Hypersplenism: Review article

ERWA ELMAKKI
Faculty of medicine-Jazan University, PO box 104,Jazan, Saudia Arabia Kingdom
*E-mail of the corresponding author: erwamakki@gmail.com

Abstract
Hypersplenism is a condition in which the spleen becomes increasingly active and then rapidly removes the blood cells. It can result from any splenomegaly. It is most common with splenomegaly secondary to portal hypertension and haematological disorders. Portal hypertension is an important cause of splenomegaly in most tropical countries. Although studies on hypersplenism are few, two studies have shown that schistosomal portal hypertension is the commonest cause of hypersplenism, other common causes include hematological disorders, and visceral leishmaniasis, Tropical splenomegaly syndrome and liver cirrhosis, however there are wide geographical variations in the etiology of hypersplenism. Also the same above papers reported that there was no direct correlation between size of spleen and severity of cytopenia.

This article reviews causes, diagnosis and management of hypersplenism but detailed discussion about management of conditions that causes hypersplenism is out of its scope.

Keywords: Hypersplenism, splenomegaly, pancytopenia, portal hypertension.

Introduction
Hypersplenism is a clinical syndrome characterized by: (1) splenomegaly, although this may be only moderate (2) pancytopenia or a reduction in the number of one or more types of blood cells, neutropenia is less common than anemia and thrombocytopenia (3) normal production or hyperplasia of the precursor cells in the marrow or a so called maturation arrest (4) decreased red blood cells survival and (5) decreased platelet survival.

In hypersplenism, its normal function accelerates, and begins automatically to remove cells that may still be normal in function. Sometimes, the spleen will temporarily sequestre 90% of the body platelets and 45% of the red cells.¹ There is some suggestion that the spleen is the principal producer of antibodies aimed at circulating blood cells but has been confirmed only for anti-platelet antibodies. Anaemia in patients who have splenomegaly is partly dilutional.²

Splenic Anatomy and Function
The spleen is the largest lymphoid organ in the body and is situated in the left hypochondrium. The normal spleen is slightly concave solid, dark, red organ measuring 3×8×14 cm, weighing 100-157 gm and frequently has fetal lobulation on its anterior edge. A thin peritoneal capsule encloses the organ and easily strips from it. It become thick and firm in any inflammatory or chronic infection process. It consists of connective tissues, vascular channels, lymphatic tissues, lymph drainage channels and cellular components of the haemopoietic and reticuloendothelial systems.³

Histologically there are two main anatomical components:
1) The red pulp consists of sinuses lined by the endothelial macrophages and cords (spaces).
2) The white pulp, which has a structure similar to lymphoid follicles.

In many times, the spleen enlarges as it performs its normal functions. The 4 most important functions of the spleen are:
1. Clearance of microorganisms from the blood stream.
2. Synthesis of immunoglobulin G (IgG), properdin (an essential component of the alternate pathway of complement activation)
3. Removal of abnormal red blood cells
4. Embryonic haemopoiesis in certain conditions.

A normal spleen weighs 150 gm, approximately 11 cm in craniocodial length, and is not easily palpable. Spleens weighing 400-500 gm indicate splenomegaly, and some clinicians consider spleen weighing more than 1 kg as massive splenomegaly. Poulin, et al consider splenomegaly as moderate if the biggest dimension is 11-20 cm and severe if the biggest dimension is greater than 20 cm.

Spleen size is not a reliable guide to spleen function, and palpable spleens are not always abnormal. Patients who have chronic obstructive pulmonary disease and low diaphragms can have palpable spleens. Normally, the spleen does not pass beyond the anterior axillary line and lies along the 9th, 10th and 11th ribs. The spleen percussion sign is a useful diagnostic method. Spleen must be at least two or three times its usual size before it can be felt (clinically).

**Causes of Splenomegaly & hypersplenism:**

Causes of splenomegaly may be conveniently grouped into the following categories:

1. Infectious causes:
   - Viral infection: infectious mononucleosis, viral hepatitis, and HIV infection.
   - Bacterial infection: enteric fever, bacterial endocarditis, brucellosis, and Tuberculosis.
   - Parasitic infections: malaria, visceral leishmaniasis, and schistosomiasis
   - Fungal infections: histoplasmosis
   - Connective tissue disorders.

2. Hyperplastic splenomegaly:
   - Hereditary spherocytosis, symptomatic elliptocytosis, thalasaemia, polycythaemia Rubra vera, myelofibrosis, and Chronic myeloid leukaemia, Chronic Lymphocytic leukaemia and Lymphoma.

