From the lab and image finding what can be inferred is:

**Patient with prolonged fever has HepatoSplenomegaly with pancytopenia and intra abdominal Lymphadenopathy.**

Spleen has enlarged due to some disease process and secondary hypersplenism has occurred with pancytopenia.

The disease process can affect the spleen in two ways:

1. Splenic enlargement– due to dis causuing impairement of venous outflow e..g. cirrhosis of liver portal vein obstruction, Bantis syndrome
2. Splenic enlargement due to disease directly affecting spleen–
3. E.g.- lymphoma . Boeckssarcois, Felty’s, gauchers etc

Although it is a common clinical problem with an extensive differential diagnosis, there is a relatively little discussion of this abnormality in major textbooks of internal medicine and hematology as far as I know.

Approach has to be multi pronged

I. Look into causes of prolonged fever and differentials for.(will be sent later)
II. Look into cause of splenomeagaly and pancytopenia and DD
III. Causes of pancytopenia and how to diagnose
IV. Causes of Fever+ splenomegaly+pancytopenia

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Here are some references from google

**REFERENCES FROM GOOGLE**

**For Fever+splenomegaly+Pancytopenia**

1. Summary statements

   **Clonal and non-clonal karyotypically abnormal cells in haemophagocytic lymphohistiocytosis**

   Haemophagocytic lymphohistiocytosis (HLH) is a rare disorder clinically characterized by fever, splenomegaly, pancytopenia, hypertriglyceridaemia and hypolibrinogenae

   mia-British Journal of Haematology

   Volume 90, Issue 1, pages 48–55, May 1995

2. **Unusual cutaneous lesions in two patients with visceral leishmaniasis and HIV infection**

   DISCUSSION. Visceral leishmaniasis in persons with HIV infection may present clinically with the typical kala-azar manifestations: massive splenomegaly, pancytopenia, fever, and wasting. The gastrointestinal tract is often involved ...

3. **Visceral leishmaniasis complicating a connective tissue disease: three case reports from Italy**
3. ... After eight months, due to the persistence of fever, splenomegaly and pancytopenia (Hb 92 g/L, ... Fever, splenomegaly, pancytopenia and increased ESR and CRP or any combination of these conditions may be frequently observed in many connective tissue disorders. ...

Real time PCR assay for clinical management of human immunodeficiency virus-infected patients with visceral leishmaniasis

Clinical manifestations include fever, hepatomegaly and/or splenomegaly, and pancytopenia. Bone marrow aspirate or biopsy followed by demonstration of Leishmania parasites by microscopic and/or cultural examination is the most common diagnostic procedure.

### SPLENOMEGALY AND HYPERSPLENISM

#### Investigations

Investigation will depend on the specific clinical presentation of the patient but may include:

- Abdominal ultrasound imaging, MRI, CT
- Full blood count, reticulocytes, blood film
- Haemoglobinopathy screen
- Liver function tests
- Virology, microbiology
- Serum protein electrophoresis
- Peripheral blood cell markers (leukaemia, lymphoma)
- Radioisotope liver and spleen scan
- Liver biopsy, bone marrow biopsy, lymph node biopsy

#### Aetiology

- Haematological
  - Haemolytic anaemias (e.g. Thalassaemia, red cell defects, Sickle cell anaemia)
  - Acute leukaemias, chronic leukaemias
  - Polycythaemia rubra vera
  - Macroglobulinaemia
  - Lymphoma (Hodgkin's disease and non-Hodgkin's lymphoma)
  - Essential thrombocythaemia
  - Myelofibrosis
- Infections
  - Malaria
  - Schistosomiasis
  - Visceral leishmaniasis (Kala-azar)
  - Tuberculosis, brucellosis
  - Glandular fever, viral hepatitis
  - Infective endocarditis
- Tumours and cysts
  - Splenic abscesses
  - Splenic metastases
  - Cysts, e.g. hydatid, dermoid
  - Tumours, e.g. haemangioma
- Congestive splenomegaly
Liver cirrhosis
- Budd Chiari syndrome
- Portal or splenic vein obstruction
- Heart failure

