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Massive Splenomegaly

Esther J. Luo, MD
Lee Levitt, MD

A 37-year-old man presented to the emergency department with complaints of a 7-kg weight loss over 5 months, early satiety associated with abdominal fullness, and nonpainful adenopathy in his left axilla and neck of unknown duration. He had no past medical history and denied fevers, chills, priapism, or easy bruising such as epistaxis and gingival bleeding. On physical examination, he was found to be afebrile with a distended abdomen. His spleen was palpable and extended into the pelvis and across the umbilicus. Multiple lymph nodes were palpated in both axillae and the posterior neck. Laboratory studies revealed the following: white blood cell count of 322,000/μL, with 44% neutrophils, 1% lymphocytes, 1% monocytes, 33% bands, 9% metamyelocytes, 10% myelocytes, 1% promyelocyte, and 1% blasts; hematocrit of 38%; platelet count of 155,000/μL; lactate dehydrogenase level of 443 U/L; and uric acid level of 8.9 mg/dL. The patient was admitted to the hospital, and hydroxyurea and allopurinol therapy were initiated. He received a bone marrow biopsy on hospital day 2; cytogenetic testing confirmed the diagnosis of chronic myelogenous leukemia. The patient was started on imatinib and was discharged home on hospital day 5.

Splenomegaly is a common finding in a wide spectrum of diseases. Massive splenomegaly, however, always indicates underlying pathology. *Massive splenomegaly* is usually defined as a spleen extending well into the left lower quadrant or pelvis or which has crossed the midline of the abdomen. Massive spleens weigh at least 500 to 1000 g. In a retrospective study evaluating splenomegaly in 2056 patients who presented to a large university medical center from 1913 to 1995, the most common disorders associated with splenomegaly were hematologic, infectious, hepatic, congestive, and inflammatory.[1,2] Among patients with massive splenomegaly, 31% had a hematologic disorder, 17% had hepatic disease, and 8% had infectious disease. Chronic leukemias were associated most frequently with massive splenomegaly. The ability to detect splenomegaly on physical examination and knowing the differential diagnosis of massive splenomegaly can facilitate the timely diagnosis and treatment of the conditions associated with massive splenomegaly. This article reviews the physical examination of the spleen as well as methods of splenic imaging and discusses the causes of massive splenomegaly. Detailed management of the diseases that cause massive splenomegaly is beyond the scope of this discussion.

NORMAL ANATOMY AND FUNCTION

The spleen lies in the posterior portion of the left upper quadrant, bounded by the diaphragm superiorly and the lower thoracic cage anterolaterally, with the long axis of the spleen lying parallel to the tenth rib in the midaxillary line.[3] On average, the weight of a normal spleen is 100 to 250 g. Spleen size depends on age, sex, and body habitus.[1,2] As a lymphopoietic organ, the spleen contains 25% of the body's lymphocytes, helps mediate both cellular and humoral immunity, and participates in immune responses against blood-borne pathogens. The spleen also functions as a filter and removes opsonized bacteria as well as senescent and damaged red blood cells (RBCs) from the circulation. Normally, approximately one third of circulating platelets are sequestered in the spleen.

APPROACH TO EVALUATION

History and Physical Examination

The signs and symptoms of splenomegaly depend on the size of the spleen and the acuity or chronicity of the underlying disease. An acute infectious process may cause tenderness in the left upper quadrant. In particular, pleuritic pain that is accompanied by fever and tenderness in the left upper quadrant may suggest a splenic abscess due to endocarditis or sepsis.[4] Splenic

Dr. Luo is an internal medicine resident, Santa Clara Valley Medical Center, San Jose, CA. Dr. Levitt is a professor of medicine, Stanford University School of Medicine, Stanford, CA; and chief, Division of Hematology/Medical Oncology, Santa Clara Valley Medical Center.

