Approaching the Anemias

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Anemia is a common problem. One study showed that 13% of community-dwelling individuals > 65 years of age were anemic.[1] Without performing bone marrow testing, one-third of anemia cases in the elderly remain unexplained.[2]

The best approach to determining the cause of anemia is dividing anemia into groups depending on the mean corpuscular volume (MCV).

Microcytic anemia

The differential diagnosis for microcytic anemia includes only five items (Table 1). Furthermore, sideroblastic anemia in adults, is usually related to a myelodysplastic syndrome and is not microcytic. Lead poisoning in this case is extremely rare.

IDA vs. ACD

The distinction between iron deficiency anemia (IDA) and anemia of chronic disease (ACD) is difficult to make and patients often do not have "classic" iron studies. Classically, IDA is associated with:

- low ferritin,
- low transferrin saturation,
- low serum iron and
- high total iron binding capacity (TIBC).

Ryan's case

Ryan, 58, has long-standing rheumatoid arthritis (RA), for which he takes periodic nonsteroidal anti-inflammatory drugs (NSAIDs). His RA has flared over the past several months and he presents to you with fatigue. His usual back pain has also worsened. He states that his stools are dark and he takes an iron supplement.

Lab results

A workup is performed and the following is noted:

- Hemoglobin is 100 g/L, with a mean corpuscular volume of 82 fl
- White blood cell and platelet counts are normal
- Normal blood cell morphology on the peripheral smear
- A "normal" reticulocyte count of 45 x10^9
- Ferritin 450 ug/L
- Normal serum protein electrophoresis
- Normal liver enzymes
- Normal lactate dehydrogenase
- Normal creatinine

Questions

1. What is the cause of Ryan's anemia?
2. Is further testing needed?

Go to page 62 for Ryan's follow-up.

Ryan's follow-up

Ryan's presentation is very consistent with anemia of chronic disease. Despite his NSAID use and report of dark stools, a ferritin of 450 ug/L essentially excludes iron deficiency and investigations for a source of blood loss are not warranted.

Because of his worsening back pain, one could be cautious and investigate further for myeloma with spine x-rays and a urine protein electrophoresis.

Ryan follows up with his rheumatologist and a disease modifying antirheumatic drug is started. His RA flare settles over several months and, at that time, a repeat complete blood count shows that his hemoglobin has improved to 125 g/L.

Table 1

Causes of microcytic anemia

- Iron deficiency anemia
- Anemia of chronic disease
- Thalassemia and thalassemic hemoglobinopathies
- Sideroblastic anemia
- Lead poisoning

Classic iron studies in ACD include:

- high ferritin,
- normal transferrin saturation,
- low serum iron and
- low TIBC.

The gold standard for distinguishing these anemias is bone marrow testing, but this is often not indicated.

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Ferritin is the most useful test in diagnosing IDA.[3] There is a perception that ferritin testing is not as useful in patients with inflammatory illnesses. However, several studies have demonstrated that ferritin remains a useful test in these patients. For example, Guyatt, *et al* showed that in hospitalized elderly patients, a ferritin of < 18 ug/L confirms iron deficiency, while a ferritin of > 100 ug/L excludes iron deficiency in most patients.[4] With iron deficiency, one must look for a source of blood loss.

IDA vs. thalassemia trait

The clinical setting is useful in distinguishing IDA from thalassemia trait, in that a bleeding history is often present with IDA and certain ethnic groups are affected by thalassemia. With IDA, the ferritin level is low. With thalassemia traits, the ferritin level is normal or slightly high. The pathologist may comment on helpful features on the blood smear (*e.g.*, target cells with thalassemia). The hemoglobin electrophoresis is normal in iron deficiency, but an increased hemoglobin A2 is seen with ß-thalassemia trait. Of the α-thalassemias, only three α–chain deletions (*i.e.*, hemoglobin H disease) can be detected on hemoglobin electrophoresis. A-thalassemia traits associated with one or two α–chain deletions can only be diagnosed by specialized testing. Other abnormal hemoglobins may also be associated with microcytosis (*e.g.*, hemoglobin E).

Normocytic anemia

There are many causes of normocytic anemia and the first test should always be a reticulocyte

count. (Though not comprehensive, the list of bone marrow disorders in Table 2 focuses on those disorders that may be present with an isolated anemia). This allows distinction of the anemia into a hyperproliferative anemia associated with a reticulocytosis, or a hypoproliferative anemia associated with a low or inappropriately normal reticulocyte count. There are only two causes of a hyperproliferative anemia: bleeding and hemolysis.

