

Patients with splenomegaly may come to medical attention for a variety of reasons. However, patients with no obvious explanation for an enlarged spleen present a difficult diagnostic problem. A detailed history taking, appropriate clinical examination and relevant investigations is tool for a diagnosis of splenomegaly. Appropriate investigations in most patients with undiagnosed splenomegaly will yield a diagnosis. Patients with undiagnosed splenomegaly, who are otherwise well and who have no evidence of systemic diseases, particularly if the spleen is minimally enlarged, may be followed with careful and regular observation.

NORMAL FUNCTIONS OF SPLEEN

In many instances the spleen enlarges as it performs its normal functions. The four most important normal functions of the spleen are 1) clearance of microorganisms and particulate antigens from the blood stream; 2) synthesis of immunoglobulin and properdin factors; 3) destruction of effete or abnormal RBCs; and 4) embryonic hematopoiesis, which can reactivate as extra-medullary hematopoiesis in certain diseases.

MECHANISMS OF SPLENOMEGALY

Many of the mechanisms of splenic enlargement are exaggerated forms of normal spleen function¹. While a wide variety of diseases are associated with enlargement of the spleen, 6 etiologies of splenomegaly are considered primary, including 1) immune response work hypertrophy such as in subacute bacterial endocarditis or infectious mononucleosis; 2) RBC destruction work hypertrophy such as in hereditary spherocytosis or thalassemia major; 3) congestive such as in splenic vein thrombosis or portal hypertension; 4) myeloproliferative

such as in chronic myeloid metaplasia; 5) infiltrative such as in sarcoidosis and some neoplasms; and 6) neoplastic such as in chronic lymphocytic leukemia and the lymphomas. Miscellaneous causes of splenomegaly include trauma, cysts, hemangiomas, and other malformations.

CLINICAL SIGNIFICANCE OF SPLENOMEGALY

It might be noted that spleen size is not a reliable guide to spleen function, because palpable spleens are not always abnormal and hypersplenic spleens are not always palpable. Patients with emphysema and low diaphragms commonly have palpable but normal-sized spleens. One study showed that 63 (3%) of 2200 healthy college freshmen had palpable spleens² and another study showed that almost 5 percent of hospital patients with normal spleens by scan were thought to have palpable spleens by their physicians³. In contrast, clinical splenomegaly rarely noted in immune thrombocytopenic purpura, despite avid destruction of antibody-coated platelets by the spleen.

Although palpable splenomegaly can be detected in only a few patients who do not have an obvious pathophysiologic disorder, the condition should be of interest to the primary care physician because it is generally this physician who detects the abnormality. The presence of a palpably enlarged spleen must be considered a physical finding that demands further evaluation.

Patients with splenomegaly may come to medical attention for a variety of reasons. Patients may complain of left upper quadrant pain or fullness or of early satiety. A splenic infarct, which typically manifests with left upper quadrant pain that sometimes radiates to the left

shoulder, can be the first clue to the existence of an enlarged spleen. Rarely, splenomegaly can initially manifest with the catastrophic symptoms of splenic rupture. Some patients are found to have splenomegaly as a result of evaluation for unexplained cytopenias. Splenomegaly can be discovered incidentally on physical examination. In recent years, splenomegaly has been frequently discovered on imaging studies of the abdomen performed for other purposes.

CLINICAL EVALUATION OF SPLENOMEGALY

Physical examination is the most practical and cost effective method of evaluation of splenomegaly⁴. The presence of an enlarged spleen can be more precisely determined, if necessary, by liver-spleen radionuclide scan, CT, MRI, or ultrasonography. The latter technique is the current procedure of choice for routine assessment of spleen size (normal = a maximum cephalocaudal diameter of 13 cm) because it has high sensitivity and specificity and is safe, noninvasive, quick, mobile, and less costly. CT will frequently give a better view of the consistency of the spleen and can identify splenic tumors or abscesses that would otherwise be missed. Radionuclide scans such as gallium scans can identify active lymphoma or infections. The technetium liver-spleen scan can be important in identifying liver disease as the cause of splenomegaly; in patients with cryptogenic cirrhosis, a technetium liver-spleen scan that shows higher activity in the spleen than the liver might be the initial hint of liver disease. None of these techniques is very reliable in the detection of patchy infiltration e.g., Hodgkin's disease⁵. Because of the spleen's location and its propensity to bleed, needle aspiration or cutting needle biopsy of the spleen is rarely performed. In general, a splenic "biopsy" involves splenectomy, which can be performed at the time of laparotomy or with laparoscopy.