Connective tissue disorders
- Systemic lupus erythematosus
- Felty's syndrome

Other disorders
- Gaucher's disease
- Niemann Pick disease
- Histiocytosis X
- Amyloidosis

Causes of massive splenomegaly

- Chronic myeloid leukaemia
- Myelofibrosis, malaria (hyper-reactive malarial splenomegaly)
- Leishmaniasis
- 'Tropical splenomegaly' (idiopathic; Africa, SE Asia)
- Gaucher's syndrome

Splenomegaly in children

This is most commonly caused by infection, autoimmune disorders or haemolysis. It may be a presenting feature of neoplasia (e.g. metastatic neuroblastoma). Causes include:

- Infection: Glandular fever, CMV, other viral infections, often accompanied by lymphadenopathy, bacterial, protozoal, and fungal infections.
- Autoimmune: juvenile rheumatoid arthritis
- Haemolysis: hereditary spherocytosis, sickle cell anaemia, Thalassaemia
- Neoplasia: ALL, Hodgkin disease and NHL, acute or chronic myeloblastic leukemia, neuroblastoma.
- Inherited diseases: Gaucher’s disease and other storage disorders.

Hypersplenism

- This is a pancytopenia occurring in patients with an enlarged spleen. It is due to large numbers of cells being pooled and destroyed in the spleen's reticuloendothelial system, and haemodilution because of an increased plasma volume.
- It can present with symptoms of anaemia, infection, or bleeding.
- Bone marrow biopsy shows normal or hyperplastic marrow.
- Splenic sequestration crisis may develop in young children with sickle cell anaemia, which can precipitate hypovolaemic shock and death, and is an indication for splenectomy.

Management

- Treatment of the cause.
- Blood transfusions may be required.
- Open or laparoscopic splenectomy may be indicated to control or stage the disease (e.g. hereditary spherocytosis, Hodgkin's disease).
- Patients with impaired splenic function need prophylactic vaccinations etc. (see separate article on Splenectomy and Hyposplenism).
Evaluation of pancytopenia

Diagnostic Approach
( reference:online.epocrates.com)

Unless the underlying cause is already apparent (and being appropriately managed) the presence of pancytopenia always warrants investigation by a hematologist; and the presence of severe pancytopenia (symptomatic anemia, WBC <500/mcL and platelets <20x10^3/mcL) calls for urgent investigation (within 24 to 48 hours).

Flow diagram for evaluation of pancytopenia. Abbreviation: GVHD, graft-versus-host disease

From authors' collection

A thorough history and physical exam are always required, preferably conducted by a hematologist. A CBC and examination of peripheral blood film by a hematologist are essential. Bone marrow exam by aspirate and biopsy is almost always required as well.

History
The causes of pancytopenia are diverse, and likely causes of pancytopenia differ in children and adults. Particular attention must be paid to patient and family history. Of significance is any history of previous pancytopenia, aplastic anemia, inherited bone marrow failure syndromes, early fetal loss, history of cancer, metabolic disorders, liver disease, or connective tissue disorders.

The most common cause of transient pancytopenia in all age groups is cytotoxic chemotherapy and radiotherapy. The symptoms and signs of pancytopenia relate to the blood cell lineages affected (RBCs, WBCs, and platelets). Mild pancytopenia is often symptomless and detected incidentally when a full blood count/CBC is performed for another reason. Spontaneous mucosal bleeding (gums, GI tract), petechiae and purpura with easy bruising secondary to thrombocytopenia are usually the first symptoms to develop directly related to more severe pancytopenia. This is often followed by symptomatic anemia (fatigue, shortness of breath, dependent edema, chest pain in patients with ischemic disease) and bacterial infection secondary to neutropenia (fever, mucositis, abscesses, rigors).

Physical exam

A thorough physical exam is required, preferably by a hematologist. Weight loss and/or anorexia are harbingers of underlying infection (either precedent to the pancytopenia or as a result of it) and malignancy. Spontaneous mucosal bleeding (gums, GI tract), petechiae and purpura with easy bruising secondary to thrombocytopenia are usually the first signs to develop directly related to more severe pancytopenia. These signs are often accompanied by lymphadenopathy (underlying infection, mononucleosis, lymphoproliferative disorder and malignancy). Abdominal discomfort is a common presentation of splenomegaly and associated conditions. Widespread bone pain and loss of height suggest myeloma, joint pain systemic lupus erythematosus (SLE), and sore throat mononucleosis.

