A 45-year-old woman presents to the emergency department with the sudden onset of confusion, severe headaches, and blurred vision. These symptoms have been progressive over the past week. On physical examination, she is febrile and disoriented with diffuse petechial hemorrhages throughout her body. Relevant laboratory results are as follows:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum BUN</td>
<td>42 mg/dL</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>4.0 mg/dL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>9.6 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>29%</td>
</tr>
<tr>
<td>MCV</td>
<td>90 fL</td>
</tr>
<tr>
<td>WBC count</td>
<td>7800/mm³</td>
</tr>
<tr>
<td>Platelet count</td>
<td>36,000/mm³</td>
</tr>
<tr>
<td>Peripheral blood smear</td>
<td>Schistocytes and reticulocytes</td>
</tr>
</tbody>
</table>

**What is the most likely diagnosis?**
Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome (TTP/HUS).

**What are the five cardinal symptoms of this condition?**
- Transient neurological problems.
- Fever.
- Thrombocytopenia.
- Microangiopathic hemolytic anemia.
- Acute renal insufficiency.

**What is the pathogenesis of these symptoms?**
TTP/HUS involves the widespread development of hyaline thrombi composed of platelet aggregates in the microcirculation. This consumption of platelets leads to thrombocytopenia and microangiopathic hemolytic anemia, which can cause widespread organ dysfunction.

**What would this patient's coagulation studies show?**
Coagulation studies will be within normal limits. This is predominantly a thrombocytopenic disease with no coagulation cascade abnormalities.

**Which inherited risk factor predisposes patients to this condition?**
A deficiency of the von Willebrand metalloproteinase (ADAMTS-13) is an inherited factor that causes very large von Willebrand factor multimers to accumulate in the plasma and promote clot formation.

**What is the appropriate management for this condition?**
Plasma exchange reverses the platelet consumption that is responsible for the thrombus formation. Severe cases may also require adjunctive immunosuppressive treatment with prednisone. Platelet transfusion is contraindicated because it may lead to new or worsening thrombosis and subsequent neurologic symptoms. Prompt initiation of treatment is essential to avoid irreversible renal failure and possibly death.

**What is a common cause of this condition in children?**
Typically, TTP/HUS is preceded by severe bloody diarrhea due most often to enterohemorrhagic *Escherichia coli* O157:H7 infection. This is thought to be due to systemic absorption of a Shiga-like toxin that binds to and damages endothelial cells, inciting platelet activation and thrombosis.
**CASE 37**

A 36-year-old sexually active man goes to his doctor after noticing that his left testicle has been swollen for the past few weeks. The patient has noticed a dull, achy sensation in this testicle but no acute pain. On physical examination, the left testicle is larger than the right, and a nontender, round, firm, rubbery mass is palpated. Transillumination with a penlight reveals an opaque mass. Laboratory tests reveal a normal chemistry panel, normal complete blood count, elevated LDH level, normal serum human chorionic gonadotropin (hCG) level, and normal α-fetoprotein (AFP) level.

**What is the most likely diagnosis?**

Testicular tumor, as suggested by the presence of a painless, nontransilluminating testicular mass. In a young man, the most likely diagnosis is a seminoma, which has a peak incidence of age 35 years and accounts for approximately 35% of testicular tumors. This diagnosis is further supported by the elevated LDH level, normal hCG level (elevated in 20% of seminomas), and normal AFP level.

**What is the differential diagnosis of a scrotal mass?**

Conditions to consider in the differential of a scrotal mass include the following:

- Orchitis.
- Epididymitis.
- Hydrocele.
- Spermatoccele.
- Varicocele.
- Hernia.
- Cancer (nonseminomatous and nongerminal).

Epididymitis and orchitis are accompanied by a painful testicle and an elevated WBC count, differentiating them from seminoma. Elevated AFP levels suggest a nonseminomatous germ cell cancer. Fluid collections, like a hydrocele, transilluminate. A hernia may be reducible or irreducible; if it is irreducible, the patient will likely be in significant pain from the presence of incarcerated bowel.

**What is the analogous condition in women?**

The analogous ovarian tumor is the dysgerminoma, the most common germ cell tumor in women. It is usually malignant and is more common in younger patients. Like seminomas, it can produce LDH. It can also produce alkaline phosphatase.

**What is the lymphatic drainage of this tumor?**

Understanding the lymphatic drainage of the testicles is important in considering metastases. Because the testicles descend from the abdomen during development, the lymph vessels ascend to the lumbar and para-aortic lymph nodes. This contrasts with the lymph drainage of the scrotum, which is an outpouching of skin. The lymph vessels of the scrotum drain to the superficial inguinal nodes.