3. Congestive splenomegaly:
   - Liver cirrhosis, hepatic schistosomiasis "portal hypertension", hepatic vein obstruction, portal vein obstruction, splenic vein obstruction, congestive heart failure with increased venous pressure, and splenic artery aneurysm.

4. Infiltrative splenomegaly:
   - Gaucher's disease, amyloidosis, Niemann-pick disease, histiocytosis, splenic tumours, and metastatic malignancy, Marble bone disease and Waldenstrom macroglobulinaemia.

5. Micellanous causes:
   - Idiopathic non tropical splenomegaly, iron deficiency anaemia, B12 deficiency, thyrotoxicosis, breylliosis.

**Table 1: Causes of gross splenomegaly**

- Chronic infections: Malaria, Schistosomiasis, Kala-zar, and Brucella melitansis.
- Myeloproliferative disorders like myelofibrosis
Lymphoproliferative disorders like lymphoma and chronic lymphatic leukaemia.

- Adult type Gaucher's disease
- Idiopathic non-tropical splenomegaly
- Hyperactive malarial splenomegaly
- Spleen cysts or tumours
- Congestive splenomegaly
- Other rare causes of massive splenomegaly which have been reported are: sarcoidosis, Q- fever and infective endocarditis.

Two studies on hypersplenism done in two different countries have shown that the main causes of hypersplenism were non-cirrhotic portal hypertension, visceral leishmaniasis, liver cirrhosis and Tropical splenomegaly syndrome.

**Diagnosis of hypersplenism:**

(A) Clinical findings: The symptoms are of 3 types:

1. Symptoms related to the enlarged spleen such as abdominal fullness associated with feeling of heaviness and discomfort and pain in the left upper quadrant of the abdomen.

2. Haematological symptoms: Symptoms related to thrombocytopenia are common, such as, bruising and epistaxis. Symptoms related to anaemia are fatigue, weakness and pallor. Leucopenia leads to recurrent infections and oral ulcerations.

3. Symptoms and signs of the underlying diseases.
   i. Laboratory findings: Anaemia, thrombocytopenia and leucopenia.
   ii. Evaluation of splenic size: with physical examination, abdominal Ultrasonography, CT and MRI.
   iii. Evaluation of splenic function: reduced red cell or platelet survival can be measured by labelling the patient's cells with Cr$^{51}$ or the platelets with indium and measuring the rate of disappearance of radioactivity from the blood.

The diagnosis of hypersplenism is ultimately confirmed by response to splenectomy, although an immediate remission may be followed in the longer term by relapse with return of cytopenia.

**TAKE HOME MESSAGE**

- **Hypersplenism is a triad of splenomegaly, pancytopenia and normocellular bone marrow.**
- **Splenomegaly due to any cause can lead to hypersplenism, but Portal hypertension and hematological disorders are the commonest causes of hypersplenism.**
- **No direct relation between splenic size and hypersplenism, however hypersplenism is more common among those who have gross splenomegaly.**
- **Differential diagnosis of gross splenomegaly includes Portal hypertension, visceral leishmaniasis, Tropical splenomegaly syndrome, Gaucher disease in addition to myeloproliferative and lymphoproliferative disorders.**
- **Treatment of the underlying disease is best option for control of hypersplenism, however splenectomy and splenic embolization can be indicated in some patients.**
Schistosomiasis as a cause of Hypersplenism

Schistosomiasis is caused by parasitic trematode worms "schistosomes" that reside in the abdominal veins of their definitive host. Five species of schistosoma are known to infect humans. Infection with any of Schistosoma mansoni, S. japonicum, S. mekongi or S. intercalatum is associated with chronic hepatic and intestinal fibrosis. While S. haematobium infection leads to fibrosis, stricturing and calcification of the urinary bladder. Infections with all types of schistosoma follow direct contact with freshwater that contain free-swimming larval forms of the parasite named cercaria. Few days later, the worms migrate to the portal venous system, in which they mature. Pairs of worms then travel to the superior mesenteric veins "in the case of S. mansoni" the inferior mesenteric & superior haemorrhoidal veins "in the case of joponicum", or the vesical plexus in the case of S. haematobium.

