac and hepatic morbidity and may, by reducing oxidative stress in the marrow niche, improve the quality of erythropoiesis. Equally important are vaccination, infection prophylaxis as indicated, and careful drug stewardship, avoiding agents that exacerbate mitochondrial dysfunction or suppress marrow function when alternatives exist. Comprehensive care involves multidisciplinary coordination among hematology, transfusion medicine, pharmacy, nutrition, endocrinology, and, when needed, genetics and metabolic specialists.

Patients benefit from education regarding medication triggers, alcohol moderation, trace-element balance (particularly zinc and copper), and adherence to chelation and vitamin regimens. For those on luspatercept or imetelstat, structured monitoring of hemoglobin, transfusion intervals, liver function tests, and potential adverse events supports safe continuation. Finally, the management plan should be dynamic, revisiting the etiologic hypothesis when responses are suboptimal. For example, failure to improve with pyridoxine warrants reassessment for coexisting iron overload, copper deficiency, or unrecognized clonal disease; conversely, increasing transfusion needs in previously stable MDS-RS should prompt marrow reevaluation for disease progression. By aligning disease-specific therapies—pyridoxine or thiamine repletion, toxin/drug withdrawal, copper supplementation, ESAs/HMAs, luspatercept, or imetelstat—with vigilant iron control and supportive care, clinicians can meaningfully reduce transfusion burden, limit organ toxicity, and improve functional outcomes in patients with sideroblastic anemia [2][30][31][32][33][34][35][36][37][14][15][38].

Differential Diagnosis

The differential diagnosis of sideroblastic anemia spans non-clonal and clonal hematologic entities as well as several common anemias that may mimic aspects of the presentation. Clinically, anchoring on microcytosis or dimorphic indices with elevated iron parameters can be helpful, but confirmation depends on integrating history, laboratory features, marrow morphology, and—when indicated—molecular testing. Non-clonal disorders include congenital sideroblastic anemias, which are subdivided into nonsyndromic forms driven by defects in heme synthesis or mitochondrial iron–sulfur cluster biology and syndromic forms that add multisystem dysfunction; these typically present in infancy or childhood but may be recognized later through family screening. Secondary acquired conditions must be considered in all age groups because they are potentially reversible and common: copper deficiency from malabsorption, bariatric surgery, parenteral nutrition without trace elements, or zinc overload; lead poisoning with basophilic stippling and neurocognitive symptoms; alcohol-related mitochondrial toxicity; and drug-induced mitochondrial suppression or pyridoxine depletion, particularly with isoniazid, linezolid, or chloramphenicol. Careful exposure and medication histories, serum copper and zinc levels, and, where relevant, blood lead testing help distinguish these causes and guide targeted therapy [14].

Clonal disorders comprise myelodysplastic syndromes and related overlap neoplasms with ring sideroblasts. These include MDS with ring sideroblasts, either with single-lineage dysplasia or multilineage dysplasia, and the myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, which often

displays an *SF3B1* mutation and, in the thrombocytosis phenotype, may harbor *JAK2V617F* [14]. In these entities, bone marrow demonstrates $\geq 15\%$ ring sideroblasts by Perls stain alongside dysplastic changes, and peripheral counts may show anemia with relative preservation or elevation of platelets in the RS-T variant. Because ring sideroblasts themselves are not pathognomonic for clonality, distinguishing clonal from secondary disease requires correlating morphology with cytogenetics and next-generation sequencing. Finally, several more common anemias must remain on the differential: iron deficiency anemia, thalassemia syndromes, anemia of chronic disease/inflammation, lead poisoning, and ongoing blood loss. Iron deficiency is suggested by low ferritin and transferrin saturation with microcytosis and responds to iron repletion; thalassemia typically shows marked microcytosis with normal or elevated RBC count and characteristic hemoglobin electrophoresis patterns; inflammatory anemia presents with normal or increased ferritin and reduced iron availability. Systematic evaluation that pairs peripheral smear findings with iron studies, trace element assessment, and marrow iron histochemistry allows clinicians to disentangle these overlapping presentations and accurately classify sideroblastic versus non-sideroblastic etiologies.

Prognosis

Prognosis in sideroblastic anemia is heterogeneous and hinges on the underlying cause, the degree of ineffective erythropoiesis, iron burden, and the presence of coexisting clonal features or reversible precipitants. In secondary acquired sideroblastic anemia, outcomes are generally favorable once the causative toxin or drug is discontinued and nutritional deficiencies are corrected; copper repletion, cessation of zinc excess or alcohol use, and withdrawal of mitochondrial-toxic medications typically normalize erythropoiesis, with ring sideroblasts disappearing over weeks to months. In X-linked sideroblastic anemia due to *ALAS2* mutations, early recognition and appropriate pyridoxine supplementation can substantially improve hemoglobin levels, reduce or eliminate transfusion dependence, and mitigate long-term complications, provided that iron overload is monitored and actively managed. Failure to address iron burden—through chelation or phlebotomy when feasible—can blunt pyridoxine responsiveness and drive progressive organ siderosis, ultimately worsening survival despite hematologic improvement. In contrast, the prognosis of acquired clonal sideroblastic anemia associated with MDS/MPN variants varies with genetic and clinical risk. Mutations in *SF3B1* are prevalent in these disorders and are generally associated with more favorable outcomes compared with other MDS genotypes, including longer overall survival and lower progression rates; however, prognosis remains modulated by co-mutations, cytopenia depth,