APPROACH TO ISOLATED SPLENOMEGALY

Splenomegaly may represent a manifestation primary disease or of associated disease or probably due to the previous illness not recognized⁴. The approach to the patient with undiagnosed splenomegaly must be individualized. The list of causes of splenomegaly is formidable; the possibilities are, however, greatly reduced by appropriate clinical evaluation and investigation.

The approach to a patient with an enlarged spleen should focus initially on excluding a systemic illness that could explain the splenomegaly (Table 1). A wide variety of diseases can lead to splenic enlargement; common in our country are malaria, leishmaniasis, hematological

Table 1: Diagnostic approach to isolated splenomegaly

1. Does the patient have a known illness that causes splenomegaly*?	<ul style="list-style-type: none"> • Infections: e.g. malaria, kala-azar, infectious mononucleosis etc • Hematological: e.g. hemolytic anemias, hemoglobinopathies, malignancies, myeloproliferative disorders, etc. • Hepatic: e.g. portal hypertension, splenic or portal vein thrombosis
	Treat and monitor for resolution.
2. Search for an occult disease**.	<ul style="list-style-type: none"> • Infections: e.g. infective endocarditis • Hematological: e.g. hereditary spherocytosis, polycythemia vera • Hepatic: e.g. cryptogenic cirrhosis • Autoimmune: e.g. systemic lupus erythematosus • Storage disease: e.g. Gaucher's disease • Miscellaneous: e.g. sarcoidosis, amyloidosis, tropical splenomegaly, splenic cysts
	If found manage appropriately.
3. Diagnostic splenectomy if	<ul style="list-style-type: none"> • Systemic symptoms are present and suggests malignancy • Focal replacement of the spleen on imaging studies • No other sites are available biopsy
4. Monitor closely and repeat studies until the splenomegaly resolves or a diagnosis is apparent if	<ul style="list-style-type: none"> • Otherwise well and no evidence of systemic diseases • Spleen is minimally enlarged

* Varies with age, associated features and geographical area

** If patient is asymptomatic look for the causes listed in Table 4

malignancies, congestive splenomegaly and anemias. Splenomegaly is a multi-disciplinary problem. The common conditions that result in isolated splenomegaly can be divided into different diagnostic groups i.e. hematological, hepatic, infective, primary splenic conditions⁶. Indian data on splenomegaly are very sparse, however, western literature⁶ showed the prevalence of different diagnostic groups resulting in splenomegaly were hematological: 25-66%, hepatic: 12-46%, infective: 13-25%, primary splenic: 2-5% and others: 8-21%.

Proper history taking, appropriate clinical examination and relevant investigations are tool for a diagnosis of splenomegaly. A detailed history (i.e. geographical area of the residence, duration of splenomegaly, progressively enlarged splenomegaly, associated signs and symptoms i.e. fever, jaundice, pain abdomen, joint pain etc, history of alcoholism, family history) is essential for splenomegaly evaluation. The differential diagnosis of splenomegaly differs with the splenic size at presen-

tation in addition to the age of the patient, clinical features, associated hepatomegaly and lymphadenopathy. As the prevalence of splenomegaly and relative incidence of diseases associated with it are subject to geographical variation, a clinician while evaluating a patient with palpable spleen should keep this factor in mind.

In one study, Swaroop, et al⁶ studied 317 patients with splenomegaly over a period of 8 years and analyzed the association of several clinical and laboratory features with different diagnostic groups. Hematological diseases had significant positive associations with massive splenomegaly, lymphadenopathy and blood cytosis i.e. erythrocytosis, leucocytosis or thrombocytosis. Hepatic diseases had highly significant positive association with hepatomegaly, abnormal liver function tests and blood cytopnia (as a part of hypersplenism). Infectious diseases showed a positive association with fever. Left upper abdominal pain had significantly positive association with hematological and primary splenic diseases. None of the patients with hepatic disease with splenomegaly had lymphadenopathy.