Chronic Schistosomiasis

(i) Gastrointestinal and liver disease: Schistosomiasis develops from the host's immune response to schistosome eggs and the granulomatous reaction stimulated by the antigen they secrete. The granulomas damage the ova but result in fibrotic deposition in host tissues. Most granulomas found at the sites of maximal accumulation of eggs (the intestine and the liver). However, periportal granulomas have been found in many tissues, such as skin, lung, brain, adrenal glands, and skeletal muscles. The inflammatory response may help in migration of eggs into the lumen of gut or urinary tract. This possibility is supported by studies showing that T-cell-deficient mice and cases of the acquired immunodeficiency syndrome have significantly decreased egg output. Eggs retained in the gut wall induce inflammation, hyperplasia, ulceration, microabcess formation, and polyposis. Colicky hypogastric pain or pain in the left iliac fossa is frequent. Occult (or sometimes visible) blood in the faeces is usual. Severe chronic intestinal disease may lead to colonic or rectal stenosis. Colonic polyposis may present as a protein losing enteropathy. Inflammatory masses in the colon may appear similar to cancer. The relation between colorectal cancer and schistosomiasis has been debated for many years. If there is an increase in the risk of colorectal cancer, it is little. Eggs of S. mansoni and S. japonicum embolize to the liver, where the granulomatous inflammatory response induces peri-sinusoidal inflammation and periportal fibrosis, known as clay-pipe-stem fibrosis, this condition occurs in 4-8% of patients who have chronic infection. It takes many years to appear and is associated with sustained severe infection. Hepatomegaly develops early in the evolution of chronic disease.

Periportal collagen deposits result in progressive obstruction of blood flow, portal hypertension, and eventually varices, variceal bleeding, and hypersplenism. Periportal fibrosis can be detected by ultrasonography Fig(1), computed tomography Fig(2), or magnetic resonance imaging and it is characteristic of schistosomiasis. Hepatocellular synthetic function is reserved till the very late stages of the disease. However cirrhotic changes do not occur. Ultrasonography plus clinical examination, is used to look for and quantify hepato-splenic disease on the basis of the criteria of the World Health Organization. S. haematobium infection occasionally causes mild colonic or hepatic diseases.

(ii) Lungs and kidneys: S. mansoni eggs may reach the lung leading to scattered pulmonary fibrosis and cor-pulmonale. S. mansoni infection with a diffuse myloid deposit in the glomeruli have been documented specially in those associated with salmonella infection.

(iii) Neurologic manifestations: Transverse myelitis is the most common neurologic manifestation of S. mansoni or S. haematobium infection.

Diagnosis of S. mansoni Infection

(i) Stool examination: The kato-kataz thick smear technique is very useful in diagnosis of S. mansoni infection and in ova counting denoting severity of such infection.

(ii) Immunological diagnosis:

- Detection of schistosomal antibodies: This is a useful epidemiological tool, but it does not differentiate between active and past infections and is not related to severity of infection. The biochemically defined
peptides of adult worm SM 31/32 that have been successfully cloned result into 98% sensitivity but low specificity (25%).

- **Detection of circulating schistosomal antigens:** The antigens of diagnostic potentials are the excretory/secretory antigens of the adult worm, also known as gut-associated antigens. These consist of polypeptides, glycoproteins etc. The presence of these antigens in a patient indicates active infection.\(^\text{19}\)

**Treatment:** Praziquantel, a pyrazinoisoquinoline derivative, is the mainstay of treatment.\(^\text{20}\)

Fig (1): Ultrasonography showing periportal fibrosis in a patient with schistosomiasis

Fig (2): CT abdomen showing periportal fibrosis in a patient with schistosomiasis

Visceral Leishmaniasis (Kalazar) as a cause of hypersplenism
The world health organization estimates that there are 500,000 new cases of Kalazar occurring annually. The disease is transmitted by the bites of infected sand-fly vectors. Transmission occurs most commonly in and around the wooded savannas.

Incubation period ranges from two to eight months, although it may be as short as 10 days and as long as nine years. Patients in whom the incubation period is short typically have an illness resembling malaria, with sudden onset of high grade fever and chills. Other group of patients have a progressive typhoid-like illness with a fever that rises gradually over a period of weeks and may become continuous or remittent after the temperature reaches a peak as high as 40°C.

Abdominal Pain, fullness and early satiety are typically the symptoms that force the patient to seek medical attention. Cough, epistaxis, diarrhoea or even night sweats may also be the chief or accompanying manifestations.

The most impressive finding in patients with kala-azar is gross splenomegaly, although in cases of acute onset it may be absent initially. Splenic enlargement is due to cellular hyperplasia with increased numbers of macrophages, some of which are parasitized. Splenic size is related to the duration of the infection. Spontaneous splenic infarcts may develop. Hypersplenism has an important role in the pathogenesis of the haematologic abnormalities in kala-azar. Lymphadenopathy, a feature has been observed frequently in patients who acquire kala-azar in East Africa but rarely occurs in patients who acquire the infection in other areas. The severity of the haematologic abnormalities rely on the duration of the illness.