TAKE HOME POINTS

- *Massive splenomegaly* is usually defined as a spleen extending well into the left lower quadrant or pelvis or which has crossed the midline of the abdomen.
- Successful palpation of the spleen is dependent on body habitus and the skill of the examiner. When palpating a massively enlarged spleen, starting in the pelvis and palpating successively upwards towards the costal margin may help prevent missing a large spleen on physical examination.
- The differential diagnosis of massive splenomegaly includes myeloproliferative diseases, Gaucher disease, lymphoma, thalassemia major, visceral leishmaniasis (kala-azar), and malaria.
- Chronic myeloid leukemia, agnogenic myeloid metaplasia, and lymphoma are the most common diseases that present with massive splenomegaly.
- Even with massive splenomegaly, systemic therapies rather than splenectomy often provide an effective therapeutic option.

infarction can present with pain, no fever, and an audible rub.[5] With a slowly enlarging massive spleen, symptoms can include pain in the left upper quadrant, a sense of abdominal fullness, referred pain in the left shoulder, or early satiety and weight loss.

Many palpation and percussion methods exist for the examination of an enlarged spleen. Three methods of palpation in supine patients have been described, including bimanual palpation, ballottement, and palpation from above the patient.[3] With bimanual palpation, the examiner's left hand is placed at the anterior lower left rib cage and is used to pull the overlying skin toward the costal margin. Pressure with the right hand is slowly applied to the left upper quadrant. A slightly enlarged spleen may be felt only on deep inspiration. Having the patient relax with the legs slightly flexed will simplify the examination. Palpation should be started in the left mid quadrant of the abdomen or even lower to ensure that a markedly enlarged spleen is not missed. If the inferior margin of a massively enlarged spleen lies low in the left lower quadrant or pelvis, it may be easier to palpate the medial edge of the spleen in the midline or even in the right upper quadrant. A natural indentation in the medial border of the spleen may sometimes be felt. With the ballottement method, the examiner's left hand reaches under the left posterior chest wall and lifts while the right hand applies pressure successively to lower levels in the left upper quadrant. Last, when palpating the spleen from above the patient, the examiner stands behind the patient's left shoulder and places his fingertips under the left costal margin as the patient is taking a deep breath. Another palpation method places the patient in the right lateral decubitus position. In this position, the spleen moves anteriorly and the abdominal wall muscles are more relaxed, which may facilitate palpation of mildly enlarged spleens.

False-positive and false-negative findings are common in examination of the spleen and are related to the patient's body habitus, spleen size, presence of ascites, skill of the examiner, or other protruding organs in the left upper quadrant.[6] In 1 study, up to 20% of spleens with an estimated weight of 900 g were not palpable.[7]

A commonly used method of percussion utilizes Traube's semilunar space, a tympanitic area overlying the gastric bubble in the lateral hemithorax. Anatomically, this space is delineated by the left sixth rib superiorly, the midaxillary line laterally, and the left costal margin inferiorly. In splenomegaly, the tympanitic area is displaced downward and/or medially and dullness to percussion over this normally tympanitic area may be found. False-positive results may be obtained in patients with left pleural thickening or effusion and in patients examined shortly after a large meal.[8] A study that used ultrasound determination of splenomegaly as the gold standard found that percussion over Traube's space had a sensitivity of 62% and a specificity of 72%.[9] Another study that used ultrasound to define splenomegaly found that dullness in Traube's space plus a palpable spleen had a sensitivity of only 46% but a specificity of 97%.[6]

Imaging

Both ultrasonography and computed tomography (CT) can be used to visualize the spleen (**Figure 1** and **Figure 2**). Ultrasonography is noninvasive and relatively inexpensive. In healthy individuals, mean spleen length by ultrasound was determined to be 10.8 cm, and a normal spleen is defined as less than 13 cm.[10] Size criteria differ with CT versus ultrasound imaging, with splenomegaly defined as a spleen greater than 10 cm using CT.[11]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of massive splenomegaly includes myeloproliferative diseases, Gaucher disease, lymphoma, thalassemia major, visceral leishmaniasis (kala-azar), and malaria (**Table 1**). Although many other diseases such as cirrhosis with portal hypertension, mycobacterial infections, Epstein-Barr virus infection,

