COLLEGE of AMERICAN PATHOLOGISTS
Education

Clinical Pathology Improvement Program (CPIP)
2024 CPIP-G Case 7: Chemistry – How to Interpret Laboratory Iron Studies

Erratum for 2024 CPIP-G Case 7: Chemistry – How to Interpret Laboratory Iron Studies

A table in the Case 2 Discussion contained incorrect headings.

The original, incorrect table was:

Table 3: Iron studies in states of iron deficiency versus chronic inflammation.*

Analyte	Chronic Inflammation	Iron Overload
Iron	Decreased	Decreased
TIBC	Increased	Decreased
Transferrin saturation (in %)	Decreased	Decreased
Ferritin	Decreased	Increased

*Compared to the expected reference interval (RI) for age and sex:

Decreased = decreased below the RI

Increased = increased above the RI

Table 3 should have contained the following correct content:

Table 3: Iron studies in states of iron deficiency versus chronic inflammation.*

Analyte	Iron Deficiency	Chronic Inflammation
Iron	Decreased	Decreased
TIBC	Increased	Decreased
Transferrin saturation (in %)	Decreased	Decreased
Ferritin	Decreased	Increased

*Compared to the expected reference interval (RI) for age and sex:

Decreased = decreased below the RI

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Case 2, with the corrected table, appears on the following pages in its entirety.

Case Presentation

Case 2

A 45-year-old woman complains of sore, swollen joints of several years' duration, especially in her hands and knees, bilaterally. She also complains of tiredness, weakness, and occasional episodes of shortness of breath, especially on exertion. There is no history of bleeding. On physical examination, she is pale and tachycardic. Her metacarpal-phalangeal joints are swollen and tender bilaterally, and her fingers display ulnar deviation. Beneath her skin, several subcutaneous nodules are appreciated. **Table 1** and **Table 2** display her CBC and iron studies.

Table 1: Patient's CBC results.

Complete blood count (CBC)	Patient results	Reference interval
RBC count (females)	2.9 x 10^6/uL	3.9-5.1 x 10^6/uL
Hemoglobin (females)	9.6 g/dL	11-16 g/dL
Hematocrit (females)	29.5%	33%-48%
Mean corpuscular volume (MCV)	78 fL	80-100 fL
White blood cell count (WBC)	10,000/uL	4,500-10,500/uL
Platelet count	425,000/uL	150,000-400,000/uL

Table 2: Patient's iron studies.

Serum tests	Patient results	Reference intervals
Serum iron	10 ug/dL	42-135 ug/dL
Total iron binding capacity (TIBC)	200 ug/dL	225-430 ug/dL
Transferrin saturation	5%	20%-45%
Ferritin	850 ng/mL	10-185 ng/mL (females)

Thought-Provoking Question

Is iron deficiency the most likely cause of the patient's anemia?

Short Answer

No.

Discussion

In states of chronic inflammation or chronic disease, iron release from splenic macrophages and iron absorption from the gut are both impaired, leading to decreased iron delivery to the bone marrow. With chronic inflammation, anemia is initially normocytic but, over time, progresses to microcytic. In chronic inflammation with iron sequestered in the spleen, plasma ferritin rises. Chronic illness often leads to low transferrin concentrations and low transferrin saturation is always expected. A comparison of the laboratory findings between iron deficiency and chronic inflammation is depicted in **Table 3**.

Table 3: Iron studies in states of iron deficiency versus chronic inflammation.*

Analyte	Iron Deficiency	Chronic Inflammation
Iron	Decreased	Decreased
TIBC	Increased	Decreased
Transferrin saturation (in %)	Decreased	Decreased
Ferritin	Decreased	Increased

*Compared to the expected reference interval (RI) for age and sex:
Decreased = decreased below the RI
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In contrast to the thalassemias, in iron insufficient states, both iron deficiency and chronic disease, the RBC count is low concordant with low hemoglobin concentrations. After many months to years of chronic inflammation, iron deficiency may supervene. This is suggested by ferritin concentrations of less than 50 ng/mL.[15]

In this case, the most likely overall clinical diagnosis is rheumatoid arthritis (RA). Positive tests for rheumatoid factor and/or citrullinated cyclic peptide autoantibodies would support this diagnosis.

As a chronic inflammatory marker, interleukin-6 (IL-6) that is secreted by macrophages stimulates the liver to produce hepcidin; hepcidin is a positive acute-phase reactant in this case. High levels of hepcidin impair iron absorption from the duodenum and impair iron release from splenic macrophages. Therefore, there is decreased iron delivery to bone marrow erythroblasts causing an iron-restricted anemia. The plasma iron is reduced because of depressed iron recycling and decreased gut absorption.

As a negative acute-phase reactant, transferrin levels decline with inflammation. However, plasma iron is even more greatly decreased than transferrin, and therefore, the transferrin saturation is greatly depressed. Other than atransferrinemia (a rare inborn error involving the failure to synthesize transferrin), transferrin levels can decline with acute inflammation, liver disease, malnutrition, or the nephrotic syndrome.

In terms of the iron cycle, in states of chronic inflammation, the iron that is derived from RBC death in the spleen is not recycled back to the developing erythroblasts appropriately, causing iron accumulation in these splenic macrophages. Such iron “trapping” in the spleen raises the circulating ferritin concentration. It must be emphasized that inflammation is not a state of iron overload, which might otherwise be suggested by the elevated ferritin concentration.

Researchers are evaluating the possible role of hepcidin antagonists in the treatment of anemia of chronic disorder, as observed in this case.[16] The iron cycle will be discussed in further detail in the case that follows.

Acute inflammation via the action of hepcidin can lower the plasma iron concentration just as acute inflammation can raise the plasma ferritin concentration. Therefore, when assessing a patient’s iron status via blood testing, the overall state of their health must be considered. While iron studies do display diurnal variation, it appears that the specific timing of phlebotomy is usually not crucial.[17]