The differential diagnostic possibilities are much fewer when the spleen is "massively enlarged," that is; it is palpable more than 8 cm below the left costal margin or its drained weight is 1000 g. The vast majority of such patients will have a hematological diseases i.e. non-Hodgkin's lymphoma, chronic lymphocytic leukemia, hairy cell leukemia, chronic myelogenous leukemia, myelofibrosis with myeloid metaplasia, or polycythemia vera⁷. Other conditions like Gaucher's disease, Sarcoidosis, Diffuse splenic hemangiomatosis, kala azar, tropical splenomegaly syndrome can result in massive splenomegaly.

Patients with no obvious explanation for an enlarged spleen present a difficult diagnostic problem. Careful follow-up of these patients sometimes reveals occult liver disease or an autoimmune process that initially defied diagnosis. Rarely splenomegaly may be the only sign of portal hypertension. Patients with congestive splenomegaly from liver disease or from splenic vein thrombosis can be asymptomatic⁷. Other common causes of asymptomatic splenomegaly are agnogenic myeloid metaplasia, Gaucher's disease and splenic cysts (Table 2). Splenic aspiration is sometimes helpful for the diagnosis of isolated splenomegaly. Splenic aspiration can detect abnormal cells i.e. LD bodies, malaria parasites, hairy cells, villous lymphocytes and metastatic deposits. Concerns about malignancy, particularly in patients with systemic symptoms such as fever, sweats, or weight loss or in patients in whom imaging studies

Table 2: Causes of asymptomatic splenomegaly

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| 1. Liver disease with portal hypertension |
| 2. Splenic vein thrombosis |
| 3. Agnogenic myeloid metaplasia |
| 4. Gaucher's disease |
| 5. Splenic cysts |
| 6. Sarcoidosis |
| 7. Amyloidosis |
| 8. Mild hereditary spherocytosis |
| 9. Early stages of polycythemia vera |

show a focal abnormality, are sometimes indications for splenectomy⁸. It is particularly important to avoid splenectomy in a patient with occult liver disease and portal hypertension.

DIAGNOSTIC SPLENECTOMY

Appropriate investigation in most patients with undiagnosed splenomegaly will yield a diagnosis. Patients with undiagnosed splenomegaly, who are otherwise well and who have no evidence of systemic diseases, particularly if the spleen is minimally enlarged, may be followed with careful and regular observation at monthly interval. If the spleen size remains unchanged, the patient may be followed up at progressively longer intervals. In patients who are unwell or who have evidence of systemic diseases, in which appropriate investigations (Table 3) have not yielded a

Table 3: Essential investigations in patients with undiagnosed splenomegaly before diagnostic splenectomy

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| 1. Radiology:
Chest X-ray
CT/MRI Chest/Abdomen |
| 2. Procedures:
Liver Biopsy**
Bone Marrow Aspirate
Bone Marrow Biopsy
Lymph Node Biopsy*
Broncho-Alveolar Lavage**
Upper GI Endoscopy |
| 3. Blood:
Rheumatoid factor
Anti-nuclear factor
Coomb's test
Blood cultures
Serology for HIV, hepatitis and other infections |

* If lymph node palpable. ** If clinically indicated.

diagnosis, resort to surgical removal of the enlarged spleen may be required⁹. In many instances, splenectomy is also therapeutic, providing relief from the consequences of splenomegaly in addition to possibly forming part of definitive therapy of the underlying condition.

In one study¹⁰, 122 of the 1280 patients underwent splenectomy for diagnosis and in 116 patients a specific disease was identified histologically that explained the splenomegaly/splenic mass. Malignancy was the most cause of unexplained splenomegaly or splenic mass, though benign neoplasms and reactive disorders were documented in 25% of cases. In another study¹¹, a definitive histological diagnosis was established in 9 out of 10 diagnostic splenectomies; seven of whom had lymphoma. The weight of the excised spleen in all patients with lymphoma exceeded 1kg; in all those with a diagnosis other than lymphoma, the spleen weighed less than 1 kg.