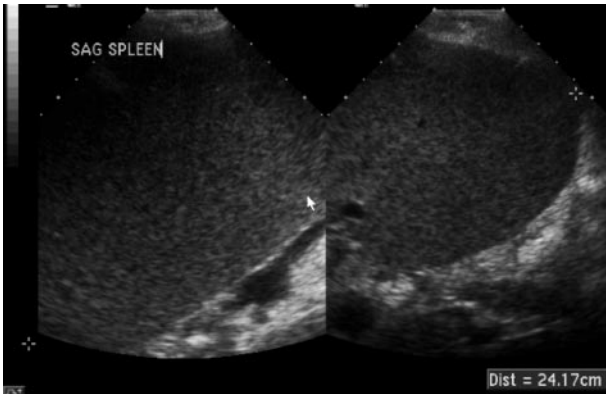

Figure 1. Ultrasound image of a massive spleen (*arrow*).

and hemolytic anemias can be associated with splenomegaly, they are rarely associated with massive splenic enlargement.

Myeloproliferative Diseases

The myeloproliferative diseases are clonal hematopoietic stem cell disorders that include 4 well-characterized subtypes: chronic myeloid leukemia (CML), agnogenic myeloid metaplasia (AMM), polycythemia vera, and essential thrombocythemia. The hallmark of CML is the presence of a balanced translocation between the long arms of chromosomes 9 and 22. This translocation involves the *ABL* protooncogene on chromosome 9 and the *BCR* gene on chromosome 22 (also known as the Philadelphia chromosome).[12] The median age at diagnosis of CML is 65 years. CML can be divided into 3 phases: chronic, accelerated, or blast phase. The disease is diagnosed during the chronic phase in over 80% of cases.[13] Up to 40% of patients may be asymptomatic at the time of diagnosis.[13] When present, symptoms may include fatigue, night sweats, weight loss, left upper quadrant abdominal discomfort, early satiety, or anorexia. Leukocytosis is a common feature of the disease with a white blood cell (WBC) count as high as 1000×10^9/L. Leukocytosis may infrequently cause leukostasis with sequelae such as retinal hemorrhage, priapism, or signs of hypervolemia. Massive splenomegaly may be found in up to 61% of CML patients.[3] Tyrosine kinase inhibitors with activity against the *BCR-ABL* fusion product, such as imatinib, dasatinib, or nilotinib, are the treatment of choice for CML presenting in the chronic phase.[12] Splenectomy is rarely indicated in CML.

AMM is characterized by bone marrow fibrosis and myelophthisis causing progressive anemia, splenomegaly, and extramedullary hematopoiesis.[14] The annual incidence of the disorder is 0.4 to 0.7 cases per 100,000 population with a median age at diagnosis of 65 years.[14]

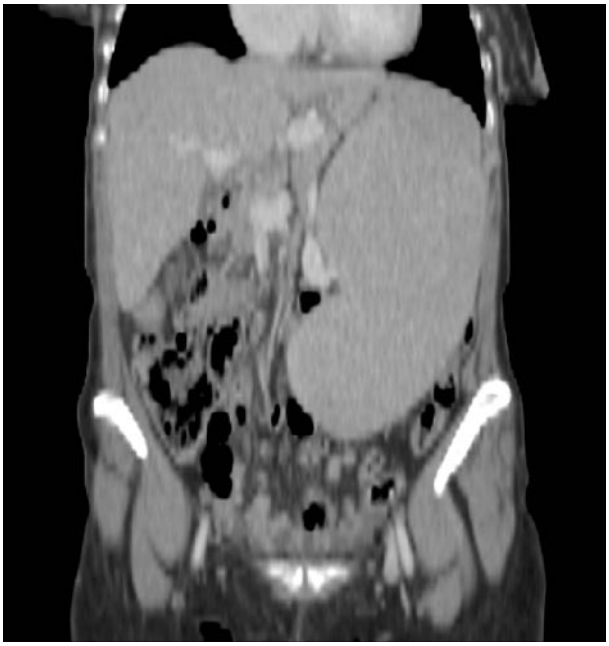

Figure 2. Computed tomography image of a massive spleen.

