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## CLINICAL VIGNETTE

# Splenomegaly, No Laughing Matter

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The spleen has long been recognized in human disease and physiology. The ancient Greek physicians Hippocrates and Galen recognized that the spleen played a role in “purifying” the blood. While there is no mention of the spleen in the Bible, it is discussed in the Talmud – where it is theorized that the spleen is the source of laughter.<sup>1</sup> The understanding of the spleen has improved since antiquity; however, the role of the spleen in human disease is often a source of consternation for the clinician. The modern day internist must often feel like Galen who is said to have called the spleen “an organ full of mystery.” This discussion will provide a brief overview of the spleen’s normal structure and function, an overview of common disorders, as well as an approach to the patient with splenomegaly. Additionally, two clinical cases from a community hematology practice will be discussed to provide practical clinical advice.

### Case 1

A 66-year-old man presented to the hematology clinic for further evaluation of splenomegaly. The patient had sought consultation with a gastroenterologist for chronic abdominal pain. Upper endoscopy was unremarkable; therefore, the patient underwent a CT scan of the abdomen and pelvis, which disclosed splenomegaly with the spleen measuring between 16 and 17 cm. The scan was otherwise unremarkable. Labs included a platelet count of 120,000 but were otherwise normal. The patient denied B symptoms, early satiety, aquagenic pruritus, or erythromelalgia. Aside from the chronic abdominal pain, he had no complaints. He had no other significant past medical history and his family history was unremarkable. Physical examination disclosed no lymphadenopathy. The spleen was not palpable on physical exam.

### Case 2

A 42-year-old man presented to the hematology clinic for further evaluation of splenomegaly, after a CT scan of the abdomen and pelvis performed following trauma revealed massive splenomegaly with the spleen measuring 28 cm. He noted lifelong anemia and reported that he had received 5 or 6 transfusions of packed red blood cells during his lifetime; however, he was unaware of his diagnosis. He had not received regular hematologic care. Review of old labs disclosed a recent baseline hemoglobin of 9.1 g/dL with a MCV in the low 60s. The leukocyte and platelet counts were normal. The patient reported a history of gallstones but denied leg ulcers. He denied early satiety, weight loss, abdominal discomfort, or shoulder pain. He states that his sister also had lifelong anemia and had

underwent a splenectomy recently. On physical examination, the patient had an enlarged spleen that was easily palpated. He was short in stature, but the exam was otherwise unrevealing.

The spleen is a sponge-like organ that resides in the posterior aspect of left-upper-quadrant of the peritoneum and in the average adult weighs around 150 grams. It is usually located at the level ninth to eleventh thoracic vertebrae. It is a highly vascular organ – receiving >5% of cardiac output despite being only approximately 0.2% of total body weight. Anatomically, the spleen is divided into the white pulp, red pulp, and marginal zone. The white pulp consists of organized B and T lymphocytes. The red pulp is a scaffold of vascular, circulatory, and phagocytic elements, while the marginal zone represents the junction of the white and red pulp with elements of both present.<sup>2,3</sup>

The spleen has two primary functions – removing red blood cells from circulation and participating in host defense. In a process termed culling, the spleen removes aged or poorly deformable red blood cells from the circulation. As a lymphoid organ, the spleen effectively removes viral and bacterial pathogens that have been opsonized by complement or antibody.

In the average adult, the spleen is not generally palpable. However, it might be palpable in thin individuals and children. In general, a palpable spleen means there is significant splenic enlargement. There are numerous techniques to assess for splenomegaly; however, studies have demonstrated that there is wide inter-observer variability in identifying an enlarged spleen, and that this variability is not associated with clinical experience.<sup>4</sup> Autopsy studies have demonstrated that a variety of imaging techniques including computed tomography and ultrasonography have a high sensitivity and specificity for detecting splenomegaly and is the gold standard for identifying splenomegaly in the modern era. There is no precise definition for what constitutes splenomegaly, but a spleen length greater than 13 cm on ultrasound is generally agreed to constitute splenomegaly.<sup>5</sup>

The differential diagnosis of splenomegaly is broad and can be considered from a mechanistic standpoint:

Infiltrative – the spleen enlarges as abnormal cells or substances accumulate in the spleen.

Congestive – the spleen enlarges because of disturbance in the venous drainage of the organ resulting in increased blood flow to the spleen.

Hypertrophy – the spleen enlarges as cells proliferative in response to an infectious or inflammatory stimulus.

Extramedullary hematopoiesis – the spleen enlarges as the formation of blood occurs outside of the bone marrow space.

Distinct from splenomegaly is hypersplenism. Hypersplenism is a pathophysiologic process that is a result of splenomegaly. Hypersplenism occurs when blood cells become sequestered in the spleen as it enlarges, decreasing the number of cells in the peripheral circulation. Platelets are most frequently affected by hypersplenism, but leukocytes and erythrocytes may also be decreased as a result of hypersplenism. It is important to note that there is not a precise correlation between degree of splenic enlargement and the severity of cytopenias. Importantly, many patients with hypersplenism and significant thrombocytopenia rarely have clinically significant bleeding – as the total platelet mass is not actually decreased and is only apparently decreased on the blood count.