The following reference points to specific organ systems and associated conditions and is helpful to guide the examination.

Eye examination

- Retinal hemorrhage (thrombocytopenia)
- Leukemic infiltrates (acute leukemia)
- Jaundiced sclera (paroxysmal nocturnal hemoglobinuria, hepatitis, cirrhosis)
- Epiphora (dyskeratosis congenita)

Oral examination

- Oral petechiae or hemorrhage (thrombocytopenia)
- Stomatitis or cheilitis (neutropenia, vitamin B12 deficiency)
- Gingival hyperplasia (leukemia)
- Oral candidiasis or pharyngeal exudate

Cardiovascular examination:

- Tachycardia, edema, congestive cardiac failure (all signs of symptomatic anemia)
- Evidence of prior cardiac surgery (cardiac disease associated with congenital syndromes)

Respiratory examination:

- Clubbing (lung cancer)
- Tachypnea (sign of symptomatic anemia)
**Abdominal examination**

- Right upper quadrant tenderness (hepatitis)
- Lymphadenopathy (infection, lymphoproliferative disorder, HIV disease)
- Signs of chronic liver disease
- Splenomegaly (infection, myeloproliferative and lymphoproliferative disorders)

**Skin examination**

- Malar rash (SLE)
- Purpura/bruising (thrombocytopenia)
- Reticular pigmentation, dysplastic nails (dyskeratosis congenita)
- Hypopigmented areas
- Hyperpigmentation, café au lait (Fanconi anemia)

**Musculoskeletal examination**

- Short stature (Fanconi anemia, other congenital syndromes)
- Swelling/synovitis (SLE)
- Abnormal thumbs (e.g., Fanconi anemia)

**Signs associated with HIV disease**

- Morbilliform rash early
- Kaposi sarcoma, ulcerating nodules later

**Laboratory**

A CBC and examination of peripheral blood film by a hematologist are essential. A standard battery of evaluative tests may include:

- Serum reticulocyte count
- Serum LFTs and hepatic serology
- Serum coagulation profile, bleeding time, fibrinogen, and D-dimer
- Serum direct antiglobulin test
- Serum B12 and folate
- Serum HIV and nucleic acid testing.

**Specific testing pinpoints diagnosis in the following conditions:**

- Fanconi anemia: diepoxybutane (DEB) test for chromosomal breakage in peripheral blood lymphocytes
- Lymphoproliferative disorders: immunophenotyping, cytogenetics, lymph node biopsy
- Multiple myeloma: immunoelectrophoresis
- Paroxysmal nocturnal hemoglobinuria (PNH): peripheral blood immunophenotyping for deficiency of phosphatidylinositol-glycan-linked molecules on peripheral blood cells (e.g., CD16, CD55, CD59)
- CMV infection: serum IgM and IgG
- Epstein-Barr: serum monospot, viral capsid antigen (VCA), and Epstein-Barr nuclear antibody (EBNA)
- Leishmaniasis and other rare infections: blood and bone marrow culture, serum ELISA
- Rare genetic and metabolic disease: leukocyte glucocerebrosides
Serum PSA in suspect cases of prostatic malignancy.

Examination of bone marrow is almost always indicated in cases of pancytopenia unless the cause is otherwise apparent (e.g., established liver disease with portal hypertension). The bone marrow exam consists of both an aspirate and a trephine biopsy, which yield complementary information in this setting. The differential diagnosis of pancytopenia may be broadly classified based on the bone marrow cellularity (reduced cellularity indicates decreased production of blood cells, whereas normal/increased cellularity indicates ineffective production or increased destruction or sequestration of blood cells).

Specifically bone marrow aspirate permits examination of:

- Cytology (megaloblastic change, dysplastic changes, abnormal cell infiltrates, hemophagocytosis and infection (e.g., Leishman-Donovan bodies))
- Immunophenotyping (acute and chronic leukemias, lymphoproliferative disorders)
- Cytogenetics (myelodysplasia, acute and chronic leukemias, lymphoproliferative disorders).