The most common presenting symptoms are fatigue, weight loss, weakness, dyspnea, fever, anorexia, and abdominal discomfort. The most common presenting sign is hepatosplenomegaly. In a study of 160 patients with AMM, 80% of patients presented with splenomegaly.[15] The presence of splenomegaly or size of the spleen does not appear to impact survival in patients with AMM. Recent studies suggest that the combination of thalidomide or lenalidomide plus corticosteroids can at least partially reverse marrow fibrosis and reduce transfusion requirements in AMM.[16] Splenectomy in AMM is controversial but may be helpful in instances of intractable symptoms from massive splenic enlargement when the marrow is not completely effaced by fibrosis.[14]

Polycythemia vera is also characterized by clonal trilineage expansion of hematopoiesis. Laboratory findings uniformly include erythrocytosis and usually also include increased WBC and/or platelet counts. Clinical manifestations may include generalized pruritus (especially after a bath or shower), erythromelalgia, thrombosis, or gout. In 1 series, 23% of patients with polycythemia vera were found to have massive splenomegaly.[1,2] Recommended treatments include phlebotomy to maintain the hematocrit at less than 45% and low-dose aspirin. In patients who are at high risk of thrombosis, hydroxyurea plus low-dose aspirin are recommended as first-line therapy.[17]

Essential thrombocythemia is a myeloproliferative disorder characterized by a chronic elevation in platelet

Table 1. Differential Diagnosis of Massive Splenomegaly

Myeloproliferative diseases	Lymphoma
Chronic myeloid leukemia	Hairy cell leukemia
Agnogenic myeloid metaplasia	Mantle cell lymphoma
Polycythemia vera	Chronic lymphocytic leukemia
Essential thrombocythemia	Prolymphocytic leukemia
Gaucher disease	Splenic marginal-zone lymphoma
	Follicular lymphoma
	Thalassemia major
	Visceral leishmaniasis
	Malarial splenomegaly

count accompanied by marrow hypercellularity, fibrosis, and clusters of megakaryocytes. Massive splenomegaly is unusual in essential thrombocythemia. Hydroxyurea has recently been shown to be the treatment of choice in patients with essential thrombocythemia requiring therapy.[18] Aspirin is also given to patients who are at high risk for thrombosis.

Gaucher Disease

Gaucher disease is an autosomal recessive lysosomal glycolipid storage disorder characterized by deficiency of the enzyme acid beta-glucosidase. This deficiency causes the accumulation of glucosylceramide in the lysosomes of macrophages leading to clinical manifestations of hepatosplenomegaly, anemia, thrombocytopenia, and bone disease. Bone manifestations include fractures, infarctions, and vertebral collapse.[19] There are 3 phenotypes of Gaucher disease: nonneuronopathic disease (known as type 1 disease), which is the most prevalent, accounting for more than 90% of cases; acute neuronopathic disease (type 2), which is rare and found mostly in infants; and chronic neuronopathic disease (type 3), which is characterized by progressive neurologic involvement.[20] One third of patients are diagnosed after age 20 years.[21] Splenomegaly is 1 of the most common presenting signs. Analysis of a registry of patients with Gaucher disease showed that the spleen was enlarged 5 to 75 times normal (median, 15.2 times normal) and frequently was massive at time of presentation.[21] Enzyme replacement therapy with recombinant glucocerebrosidases is the preferred treatment for many symptomatic patients with type 1 disease.[22]