A moderate increase in IgG concentration is another characteristic feature of kala-azar and is important in distinguishing it from the tropical splenomegaly syndrome in which IgM is selectively elevated. Circulating immune complexes, including rheumatoid factor, have been detected. The erythrocyte sedimentation rate is typically raised.

Diagnosis of Kalazar is established by bone marrow aspiration with examination for amasigotes on Geimsa stained or Wright Geimsa stained smears. This procedure yields a definitive diagnosis in approximately 80% of cases of symptomatic kala-zar and is second only to examination of splenic aspirates, in which the sensitivity reaches 100%. Alternative but less sensitive diagnostic methods include liver biopsy and lymph node aspiration when lymphadenopathy is present.

-Cultivation of the parasites in specialized media are rarely used. The leishmanin skin test, a test of delayed hypersensitivity to injected killed parasites, is typically negative in patients with symptomatic kala-azar but becomes positive after successful treatment.

The standard treatment of kala-azar is with one of the pentavalent antimonials, sodium stibogluconate or N-methylglucamine, alternative treatments are pentamidine or amphotericin B.

**Tropical splenomegaly syndrome and hypersplenism**

Tropical splenomegaly syndrome (TSS) or Hyper-reactive malarial splenomegaly is massive enlargement of the spleen resulting from abnormal immune response to recurrent attacks of malaria. It is seen in children and adults who live in malaria endemic areas.

TSS is characterized by massive splenomegaly, hepatomegaly, marked elevations in levels of serum IgM and malaria antibody. Hepatic sinusoidal lymphocytosis is also seen. In about 10% of African patients, it may be associated with peripheral lymphocytosis (B cells).

Majority of patients present during adult life. Patients present with dragging pain in the left hypochondriun, or sometimes may even complain of a palpable mass. Some may develop recurrent sharp pains in the upper abdomen, probably due to perisplenitis or splenic infarcts. Another group of patients may have weight loss and cachexia. On examination, there is gross splenomegaly and hepatomegaly. The patients typically lack malarial parasitaemia and fever on presentation.

The peripheral smear shows normocytic normochromic anaemia with increased reticulocyte number. Pancytopenia
may also be seen as a result of hypersplenism. Malarial parasites are not usually found in the peripheral blood. There is increase in the serum levels of polyclonal IgM with cryoglobulinaemia, reduced C3 and the rheumatoid factor may be positive. Increased levels of IgM and antimalarial antibody, hepatic sinusoidal lymphocytosis on liver biopsy and response to antimalarial therapy (improvement in clinical condition as well as reduction in IgM and malarial antibody titre within three months of continuous antimalarial treatment) favor a diagnosis of TSS.

**Treatment:** The choice of antimalarial depends on the local sensitivity pattern. Chloroquine weekly or Proguanil daily for a long period of time have been found to be useful.

**Felty's Syndrome and Hypersplenism**

Felty syndrome is a potentially serious condition that is associated with seropositive rheumatoid arthritis; it is characterized by the triad of rheumatoid arthritis, splenomegaly and pancytopenia. It affects approximately 1-3% of all patients diagnosed with rheumatoid arthritis.

Although the pathophysiology of Felty's syndrome is not fully known, evidence points to splenic sequestration and subsequent granulocyte destruction. Studies performed almost 50 years ago demonstrated lower granulocyte counts in the splenic vein compared with those in the splenic artery.

**Treatment:** The best treatment for Felty syndrome is to control the underlying rheumatoid arthritis.

**Gaucher disease as a cause of hypersplenism**

Gaucher disease, a rare, inherited, and potentially fatal disorder, is characterized by decreased levels of the enzyme glucocerebrosidase. Deficiency of glucocerebrosidase results in the accumulation of the lipid glucocerebroside within the lysosomes of the monocyte macrophage system.

Lipid-engorged cells with eccentric nuclei, known as Gaucher cells, constitute the primary defect in Gaucher disease. Gaucher cells lead to the displacement of healthy, normal cells in bone marrow, hepatosplenomegaly, organ dysfunction, and skeletal deterioration.

**Clinical presentation:** Type I Gaucher disease presents with any one of the following features: Skeletal complications, anaemia, hepatosplenomegaly, or thrombocytopenia.

**Diagnosis:** Enzyme analysis of leukocytes or fibroblast cultures will confirm or exclude the diagnosis of Gaucher disease.

Enzyme assay is more precise and less invasive than bone marrow biopsy in which pseudo-Gaucher cells can be misread as indicative of Gaucher disease.