In another study from India¹², 41 splenectomies were carried out for diagnostic purposes. Histopathology of the spleen showed lymphoma in 15 (37%), tuberculosis in five (12%) and other lesions in five (12%) patients. Sixteen (39%) patients had only congestive splenomegaly. In our experience in last 2 years, out of 12 diagnostic splenectomies, 8 had lymphoma, 3 patients had congestive splenomegaly and another 1 showed extramedullary hematopoiesis. One out of three patients with congestive splenomegaly subsequently developed to malignant lymphoma after one and half years. Patients with splenomegaly in whom diagnosis is not reached preoperatively utilizing conventional investigations are likely to have a lymphomatous process, particularly if the spleen is grossly enlarged.

HYPERSPLENISM

Splenomegaly is often accompanied by hypersplenism. This is a complication of splenomegaly and not a diagnosis¹³. The specific cause of the splenomegaly must be determined. Classically it refers to 1) splenomegaly; 2) any combination of anemia, leukopenia and/or thrombocytopenia; 3) compensatory bone marrow hyperplasia; and 4) improvement after splenectomy. Within this framework, however, different diseases may cause different forms of hypersplenism due to diverse pathophysiological mechanisms (Table 4). Furthermore, an enlarged spleen can cause problems for the patient without meeting the aforementioned definition of hypersplenism. Thus perhaps hypersplenism could be redefined to mean that the spleen in question has become more harmful than beneficial.

Table 4: Etiology of Hypersplenism in different conditions

<i>Disease</i>	<i>Most likely mechanism</i>
Hairy cell leukemia	Retention of hairy cells in red pulp
Cirrhosis; splenic Vein thrombosis	Increased pooling of blood cells
Gaucher's disease	Increased pooling and dilutional anemia
Felty syndrome	Immune system work hypertrophy
Thalassemia major	RE system work hypertrophy

TROPICAL SPLENOMEGALY SYNDROME

This condition has recently been termed (more appropriately) as hyperreactive malarial syndrome (HMS). This is one of the important conditions associated with isolated splenomegaly¹⁴. Evidence linking HMS to malaria is reasonably convincing, although parasitemia is not demonstrated in these patients. Certain diagnostic criteria must be fulfilled to make a definitive and accurate diagnosis of HMS. The defining criteria include the following:

1. Residence of malaria endemic area.
2. Chronic splenomegaly, often massive.
3. Serum IgM at least 2 standard deviations (SD) above local mean.
4. High malarial antibody titer.
5. Hepatic sinusoidal lymphocytosis.
6. Clinical and immunological response to antimalarial prophylaxis.

Pathophysiology

Although the exact mechanism is unknown, evidence suggests that exposure to malaria elicits an exaggerated stimulation of polyclonal B-lymphocytes, leading to excessive and partially uncontrolled production of immunoglobulin M (IgM) as the initiating event. IgM is polyclonal and not specific for any one particular malaria species. Defective immunoregulatory control of B-lymphocytes by suppressor or cytotoxic T lymphocytes causes an increase in B lymphocytes and a decrease in T lymphocytes in the peripheral blood. This is accompanied by T cell infiltration of the hepatic and splenic sinusoids. An increase occurs in serum cryoglobulin levels, autoantibody levels, and high-molecular-weight immune complexes. This leads to anemia, deposition of large immune complexes in Kupffer cells in liver and spleen, reticuloendothelial cell hyperplasia, and hepatosplenomegaly.

Clinical Manifestations

HMS is most frequently observed in young and middle-aged adults and uncommon in children younger than 8 years. Abdominal swelling and pain generally chronic, and a dragging sensation are the most common presenting symptoms of HMS. Patients may rarely have intermittent fever, but the presence of fever should raise questions regarding an alternative diagnosis. Splenomegaly, usually moderate to massive, is the hallmark of HMS. Most patients have accompanying hepatomegaly. Hematologic manifestations include the following:

1. Anemia (normocytic normochromic) is almost always present and is related to the degree of splenomegaly. Several factors contribute to its etiology, including pooling of red cells in the spleen, hypersplenism, and increased red cell destruction and turnover, but the major factor is increased plasma volume. The reticulocyte count is increased, reflecting erythroid hyperplasia.
2. Leukopenia is common and sometimes associated with lymphocytosis.
3. Thrombocytopenia is generally mild. Both neutropenia and thrombocytopenia are due to splenic pooling.
4. Peripheral smear examination does not reveal the presence of malarial parasite in most cases.