Lymphoma

Lymphomas are a heterogeneous group of disorders characterized by malignant transformations of normal lymphoid cells into neoplastic lymphoid cells. In 1995, the World Health Organization developed a classification system based on morphology, immunophenotyping, genetic features, and clinical syndromes.[23] Massive splenomegaly can occur in many lymphoma subtypes, including the indolent lymphomas. A full description of all lymphomas causing splenomegaly is beyond the scope of this paper, and lymphomas where massive splenomegaly is more commonly observed will be discussed. These subtypes include hairy cell leukemia (HCL), splenic marginal-zone lymphoma (MZL), splenic lymphoma with villous lymphocytes (SLVL), mantle cell lymphoma (MCL), prolymphocytic leukemia (PLL), and chronic lymphocytic leukemia (CLL). Massive splenomegaly can also be seen on occasion in indolent low-grade follicular lymphomas and intermediate-grade large cell lymphomas.

HCL is an uncommon chronic B-cell lymphoproliferative disease. The median age of presentation is approximately 55 years, with a male predominance of 4:1.[24] Symptoms include abdominal fullness, fatigue, weakness, weight loss, and bruising. Approximately a quarter of patients present with abdominal discomfort and fullness due to splenomegaly, which can be massive. The spleen is palpable in 80% to 90% of patients.[24] In a study of 71 cases of HCL, 5% of patients had a spleen tip that was 20 cm below the left costal margin.[25] Adenopathy is unusual, and 60% to 80% of patients present with pancytopenia. Circulating distinctive cells with cytoplasmic projections ("hairy cells") and a characteristic immunophenotype are found in 90% of patients with HCL. Marrow biopsy usually demonstrates a hypercellular marrow with increased reticulin and a diffuse, focal, or interstitial infiltrate of hairy cells.[26] The majority of HCL patients achieve durable remission following therapy with purine analogues, cladribine, or pentostatin.[26] Splenectomy is infrequently required.

Splenic MZL is a relatively indolent B-cell neoplasm that results from proliferation of small lymphocytes that surround and replace the splenic white and red pulp.[27] In a group of over 3000 patients with non-Hodgkin's lymphoma, splenic MZL was found in 81 patients, accounting for 2.7% of all lymphomas.[28] Splenic MZL is usually found in the elderly with a median age at diagnosis of 65 years. Patients with splenic MZL present with splenomegaly, anemia, and thrombocytopenia. In a series of 81 patients with splenic MZL, 95% presented with bone marrow involvement and 64% with peripheral blood involvement.[27] The hallmark clinical presentation of splenic MZL is massive splenomegaly. Although up to 40% of patients with splenic MZL in 1 series had cytogenetic abnormalities involving the long arm of chromosome 7,[27] no cytogenetic changes

are considered diagnostic for splenic MZL. Massive splenomegaly and cytopenias often necessitate splenectomy, which is the treatment of choice.

SLVL is considered a variant of MZL and is closely related to splenic MZL. Villous lymphocytes account for more than 20% of circulating lymphoid cells.[29] The clinical presentation with massive splenomegaly, anemia, and thrombocytopenia is similar to that of patients with splenic MZL. Although splenectomy is often performed in symptomatic patients, recent studies suggest that in patients with SLVL who are coinfected with hepatitis C, treatment with interferon can lead to regression of the lymphoma.[30]

MCL is a neoplasm of monomorphic small- to medium-sized B lymphocytes with irregular nuclei. Nuclear staining for cyclin *D1* is present in more than 70% of cases of MCL.[31] Most cases of MCL demonstrate the genetic abnormality t(11;14)(q13;q32), which consists of a translocation between the cyclin *D1* gene and the immunoglobulin heavy chain locus. Although characteristic of MCL, t(11;14) can be seen infrequently in other B-cell neoplasms such as multiple myeloma.[32] MCLs comprise 7% of non-Hodgkin's lymphomas. The median age at diagnosis is 63 years with a male predominance.[33] Seventy percent of patients present with stage IV disease, and 45% to 60% of patients present with involvement or enlargement of the spleen.[34] Other frequently involved sites include lymph nodes, bone marrow, blood, and the gastrointestinal tract. The disease is aggressive with a median survival of 3 to 4 years with no plateau in the survival curve.[35] Most patients require combination chemotherapy with the addition of rituximab, although few patients are cured with this approach. Hematopoietic stem cell transplantation is an active area of investigation in patients with MCL.