**What other conditions are characterized by an elevated hCG level?**

Only 10%–20% of seminomas present with elevated hCG levels. Tumors in women that are likely to present with an elevated hCG level include hydatidiform moles, choriocarcinomas, and gestational trophoblastic tumors.
A 66-year-old postmenopausal woman presents to her physician with complaints of fatigue, dyspnea, dizziness, and tachycardia. She says she craves chewing on ice cubes. Physical examination reveals pallor of the mucous membranes of her mouth. The cells on a PBS are microcytic and hypochromic (Figure 8-19). Relevant laboratory findings are as follows:

- Hemoglobin: 11 g/dL
- Hematocrit: 30%
- Reticulocyte count: 0.2%
- MCV: 74 fL

![Image of blood smear](image-url)

**What is the most likely diagnosis?**
Iron deficiency anemia. This diagnosis would be supported by laboratory studies demonstrating a decreased iron concentration, increased total iron binding capacity, and decreased ferritin levels. The cause for a patient's iron deficiency, however, needs to be further pursued. In addition, comorbid inflammatory conditions can raise serum ferritin, resulting in values within the normal range.

**What factors can lead to this condition?**
Causes of iron deficiency anemia include the following:

- Chronic blood loss (especially gastrointestinal blood loss secondary to colon cancer).
- Dietary deficiency (increased demand or decreased absorption).
- Intestinal hookworm infection (this is the most common cause worldwide and should be considered in patients who have immigrated from developing countries).

In general, in a postmenopausal woman and all men, one must look for GI blood loss in any newly diagnosed patient with iron deficiency anemia unless the cause of the iron loss is obvious (nose bleeds, recent trauma, etc).

**Why are total iron binding capacity (TIBC) measurements important in this condition?**
TIBC is high in iron deficiency anemia and low in anemia of chronic disease. Both illnesses have decreased serum iron levels. A low ferritin (< 41 ng/mL) is sensitive and specific for iron deficiency anemia. The normal iron/TIBC ratio is typically 0.25–0.45, and levels < 0.12 indicate iron deficiency. Anemia of chronic disease often has a normal iron/TIBC ratio because of the concomitant decrease of TIBC and serum iron.

**What other conditions is this patient at greatly increased risk for developing?**
Because of the extreme lack of iron, this patient is at risk for Plummer-Vinson syndrome. This syndrome is characterized by atrophic glossitis, esophageal webs, and anemia.

**What are the common causes of microcytic, hypochromic anemia?**
Microcytic anemia results from either decreased hemoglobin production or faulty hemoglobin function. Common causes include iron deficiency, thalassemia, sideroblastic anemia, and lead poisoning.
A mother brings her 4-month-old infant to the pediatrician because the child has had watery diarrhea almost daily for the past month. Previously a good eater, the baby is now refusing to feed and is irritable most of the time. While holding the baby, the mother also calls attention to a mass in his belly that has not resolved in several days.

**What is the most common tumor in infants?**

Neuroblastoma is a malignancy of the sympathetic nervous system that arises during embryonic development. In the embryo, neuroblasts (pluripotent sympathetic stem cells) invaginate and migrate along the neuraxis to the adrenal medulla, the sympathetic ganglia, and various other sites. Figure 8-20 shows a large neuroblastoma occupying the right flank in an older child. The site of disease presentation depends on the area of neuroblast migration.


**What are the types of small, round, blue-cell tumors?**

- Neuroblastoma is a common tumor of the adrenal medulla in children. It is characterized by homovanillic acid (dopamine breakdown product) present in urine. It is associated with the \( N\)-\( myc \) oncogene.
- Wilms tumor is the most common childhood renal malignancy and presents with flank mass and hematuria. It is associated with deletion of \( WT1 \) on chromosome 11.
- Acute leukemia is caused by unregulated growth of leukocytes in the bone marrow.
- Mesothelioma is associated with smoking and asbestos exposure.
- Rhabdomyosarcoma is a tumor of skeletal muscle.
- Medulloblastoma is a highly malignant cerebellar tumor. It often compresses the 4th ventricle to cause hydrocephalus.
- Retinoblastoma is associated with 13q mutation of \( Rb \) gene.

**What prognostic factors are important in this condition?**

Tumor stage and the patient’s age at diagnosis are the two most important prognostic factors. Patients with localized disease, regardless of age, have a favorable prognosis (5-year survival rate: 80%–90%). Overall, younger age at diagnosis carries a more favorable prognosis.

**What are the likely biopsy findings in this condition?**

Histologically, neuroblastoma presents as dense nests of small, round, blue tumor cells with hyperchromatic nuclei. Homer-Wright pseudorosettes are seen in 10%–15% of cases. These pseudorosettes are composed of neuroblasts surrounding neuritic processes and are pathognomonic for neuroblastoma.