Bone marrow trephine biopsy permits specific examination of cellularity:

- Normal or increased in myelodysplasia, acute and chronic leukemia, myeloma with plasma cells, carcinomatus marrow infiltration, peripheral destruction/sequestration conditions, early HIV disease, and megaloblastic anemia
- Decreased after chemotherapy, acute infection/sepsis, advanced HIV disease, hypoplastic myelodysplastic syndrome, congenital/inherited bone marrow failure syndromes, idiopathic aplastic anemia, systemic lupus erythematosus, and paroxysmal nocturnal hemoglobinuria.

Trephine biopsy also permits examination of histology and evaluation for:

- Cellular infiltration
- Blasts
- Features of myelodysplasia (e.g., abnormal localization of immature precursors)
- Reticulin stain (fibrosis)

Radiology

Abdominal ultrasound scan or CT scan of the abdomen is indicated to evaluate for splenomegaly. CXR may reveal tumor masses responsible for pancytopenia (e.g., carcinoma, thymoma). In cases where metastatic infiltration of the bone marrow is suspected, thyroid ultrasound or breast imaging may also be appropriate.
Pancytopenia may be due to decreased bone marrow production or bone marrow failure; clonal disorders of haematopoiesis, increased non-immune mediated destruction or sequestration, or an immune-mediated destruction of blood cells.

<table>
<thead>
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<th>Classification</th>
<th>Congenital/Inherited</th>
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Table of aetiologies for pancytopenia. Abbreviation: GVHD, graft-versus-host diseaseFrom authors’ collection

**Decreased bone marrow production**

After birth, the bone marrow is the site of production of RBCs, WBCs, and immature platelets. Once the cells are made they are released into the peripheral circulation. For this process to occur, adequate haematopoietic stem cell activity is required along with a functional bone marrow stromal environment. In addition, the high proliferative rate of the marrow requires
adequate nutritional status, particularly vitamin B12 and folic acid, and trace amounts of other elements.

- Chemotherapy is a common cause of transient pancytopenia, although this rarely presents a diagnostic dilemma, most commonly resolving within 1 to 2 weeks. Some regimens are associated with significantly longer periods of pancytopenia. The most common cause of transient pancytopenia in all age groups is cytotoxic chemotherapy and radiotherapy.
- Although most cases of megaloblastic anaemia cause a macrocytic anaemia without leukopenia or thrombocytopenia, severe megaloblastic anaemia can result in pancytopenia. Megaloblastic anaemia most commonly arises from deficiency of vitamin B12, (e.g., pernicious anaemia, an autoimmune condition where autoantibodies interfere with the function of intrinsic factor, which is required for absorption of vitamin B12 within the GI tract). Less commonly B12 deficiency is caused by dietary deficiency (in vegans) or by malabsorption in the gut.
- Folic acid deficiency, almost always dietary in origin, also results in megaloblastic anaemia.
- Infiltration of the bone marrow is a common cause of pancytopenia and commonly results from malignant disease. In general, the infiltrate is cellular and may be of haematological origin (e.g., acute myeloid and lymphoblastic leukaemia, myeloma, non-Hodgkin's lymphoma, hairy cell leukaemia, chronic lymphocytic leukaemia, and myelofibrosis) or non-haematological malignancies (e.g., breast, lung, kidney, prostate, and thyroid). In children, pancytopenia can be caused by neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma, and retinoblastoma.
- Lysosomal storage disorders (e.g., Gaucher's disease) can infiltrate the marrow resulting in pancytopenia. The infiltrate may be largely reticulin fibrosis, which is also associated with malignant conditions. Gaucher's disease patients may have massive splenomegaly and functional hypersplenism in addition to infiltration of the bone marrow.
- Rarer causes of pancytopenia arising from decreased bone marrow production of blood cells include anorexia nervosa, transfusion-associated graft-versus-host disease in immunosuppressed patients, heavy metal poisoning (e.g., arsenic). [1] Infections such as HIV have also been associated with pancytopenia secondary to underproduction (see further below) as has parvovirus in individuals with specific predisposing conditions (most prominently sickle cell anaemia).