PLL is a variant of CLL and accounts for less than 1% of B-cell leukemias. It is a malignant disorder of prolymphocytes, which comprise more than 50% of the cells in blood and marrow. These cells are about twice the size of a small lymphocyte and contain a prominent nucleolus. In contrast to CLL, prolymphocytes strongly express *CD20*, and both *CD5* and *CD23* expression is weak or absent.[26] Patients with PLL present with massive splenomegaly and WBC counts usually of more than 100,000/μL.[26] Fifty percent of cases present with anemia and thrombocytopenia.[26] The median age at presentation is 70 years. T-cell PLL is less common than B-cell PLL, and although it shares many clinical features, it is more aggressive with a median survival of only 8 months compared with 3 to 5 years in B-cell PLL.[36] No single modality of treatment is clearly superior in PLL, and combination chemotherapy, purine analogues, splenectomy, and rituximab have all been utilized for this uncommon disorder.[37]

CLL is the most common form of leukemia in the Western hemisphere. Approximately 10,000 new cases are diagnosed each year in the United States.[38] The median age at diagnosis is 55 years. Adenopathy was found in 85% of patients and splenomegaly was found in 54% in a series of 174 patients.[39] Although relatively uncommon, massive splenomegaly does occur in CLL. A tender, painful spleen may be indicative of splenic infarction. Combination chemotherapy regimens including fludarabine, cyclophosphamide, and rituximab can be effective with high complete and overall response rates. Splenectomy can be beneficial in patients with massive enlargement and cytopenias unresponsive to chemotherapy.[40]

Thalassemia Major

β-Thalassemia major is a hereditary anemia resulting from decreased production of β-globin chains. It is usually diagnosed in young children. In thalassemia major, decreased β-chain synthesis results in excess free α chains, resulting in elevated hemoglobin F ($\alpha_2\gamma_2$) or hemoglobin A2 ($\alpha_2\delta_2$).[41] Free α chains also form insoluble tetramers that precipitate within the RBC, causing increased fragility and cell death.[42] β-Thalassemia is often diagnosed in children at about 6 months of age and presents as severe microcytic anemia with signs of cardiac dysfunction, pallor, jaundice, hepatosplenomegaly, and growth failure.[43] Hemolytic anemia and sequestration can cause massive splenomegaly; however, this finding is unusual in hypertransfused patients. Splenectomy is often indicated for a progressive increase in RBC transfusion requirements but should be deferred until after age 5 to 6 years to diminish the frequency of overwhelming postsplenectomy infections.

Visceral Leishmaniasis

Visceral leishmaniasis is a parasitic disease caused by the obligate intracellular protozoa *Leishmania*. Visceral leishmaniasis, also known as kala-azar (Hindi for black sickness or fever),[44] is a systemic disease that can be life-threatening. This vector-borne disease is transmitted by bites of infected sandflies. There are an estimated 500,000 new cases of leishmaniasis each year, and over 90% of these cases are in Bangladesh, northeastern India, Nepal, Sudan, and northeastern Brazil.[44] Clinical features of leishmaniasis include splenomegaly, pancytopenia, fever, cachexia, and hypergammaglobulinemia. Splenomegaly is frequently massive. The diagnosis is usually made by examination of

bone marrow aspirate for visualization of amastigotes on Giemsa-stained slides. Spleen aspiration has a sensitivity that approaches 100% but is associated with a risk of splenic rupture.[45] Patients with visceral leishmaniasis usually respond to parenteral pentavalent antimonial compounds or amphotericin.