More commonly, the reticulocyte count is low or inappropriately normal. In this circumstance, there is a broad differential diagnosis and it is useful to divide such anemias into those associated with a normal bone marrow vs. those associated with an abnormal bone marrow. Other tests that might be helpful include blood workup, such as:

- iron studies,
- creatinine,
- liver enzymes and
- hormone levels.

It is difficult to diagnose a bone marrow disorder without a bone marrow examination, but bloodwork, such as a serum protein electrophoresis, looking for myeloma, may provide some hints.

Unfortunately, the straightforward distinction into hyperproliferative anemia vs. hypoproliferative anemia is not always easy, as it is not uncommon that multiple mechanisms coexist (*e.g.*, a patient may have both hemolysis and marrow infiltration with lymphoma).

Lastly, when considering normocytic and macrocytic anemias, some of the items on the differential diagnosis are common to both categories of anemia.

Table 2

Causes of normocytic anemia

Hyperproliferative
- Bleeding
- Hemolysis

Hypoproliferative
- Bone marrow: normal
  - Anemia of chronic disease
  - Early iron deficiency
  - Systemic illness
    - > Liver disease
    - > Renal disease
  - Endocrine
    - > Hypogonadism
    - > Hypothyroidism
    - > Hypoadrenalism
    - > Hypopituitarism
- Bone marrow: abnormal
  - Bone marrow failure
    - > Myelodysplastic syndrome
    - > Pure red cell aplasia
  - Bone marrow infiltration
    - > Myeloma
    - > Indolent lymphoma

Table 3

Causes of macrocytic anemia

Megaloblastic
- B12 or folate deficiency
- Drugs interfering with B12, folate metabolism or DNA synthesis

Non-megaloblastic
- Bone marrow: normal
  - Alcohol abuse
  - Liver disease
  - Hypothyroidism
- Bone marrow: abnormal
  - Myelodysplastic syndrome
  - Pure red cell aplasia
  - Myeloma

Take-home message

- Dividing anemias into categories, based on the mean corpuscular volume, remains the most effective way to differentiate between the anemias
- There are only three common causes of microcytic anemia. These are:
  - iron deficiency,
  - anemia of chronic disease and
  - thalassemia
- The reticulocyte count is the first test to order when trying to distinguish the cause of normocytic anemia
- For normocytic and macrocytic anemias, consider whether the patient might have a bone marrow disorder

Frequently Asked Questions

1. Are full iron studies needed to diagnose iron deficiency?

In most circumstances, a ferritin test alone is sufficient, but higher cut-off values may be appropriate in patients with inflammatory diseases.

2. What is the best way to start sorting out the many causes of normocytic anemia?

Measuring a reticulocyte count allows differentiation of the anemia into a hyperproliferative vs. a hypoproliferative anemia.

3. When should hematological consultation and bone marrow examination be considered?

When the patient is constitutionally unwell or has concerning symptoms such as back pain, when the anemia is severe and unexplained or when there are additional cytopenias.

Macrocytic anemia

When considering macrocytic anemia, reticulocytosis, causing a slight macrocytosis, should first be excluded. The next question is whether or not the anemia is megaloblastic (Table 3 presents bone marrow disorders that might be present with an isolated anemia). This term refers to the morphologic changes associated with impairment in DNA synthesis in the bone marrow. In megaloblastic anemias, the pathologist will see hypersegmented neutrophils and oval macrocytes. However, this information is often not available. Measurement of the following may be helpful:

- the reticulocyte count,
- B12 and folate levels,
- liver enzymes and
- thyroid stimulating hormone.

However, if this testing is normal and the patient is unwell or has a severe anemia, bone marrow testing may be needed.

In all circumstances and with any anemia, when patients present with multiple cytopenias, one should consider a bone marrow disorder.

References
1. Culleton BF, Manns BJ, Zhang J, et al: Impact of anemia on hospitalization and mortality in older adults. Blood 2006; 107(10):3841-6.
2. Guralnik JM, Eisenstaedt RS, Ferrucci L, et al: Prevalence of anemia in persons 65 years and older in the United States: Evidence for a high rate of unexplained anemia. Blood 2004; 104(8):2263-8.
3. Guyatt GH, Oxman AD, Ali M, et al: Laboratory diagnosis of iron-deficiency anemia: An overview. J Gen Intern Med 1992; 7(2):145-53.
4. Guyatt GH, Patterson C, Ali M, et al: Diagnosis of iron-deficiency in the elderly. Am J Med 1990; 88(3):205-9.