**What are the appropriate treatments for this condition?**

For patients with localized disease, surgical excision is curative. For more advanced disease, treatment consists of surgical excision followed by chemotherapy. Chemotherapy for neuroblastoma consists of combination regimens, typically vincristine, cyclophosphamide, and doxorubicin. Other regimens include etoposide in combination with either cisplatin or carboplatin.
CASE 2

The parents of a 4-year-old girl bring their daughter to the pediatrician because they are concerned about her fever, which has lasted for more than a week. Her parents have also noticed that she is less energetic and now walks with a limp. Physical examination is significant for hepatomegaly, scattered petechiae, and bruising over many surfaces of her body. Relevant laboratory findings include the following:

- Hemoglobin: 6 g/dL
- White blood cell (WBC) count: 25,000/mm³
- Platelet count: 39,000/mm³
- Peripheral smear: Many immature white cells with condensed chromatin, absent nucleoli, and scant agranular cytoplasm (Figure 8-2)

**What is the most likely diagnosis?**

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood. The classic presentation and laboratory findings include fever (the most common sign), fatigue, lethargy, bone pain, arthralgia, and elevated serum lactate dehydrogenase (LDH). Less common symptoms include headache, vomiting, altered mental function, oliguria, and anuria.

**What conditions should be considered in the differential diagnosis?**

All of the following conditions feature anemia, low platelet count, and/or symptoms similar to this patient's:

- Idiopathic thrombocytopenic purpura.
- Aplastic anemia.
- Infectious mononucleosis.
- *Bordetella pertussis*.
- Epstein-Barr virus.
- Small, round, blue-cell tumors.

However, the markedly elevated WBC and blood smear in this patient make a form of leukemia, in this case ALL, the most likely diagnosis.

**What is the etiology of the physical examination findings?**

Most findings derive from leukemic expansion and crowding out of the normal marrow. This causes anemia and thrombocytopenia as well as bone or joint pain from invasion into the periosteum. Fever results from pyrogenic cytokines released from leukemic cells. Elevated LDH is a consequence of increased cellular turnover. Painless enlargement of the scrotum and central nervous system symptoms may also be signs of more extensive extramedullary invasion.

**What is the appropriate treatment for this condition?**

Complex chemotherapy regimens are standard and divided into induction, consolidation, and maintenance phases. Most regimens involve combinations of cyclophosphamide, doxorubicin, vincristine, dexamethasone/prednisone, methotrexate, asparaginase, and cytarabine. Recent advances in treatment have resulted in complete remission rates as high as 80% in children with ALL.
A 67-year-old man presents to his physician with a 10-day history of fatigue, bleeding gums, cellulitis, and a recent weight loss of 9 kg (20 lb). On physical examination, the patient is pale but has no evidence of lymphadenopathy or hepatosplenomegaly. Results of a complete blood count are as follows:

- **WBC count:** 18,300/mm³ (75% blastocytes, 20% lymphocytes)
- **Hemoglobin:** 9.1 g/dL
- **Hematocrit:** 29%
- **Platelet count:** 98,000/mm³

**What is the most likely diagnosis?**
Acute myelogenous leukemia (AML) is the most common acute leukemia in adults. The median age of diagnosis in the United States is 65 years.

**What other symptoms are common at presentation in this condition?**
- Epistaxis, skin rash, petechiae, bone pain, and shortness of breath.
- Gingival hyperplasia (leukemic invasion).
- Leukemia cutis (skin infiltrates).
- Neurologic deficits.
- Disseminated intravascular coagulation (often seen with the acute promyelocytic leukemia variant of AML).

**What are the likely bone marrow biopsy findings in this condition?**
The proliferation of myeloblasts with characteristic eosinophilic, needle-like cytoplasmic inclusions, or Auer rods, is pathognomonic for AML (Figure 8-3).

**What cells are affected in this condition?**
AML is a neoplasm of myelogenous progenitor cells. The progenitor cells may appear as granulocyte precursors, monoblasts, megakaryoblasts, or erythroblasts.

**How can genetic testing influence treatment?**
Genetic abnormalities are critical in the diagnosis and treatment of AML. For example, t(15;17) chromosomal translocation indicates acute promyelocytic leukemia (M3 variant) as the specific diagnosis. This can be treated with targeted drugs such as all-trans retinoic acid, which differentiates promyelocytes into mature neutrophils, thereby inducing apoptosis of the leukemic promyelocytes. This results in a high likelihood of remission and cure.

**Why is cellulitis commonly associated with this condition?**
Neutropenia caused by replacement of mature WBCs with leukemic cells increases susceptibility to infection.