Malarial Splenomegaly

Malaria can frequently cause splenomegaly, but massive splenomegaly is rare. Hyperreactive malarial splenomegaly is a complication of malaria that can cause chronic massive splenomegaly. It is thought to occur as a result of abnormal immune response to repeated malaria infections. This syndrome has features of fever, anemia, pancytopenia, weight loss, abdominal discomfort, and lassitude.[46]

LABORATORY FINDINGS

Selected laboratory abnormalities that are characteristic of the illnesses causing massive splenomegaly are briefly summarized in this section. CML and AMM commonly present with elevated WBC counts and leukoerythroblastosis with immature myeloid cells and nucleated RBCs. Tear-shaped RBCs are almost always seen on the peripheral smear in AMM. The *BCR-ABL* fusion transcript is detected by fluorescence in situ hybridization (FISH) and/or polymerase chain reaction (PCR) in virtually all patients with CML. Approximately 50% of patients with AMM or essential thrombocythemia will exhibit the acquired JAK2 mutation, and over 90% of patients with polycythemia vera exhibit the JAK2 mutation by peripheral blood PCR.[47,48] Leukocytosis is seen in approximately 65% of patients with polycythemia vera.[48] In essential thrombocythemia, the peripheral smear will frequently show large hypogranular platelets and may contain nucleated megakaryocyte fragments.

In Gaucher disease, variable pancytopenia is common, usually as a consequence of hypersplenism. Chitotriosidase reflects macrophage stimulation and its activity is often increased in patients with Gaucher disease.[49] The activity decreases following enzyme replacement therapy, and measurement of chitotriosidase activity can be used to monitor clinical responses during therapy.

Anemia and thrombocytopenia are present in 85% of patients with HCL at the time of diagnosis and monocytopenia is present in 80% of patients.[26] Leukocytosis is seen in only 10% to 20% of patients, but at least 90% of patients will have circulating hairy cells. These cells are mononuclear, about 1½ to 2 times the size of a small lymphocyte, often with a large eccentric nucleus and cytoplasmic projections.[26] Splenic MZL and SLVL frequently present with peripheral blood lymphocytosis. These cells may exhibit characteristic short polar or asymmetric villi; some cells may have a plasmacytoid appearance. Peripheral blood involvement is found in 25% to 50% of patients with MCL.[50] Most often, the cells are small- to medium-sized lymphocytes with irregular cleaved nuclei and inconspicuous nucleoli.

A threshold absolute lymphocyte count of 10,000/μL is often recommended for the diagnosis of CLL, although many patients will have a total WBC count in excess of 50,000 to 100,000/μL.[39] The peripheral smear often contains flattened, distorted ("smudge") cells, which likely reflect the fragility of CLL lymphocytes to mechanical manipulation. Up to one third of CLL patients have a positive Coomb's test, and approximately 10% have circulating spherocytes and active autoimmune hemolytic anemia.[51] Immune thrombocytopenic purpura occurs in 3% to 5% of patients. Hypogammaglobulinemia is seen in 65% of patients during the course of the disease and reflects both the arrest in B-cell differentiation and the abnormal immunoregulation that is a characteristic of CLL. Monoclonal gammopathies are seen in 5% of patients, and pure red cell aplasia is found in 1% to 6% of patients.[51]

A profound microcytic anemia with bizarre RBCs typically occurs with β-thalassemia major. Profound hypochromia, target cells, tears, and basophilic stippling are seen. Intracellular inclusions are indicative of precipitated α globin and can be readily identified after staining RBCs with a supravital stain.[52] Elevations of indirect bilirubin and lactate dehydrogenase and low levels of haptoglobin reflect both hemolysis and ineffective erythropoiesis. Similarly, the reticulocyte count is often not highly elevated because of the massive destruction of RBCs in the marrow. Findings on hemoglobin electrophoresis vary; hemoglobin F is elevated and reflects 10% to 90% of the patient's total hemoglobin.[52] The hemoglobin F is heterogeneously distributed in RBCs. Hemoglobin A is absent in patients with homozygous β^0-thalassemia but is variably present in patients with the usual variant of homozygous β^+-thalassemia.