### Clonal disorders of haematopoiesis

Myelodysplasia (MDS) is a common acquired clonal disorder of haematopoietic cells, characterised by ineffective and dysplastic haematopoiesis and a propensity for evolution to acute myeloid leukaemia. The bone marrow may be either hypercellular or hypocellular. In both cases there is commonly peripheral blood pancytopenia. In addition to decreased or inadequate production of blood cells within the marrow, there is sometimes an immune-mediated mechanism contributing to the peripheral blood pancytopenia in MDS.

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare (1 to 2 cases per million general population) acquired clonal disorder of haematopoietic cells, caused by somatic mutation of the X-linked phosphatidylinositol glycan A gene and resulting in deficient expression of
glycosylphosphatidylinositol-anchored proteins. PNH is clinically characterised by intravascular haemolysis and thrombosis, and evolution of pancytopenia is common (probably arising from a combination of decreased bone marrow production secondary to acquired defects in haematopoietic stem cells and cell destruction). There is an overlap in clinical and laboratory features between PNH patients and those with idiopathic aplastic anaemia (IAA).

### Bone marrow failure

Congenital and inherited bone marrow failure syndromes (IBMFS) most often present in childhood, although diagnosis in adulthood is reported.

- Fanconi's anaemia is primarily an autosomal recessive disorder where a variety of dysfunctional proteins result in decreased haematopoiesis and BMF. [2] In addition, Fanconi's anaemia is variably characterised by short stature, hyperpigmentation, skeletal anomalies, increased incidence of solid tumours and leukaemia, and an increased cellular sensitivity to DNA damaging agents. [3] [4]

- IAA is a rare acquired condition (2 to 6 cases per million general population). The diagnosis of IAA requires the presence of pancytopenia in combination with decreased bone marrow cellularity without infiltration or fibrosis. [5] IAA is therefore a diagnosis of exclusion, and has to be differentiated carefully from congenital and inherited BMF syndromes. [6] Some patients have an antecedent history of viral infection, hepatitis, or exposure to drugs. Severe IAA (where neutropenia and thrombocytopenia are more profound) is a life-threatening condition.

### Increased destruction or sequestration

Most cases of pancytopenia that are accompanied by adequate bone marrow production of blood cells result from increased sequestration of blood cells within the spleen. Conditions that result in pancytopenia from functional hypersplenism include:

- Liver disease (with associated portal hypertension) caused by alcoholic liver cirrhosis, chronic hepatitis B and C infection, autoimmune hepatitis, or idiopathic portal hypertension.

- Myeloproliferative disorders (e.g., chronic myeloid leukaemia may present with massive splenomegaly resulting in pancytopenia despite adequate production of blood cells within the bone marrow). These conditions rarely occur in children.

- Acute and chronic infections that result in hypersplenism (e.g., brucellosis and visceral leishmaniasis). Consideration of exposure and travel history is of particular relevance.

- Haemophagocytic syndromes, a heterogeneous group of disorders characterised by increased macrophage or histiocyte activity within the bone marrow and other organs. Hepatomegaly and splenomegaly are common clinical features. Haemophagocytic syndromes may be categorised as primary (where the haemophagocytic syndrome dominates the clinical features of the condition, as in haemophagocytic lymphohistiocytosis) or may be reactive to systemic conditions with a range of other clinical features (e.g., T-cell lymphoma).
Drug-induced immune pancytopenia arises when antibodies with cross-reactivity for drug and haematopoietic cells are generated. This is associated most frequently with quinine, sulfonamides, and rifampicin.

Immune pancytopenia may be seen in up to 20% of patients with Evans' syndrome (classically the combination of autoimmune thrombocytopenia and haemolytic anaemia), which is seen more commonly in children than in adults.

Combination pancytopenia

Many conditions associated with pancytopenia result from a combination of decreased bone marrow production and increased destruction or sequestration of blood cells. They include:

- Connective tissue disorders (most commonly rheumatoid arthritis and systemic lupus erythematosus)
- Acute CMV infection
- Mycobacterial infection
- Infectious mononucleosis
- HIV has also been associated with pancytopenia secondary to underproduction of blood cells
- Felty's syndrome (rheumatoid arthritis, splenomegaly, and neutropenia) may also be associated with pancytopenia.