Treatment

Antimalarial drugs are effective therapy for HMS. The treatment should be continued regularly for a prolonged period to be effective. Months may pass before response is noticed, and relapses may occur when therapy is discontinued. No documented studies address the duration of adequate treatment, and no studies compare the different antimalarial medications. The role of lifelong prophylaxis for individuals residing in endemic areas is also not clear. Treatment may have to be continued for more than a year, sometimes even longer. Response to therapy is guided by the splenic size, decrease in serum IgM levels, improvement of anemia, and general improvement in the well being of the patient.

Nontropical Idiopathic Splenomegaly

In nontropical countries isolated splenomegaly is usually due to lymphoma, myeloid metaplasia or collagen vascular diseases. Massive splenomegaly of unknown cause is also known as primary hypersplenism or Dacie's syndrome¹⁵. The syndrome as described by Dacie, et al, is characterized by splenomegaly and pancytopenia of variable severity, which responds

dramatically to splenectomy. Histologically, the spleen reveals lymphoid hyperplasia with prominent germinal centers throughout parenchyma, which are not found in the normal spleen. The etiology of this condition remains obscure. There is no evidence to support an infectious origin such as in the tropical splenomegaly syndrome, which is due to chronic malarial infection. The possibility of prelymphoma was raised by dacie et al after the observation that 40% of patients they treated, malignant lymphomas subsequently developed. Review of literature¹⁶ reveals that in 20% of patients with massive splenomegaly of unknown origin reported from nontropical countries have subsequently had malignant lymphoma.

REFERENCES

1. Eichner ER. Splenic function: normal, too much and too little. *American Journal of Medicine* 1979;66:311-20.
2. McIntyre OR, Ebauch FG Jr. Palpable spleens in college freshmen. *Ann Intern Med* 1967;66:301.
3. Sullivan S, Williams R. Reliability of clinical techniques for detecting splenic enlargement. *BMJ* 1976;4:1043.
4. Bruckstein AH. Splenomegaly: When and how to treat. *Postgrad Med J* 1986;79(5):289-96.
5. Fritscher-Ravens A, Mylonaki M, Pantes A, et al. Endoscopic ultrasound-guided biopsy for the diagnosis of focal lesions of the spleen. *Am J Gastroenterol* 2003;98:1022-7.
6. Swaoop J, O'Reily RA. Splenomegaly at a University Hospital compared to a nearby county hospital in 317 patients. *Acta Haematol* 1999;102:83-8.
7. Eichner ER, Whitfield CL. Splenomegaly: An algorithmic approach to diagnosis. *JAMA* 1981;246(24):2858-61.
8. Grover SA, Barkun AN, Sackett DL. Does this patient have splenomegaly? *JAMA* 1993;270:2218-21.
9. Deodhar M, Kakkar N. An audit of splenectomies in a teaching hospital in north India. Are postsplenectomy guidelines being complied with? *J Clin Pathol* 2004;57:407-10.
10. Kraus MD, Fleming MD, Vonderheide RH. The spleen as a diagnostic specimen. *Cancer* 2001;91(11):2001-9.
11. Cronin CC, Brady MP, Murphy C, et al. Splenectomy in patients with undiagnosed splenomegaly. *Postgrad Med J* 1994;70:288-91.
12. Pottakkat B, Kashyap R, Kumar A, et al. Redefining the role of splenectomy in patients with idiopathic splenomegaly. *ANZ J Surg* 2006;76(8):679-82.
13. Coetzee T. Clinical anatomy and physiology of spleen. *S Afr Med J* 1982;61:737-46.
14. Gupta OP, Bajaj S, Gupta SC. A study on tropical splenomegaly syndrome and chloroquine prophylaxis. *J Assoc Physicians India* 1989;37(9):570-5.
15. Dacie JV, Brain MC, Harrison CV. Nontropical Idiopathic Splenomegaly (primary hypersplenism): A review of ten cases and their relationship to malignant lymphomas. *Br J Haematol* 1969;17:317-33.
16. Wohlgenuth SD, Clifford TG. Nontropical Idiopathic Splenomegaly. *Southern Medical Journal* 1988;81(12):1569-70.