Laboratory manifestations of visceral leishmaniasis include variable pancytopenia as a consequence of both massive splenomegaly and marrow suppression. Hypergammaglobulinemia is also common. Eosinopenia is usually present. Immunosuppressed patients with a high burden of disease may have parasites that are visible within monocytes on the peripheral blood smear.

Thick and thin blood smears are essential for the diagnosis of malaria. Thick smears are more sensitive, but thin smears permit better assessment of the

morphologic features of the parasite. Smears should be obtained every 6 to 12 hours for 48 hours before excluding the diagnosis. Clues to the presence of *Plasmodium falciparum* malaria include banana-shaped gametocytes, ringed trophozoites, and multiple parasites per RBC.

MANAGEMENT

Treatment of massive splenomegaly often involves primary therapy directed at the underlying disease (**Table 2**). Splenectomy may be indicated in some disorders for symptom relief or for worsening pancytopenia. Laparotomy is usually required to remove a massive spleen. Possible complications after open splenectomy include the development of a subphrenic abscess and splenic or portal vein thrombosis, especially in patients with myeloproliferative disorders. Overwhelming post-splenectomy septicemia is relatively uncommon in immunocompetent adults, and the risk can be further reduced with the administration of preoperative polysaccharide vaccines against *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis.* Although difficult in patients with massive spleens, splenic radiation can sometimes also provide palliation in patients with lymphoproliferative or myeloproliferative disorders. Studies have shown that laparoscopic splenectomy can sometimes be performed even for massive spleens, with a resultant decrease in blood loss, a shorter postoperative hospital stay, and a decrease in postoperative morbidity and mortality.[53]

CONCLUSION

Massive splenomegaly is an important physical examination finding. Hematologic diseases such as lymphomas and myeloproliferative diseases are the most common causes of a massive spleen. Although a massive spleen due to infectious causes is rarely encountered in the United States, it is important to obtain an accurate travel history in patients with otherwise unexplained massive splenomegaly. Many techniques exist for detecting enlarged spleens on physical examination, but their sensitivity can be low and they are limited by body habitus. Imaging studies such as ultrasound and CT are helpful modalities in the diagnosis of massive splenomegaly. Treatment depends on the underlying disease. Although systemic therapies are usually the primary modality of treatment for most disorders causing massive splenomegaly, splenectomy may be helpful, particularly in disorders such as splenic MZL and thalassemia major. **HP**

Corresponding author: Esther J. Luo, MD, Internal Medicine Residency Program, 751 South Bascom Avenue, Department of Medicine, 4th floor, San Jose, CA 95128; estherluo07@gmail.com.

Table 2. Specific Treatment of Diseases That Cause Massive Splenomegaly

Disease	Primary Treatment
Myeloproliferative diseases	
Chronic myelogenous leukemia	Tyrosine kinase inhibitors including imatinib, dasatinib, nilotinib
	Allogeneic hematopoietic cell transplantation
Agnogenic myeloid metaplasia	Thalidomide plus prednisone, hydroxyurea
	Allogeneic hematopoietic cell transplantation
Polycythemia vera	Phlebotomy, hydroxyurea
Essential thrombocythemia	Hydroxyurea in high-risk patients
Gaucher disease	Recombinant glucocerebrosidases
Lymphoma	
Hairy cell leukemia	Pentostatin or cladribine
Splenic marginal-zone lymphoma	Splenectomy
Splenic lymphoma with villous lymphocytes	Splenectomy
Mantle cell lymphoma	A combination of chemotherapy with rituximab, possible hematopoietic stem cell transplantation
Chronic lymphocytic leukemia and prolymphocytic leukemia	No standard treatment; options include combination chemotherapy with fludarabine, cyclophosphamide, and rituximab
Thalassemia major	Hypertransfusion, iron chelation, splenectomy
Visceral leishmaniasis	Sodium stibogluconate, meglumine antimoniate, amphotericin, miltefosine
Malarial splenomegaly	Regimens depend on presence of chloroquine resistance and include a quinine-based regimen, atovaquone/proguanil, mefloquine, artemisinin derivatives or chloroquine

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