The role of splenectomy in the management of hematologic disorders has evolved and remains an important therapy for many conditions. Laparoscopic splenectomy emerged in the 1990s and replaced open splenectomy as the preferred surgical approach because of decreased complications and faster recovery, even in cases of massive splenomegaly.<sup>6</sup> Despite the improved outcomes with a laparoscopic approach, the frequency with splenectomy is performed has been steadily decreasing.<sup>3,7</sup>

Splenectomy remains important in the management of patients with immune thrombocytopenia (ITP) who fail to maintain a hemostatic platelet count with first-line therapy of steroids and/or intravenous immunoglobulin. Splenectomy achieves a durable improvement in the platelet count in nearly 90% of patients with nearly 70% achieving sustained complete remission.<sup>8</sup> Splenectomy is also an accepted second-line therapy for autoimmune mediated hemolytic anemia.

Laparotomy with splenectomy used to be part of the standard staging evaluation for patients with Hodgkin lymphoma. However, in the era of PET/CT scanning and improved medical therapies, splenectomy is rarely indicated in the evaluation of Hodgkin lymphoma. While the spleen is often involved in non-Hodgkin lymphoma, it is rarely the primary or sole site of involvement. In such instances of non-Hodgkin lymphoma resulting in hypersplenism, splenectomy can be considered to improve counts but it does not impact survival.<sup>9</sup>

Complications of splenectomy include peri-operative bleeding, pancreatic injury, and thrombosis. Of particular interest is post-operative portal vein thrombosis – as if untreated can be associated with significant morbidity and even mortality. The incidence of post-splenectomy portal vein thrombosis has likely been underestimated. The risk of infection following splenectomy is well-documented and lifelong. Overwhelming postsplenectomy infection (OPSI) has been described since the late 1960s. OPSI is most common in the time immediately following splenectomy but may occur as late as 4 decades after

surgery. The risk of OPSI is highest in children under 5 who undergo splenectomy.<sup>3</sup> Because of the high risk of infection with encapsulated bacteria, it is recommended to vaccinate against *pneumococcus*, *meningococcus*, and *Haemophilus influenzae* type B 14 days prior to splenectomy. If it is not possible to give the vaccinations prior to the surgery, it is recommended to vaccinate on the 14<sup>th</sup> postoperative day.<sup>10</sup>

### Case 1

When approaching a patient with isolated splenomegaly and no obvious cause, it can be helpful to consider the diagnosis based on the pathophysiologic mechanisms of splenomegaly. The most common mechanisms being: infiltrative, congestive, hypertrophy/proliferative, and extramedullary hematopoiesis. In infiltrative splenomegaly – abnormal cells accumulate in the spleen. This occurs commonly in non-Hodgkin lymphoma. Less common causes of infiltrative splenomegaly include inborn errors of metabolism like Gaucher's disease, in which abnormal monocytes laden with lipid accumulate in the spleen. While in congestive splenomegaly, there is increased pooling of blood cells in the spleen as result of a venous outflow obstruction. Portal hypertension and portal vein thrombosis may cause congestive splenomegaly. The spleen may proliferate or hypertrophy in response to an inflammatory stimulus or with increased erythrocyte destruction. This occurs when individuals develop mild splenomegaly with viral infections but may also result in more massive splenomegaly, e.g., visceral leishmaniasis. In extramedullary hematopoiesis, hematopoietic tissue expands outside of the marrow space. This occurs in myeloproliferative disorders, especially in myelofibrosis as the marrow space is replaced by fibrosis. While in thalassemia, hematopoietic tissue in the spleen expands in response to the increased erythropoietic drive because of ineffective hematopoiesis. After careful consideration of this patient's presentation, there was no obvious explanation for his splenomegaly. There was clearly no infection and further imaging ruled out a congestive process. There was no evidence for a myeloproliferative disorder. He is being clinically observed at this time. In instances when the cause of splenomegaly remains unexplained, it cannot be overstated that a diagnostic splenectomy should only be performed as a last resort and after careful consideration.

### Case 2

The patient described in this case presented with a history highly suggestive of thalassemia, which would account for his massive splenomegaly. Further evaluation disclosed beta thalassemia intermedia – he had an elevated hemoglobin A2 and fetal hemoglobin on hemoglobin electrophoresis. His case is instructive when considering splenomegaly. Patients with beta-thalassemia and to a lesser extent alpha-thalassemia develop splenomegaly as a result of ineffective hematopoiesis. In beta-thalassemia, excess alpha-chains precipitate in the developing erythrocyte. The precipitated alpha-chains are highly toxic to the erythrocyte, leading to apoptosis and hemolysis of the developing erythrocyte. This process of ineffective erythropoiesis triggers increased erythropoietic demand and extramedullary hematopoiesis. While splenomegaly may be massive, in general splenectomy is rarely indicated. Following splenectomy, there is an increased risk of

thromboembolic events both arterial and venous. Additionally, there are increased risks of pulmonary hypertension and infection. Splenectomy is generally indicated for persistent symptoms or significant cytopenias resulting from hypersplenism. The patient was assessed for iron overload and started on folate supplementation. He was discouraged from undergoing a splenectomy.

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