DNA analysis is of great value for all individuals with glucocerebrosidase deficiency to confirm diagnosis, but is not predictive of clinical course.

**Treatment:** Enzyme replacement therapy (ERT) stops and reverses the symptoms of Gaucher disease and improves quality of life.

**Management of Hypersplenism**

**Medical treatment:**

Successful medical treatment of the primary disorder can result in regression of the Hypersplenism without the need for surgery.

**Surgical treatment:**
i. Splenectomy:

It is known that the spleen represents one fourth of the total lymphatic mass and it acts as a biological filter for the clearance of bacteria. The spleen is essential for rapid antibody production after challenge with blood borne pathogens in the absence of pre-existing antibodies. In addition the spleen appears to be the site of production of nonspecific leucophic immunoglobulin tuftsin which increases the phagocytic activity of polymorphnuclear leucocytes. Thus the spleen has important functions and its resection is not to be taken lightly. Splenectomy is indicated in cases of chronic/severe hypersplenism. Surgical splenectomy causes significant postoperative morbidity and a long-term risk of overwhelming infection in 1 to 2% of patients. Total splenectomy should be avoided whenever possible in favour of conservative medical and surgical methods. Total occlusion of the splenic artery will also leads to similar complications including death.

The complications in coincidence with splenectomy can arise early up to 30 days after surgery or later on. Early complications can involve infections of the respiratory tract especially bronchopneumonia, or sub-phrenic abscess. Late complications are the fulminant sepsis known as O.P.S.I syndrome (overwhelming post-splenectomy infection), also known as postsplenectomy sepsis syndrome. In most conditions serious infection are due to encapsulated bacteria, such as pneumococci. Pneumococcal infections account for 50-90% of cases documented in the literature and may be associated with a mortality rate of up to 60%. H. influenza type B, meningococci, and group A streptococci account for an additional 25% of infections. The risk increases in children, in immunodeficient states and immunosuppressive therapy. 60% of patients develop OPSI during the first two years following splenectomy. Possible OPSI involving a splenic individual represents a medical emergency. The diagnostic workup should never delay the use of empiric treatment. Choices of empiric antimicrobial drugs include iv cefotaxime (adult dose) or iv ceftriaxone. Unfortunately, some penicillin resistant pneumococcal strain is also resistant to cephalosporins. If such resistance is suspected, consider using vancomycin.

The prevention of infection in coincidence with splenectomy is achieved with means of immunization, antibiotic prophylaxis and via education of patients; immunization includes the administration of a polyvalent pneumococcus vaccine. It should be given 2-3 weeks prior to splenectomy. The vaccination can be repeated 5-10 years. H. influenzae type B vaccine should be given to individuals who were not previously immunized. Meningococcal immunization is not routinely advised, except for travelers to areas where there is an increased risk of group A infection. Long-term prophylactic penicillin (Penicillin V) is recommended.

ii. Splenic embolization:

The modified technique of partial splenic embolization which leads to embolization of 60% to 80% of the spleen with sterile technique and intravenous antibiotics coverage before and after the procedure gives better outcomes. Apart from the expected immunological advantage, partial splenic embolization might prevent the development of a splenic abscess by preservation of the normal direction of blood flow through the circulation inside spleen. In total splenic embolization, the arterial blood flow to the spleen is completely changed and the direction of flow in the splenic vein is reversed. Since partial splenic embolization causes permanent ablation of sufficient splenic parenchyma to allow for subsequent improvement of haematological status, it will become an alternative to splenectomy in some patients with hypersplenism. Partial splenic embolization is simple to perform, safe and effective modality for treatment of hypersplenism.

Conclusion:

Hypersplenism is an important clinical finding in many medical conditions particularly in those causing massive splenomegaly. Among the wide list of causes of hypersplenism portal hypertension remains the commonest one. Diagnosis of hypersplenism is established by a triad of splenomegaly, cytopenia or pancytopenia and normal bone marrow study. Correction of hypersplenism rely on treatment of the underlying causative disease, however splenectomy can be beneficial in certain circumstances.
Acknowledgment:
I would like to express my deepest gratitude to Mr. Ata Elmanan Eltayib for technical support of this paper. Also gratitude are extended to my lovely family, my wife and two kids.

References
20. Brindley PJ, Sher A. The chemotherapeutic effect of praziquantel against schistosoma mansoni is dependent on


41. Likit VV. Immunological impairment and susceptibility to infection after splenectomy. JAMA 1987; 236: 1376-1377.


47. Kumar and Clark. Prophylaxis against infection after splenectomy or splenic dysfunction. Clinical Medicine, 14th ed. chap 6; p: 395.