transfusion burden, and marrow blast percentage [23]. Older age at diagnosis, multilineage dysplasia, and increasing blasts portend a higher risk of evolution to acute myeloid leukemia (AML) and reduced survival, while robust responses to erythropoiesis-stimulating agents, luspatercept, hypomethylating agents, or newer agents such as imetelstat can translate into improved quality of life and, in some cohorts, longer survival [39]. Across etiologies, the tempo of iron accumulation is a key determinant of non-hematologic morbidity—cardiac, hepatic, and endocrine—and aggressive iron management improves functional outcomes and may enhance responsiveness to disease-directed therapies. Ultimately, individualized risk stratification incorporates molecular profiling, blast counts, transfusion needs, and comorbidities yields the most accurate prognostic outlook and guides intensity of monitoring and therapy.

Complications

Complications of sideroblastic anemia arise from three interrelated domains: chronic ineffective erythropoiesis with anemia, systemic iron overload, and, in clonal disease, marrow failure with leukemic evolution. In hereditary forms caused by *ALAS2* (XLSA), *GLRX5*, or *SLC25A38* mutations, persistent ineffective erythropoiesis suppresses hepcidin and augments intestinal iron absorption, while transfusion therapy adds exogenous iron. The resulting hepatic siderosis can progress to fibrosis and cirrhosis, paralleling hereditary hemochromatosis in pathophysiology; cardiac iron deposition predisposes to dilated or restrictive cardiomyopathy and arrhythmias; and endocrine iron accrual contributes to hypogonadism, hypothyroidism, or diabetes mellitus. Clinically, patients may develop hepatomegaly, heart failure symptoms, or endocrine dysfunction over time if iron overload is not prevented or treated. Importantly, organ toxicity can occur even in the absence of heavy transfusion exposure, underscoring the need for proactive monitoring and early chelation or phlebotomy when appropriate [2]. In acquired clonal sideroblastic anemia due to MDS/MPN variants, complications reflect both anemia severity and multilineage marrow dysfunction. Symptomatic anemia leads to fatigue, exertional dyspnea, reduced exercise capacity, and, in advanced cases, high-output cardiac failure. Leukopenia increases susceptibility to bacterial and fungal infections, while thrombocytopenia predisposes to mucocutaneous bleeding, easy bruising, and in severe cases gastrointestinal or intracranial hemorrhage. Thrombotic and vascular events are particularly relevant in the RS-T phenotype, especially when *JAK2V617F* is present, mandating careful risk assessment and prophylaxis when indicated. The most feared long-term complication is progression to AML, a risk heightened by adverse cytogenetics, clonal patterns, and rising blasts; such transformation is associated with poor outcomes and

intensive treatment requirements. Additionally, transfusion-related hemosiderosis adds a second layer of organ risk in clonal disease, amplifying hepatic and cardiac morbidity if chelation is delayed or inadequate. Across etiologies, the complication profile is therefore dynamic: it evolves with transfusion exposure, iron burden, marrow reserve, and disease biology. Regular surveillance of ferritin and organ iron by MRI, infection prophylaxis where indicated, vaccination, judicious use of growth factors and disease-modifying agents, and early consideration of iron chelation are central to mitigating these risks and improving long-term outcomes [40][2].

Conclusion:

In conclusion, sideroblastic anemia represents a complex diagnostic and therapeutic challenge, characterized by the unifying morphologic finding of ring sideroblasts but stemming from a wide spectrum of etiologies. The central pathophysiology involves a failure of mitochondrial heme synthesis, leading to ineffective erythropoiesis and the paradoxical state of anemia with systemic iron overload. A meticulous and systematic evaluation is paramount, beginning with basic hematologic and iron studies and culminating in a bone marrow biopsy with iron staining. This diagnostic pathway is essential for differentiating between hereditary forms, which require genetic testing and may respond to pyridoxine; acquired reversible causes, such as copper deficiency or drug toxicity, where correction of the underlying issue can resolve the condition; and clonal myelodysplastic syndromes, which necessitate molecular profiling and disease-specific therapies like luspatercept. Ultimately, successful long-term management extends beyond merely addressing the anemia. It mandates vigilant and proactive management of iron overload through chelation or phlebotomy to prevent irreversible damage to the liver, heart, and endocrine organs. A tailored, etiology-driven approach, combined with interdisciplinary care, is critical to reducing transfusion dependence, mitigating complications, and improving the overall prognosis and quality of life for patients with this diverse group of disorders.

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