BMJ Best Practice

Assessment of pancytopenia

Straight to the point of care

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Summary

Pancytopenia is a reduction in the number of red blood cells, white blood cells, and platelets in the peripheral blood below the lower limits of the age-adjusted normal range for healthy people. It is therefore the combination of anaemia, leukopenia, and thrombocytopenia.

Pancytopenia may result from decreased production of blood cells, bone marrow failure, immune-mediated destruction of blood cells, or non-immune-mediated sequestration in the periphery.

The diagnosis of pancytopenia is made from the results of an automated full blood count but, as the aetiology of pancytopenia varies significantly, a detailed diagnostic evaluation is required in every instance.

THEORY

Aetiology

Pancytopenia may be due to decreased bone marrow cell production or bone marrow failure, clonal disorders of haematopoiesis, increased non-immune-mediated destruction or sequestration, or an immune-mediated destruction of blood cells.

Classification	Congenital/inherited	Acquired	Acquired
Mechanism	**Decreased bone marrow production**	**Decreased bone marrow production**	**Increased destruction/sequestration**
Common	Gaucher's disease (marrow infiltration, splenomegaly) Fanconi's anaemia (bone marrow failure)	Cytotoxic chemotherapy Radiotherapy Megaloblastic anaemia Bone marrow infiltration Myelodysplasia Myelofibrosis Idiopathic aplastic anaemia	Liver disease Portal hypertension
		Connective tissue disorders (rheumatoid arthritis, SLE) Acute viral infections (CMV, EBV, HIV) HIV disease Mycobacterial infection	
Uncommon	Various childhood, metabolic, and complex multisystem disorders and inherited bone marrow failure syndromes (e.g., dyskeratosis congenita, congenital amegakaryocytic thrombocytopenia, Shwachman syndrome)	Paroxysmal nocturnal haemoglobinuria Anorexia nervosa Transfusion-associated GVHD Heavy-metal poisoning Infection (parvovirus B19 infection, HHV6 or CMV in transplant recipients, legionnaires' disease)	Hypersplenism secondary to myelo/lymphoproliferative disorders Haemophagocytic syndromes Drug-induced immune pancytopenia Evans syndrome with tricytopenia Infection (brucellosis, visceral leishmaniasis)

Table of aetiologies for pancytopenia (SLE: systemic lupus erythematosus, CMV: cytomegalovirus, EBV: Epstein-Barr virus, GVHD: graft-versus-host disease)

From the collection of Jeff K. Davies

Decreased bone marrow production

The bone marrow is the site of production of red blood cells, white blood cells, and megakaryocytes, from which platelets arise. Once the cells are made they are released into the peripheral circulation. This process requires adequate haematopoietic stem cell activity and a functional bone marrow stromal environment. The high proliferative rate of the marrow requires adequate nutritional status, particularly vitamin B12 and folic acid, and trace amounts of other elements.

Chemotherapy

- The most common cause of transient pancytopenia in all age groups is cytotoxic chemotherapy and radiotherapy. Chemotherapy-related pancytopenia rarely presents a diagnostic dilemma,

and usually resolves within 1 to 2 weeks. Of note, some individuals may have known or unknown proliferative defects or particular pharmacogenetics, which may predispose them to more severe and longer duration pancytopenia. Some regimens are associated with significantly longer periods of pancytopenia. Longer than expected post-chemotherapy-related pancytopenia should be investigated.

Megaloblastic anaemia

- 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 gastrointestinal 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.

Bone marrow infiltration

- 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

- 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.

Other causes

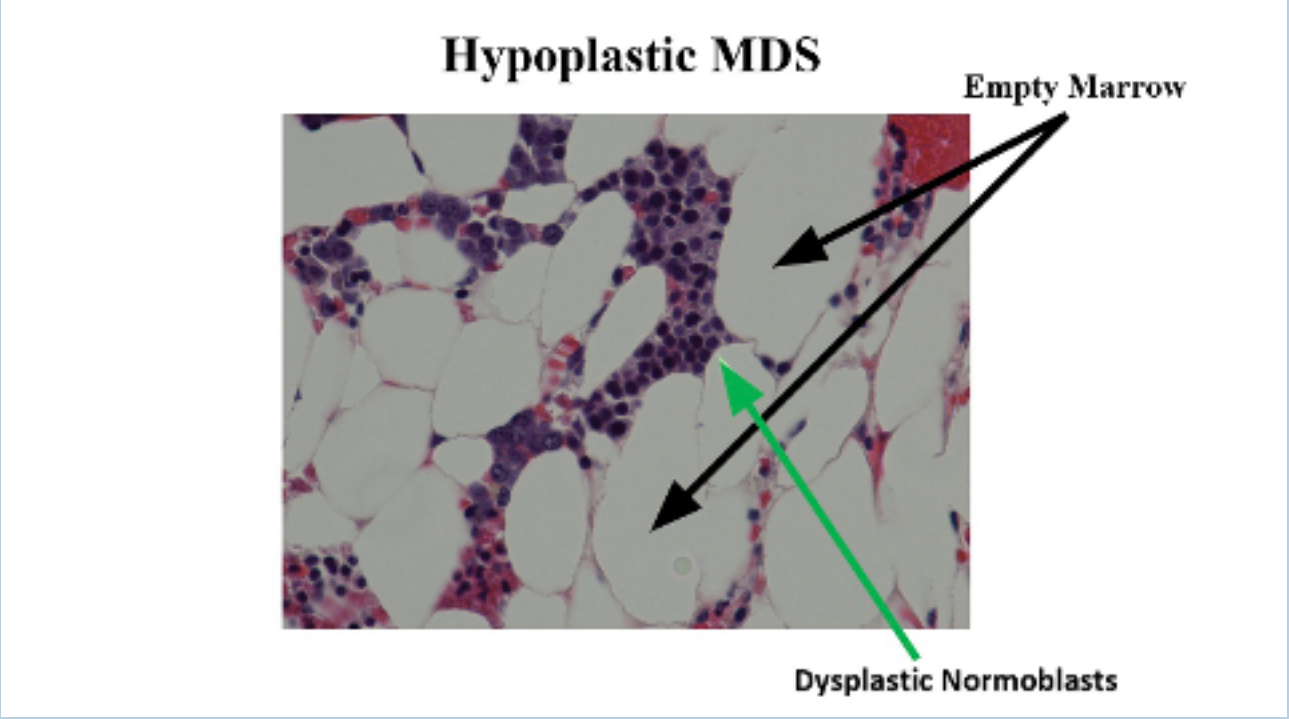
- Rarer causes of pancytopenia arising from decreased bone marrow production of blood cells include anorexia nervosa, transfusion-associated graft-versus-host disease in immunosuppressed patients, and heavy metal poisoning (e.g., arsenic).[1] Infections such as HIV have also been associated with pancytopenia secondary to underproduction, as has parvovirus in individuals with specific predisposing conditions (haemolytic anaemia; most prominently sickle cell anaemia).

Clonal disorders of haematopoiesis

Myelodysplastic syndrome (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 (1-2 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.[2]

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).



Hypoplastic myelodysplastic syndrome with dysplastic normoblasts

Morris Edelman, MD and Peihong Hsu, MD

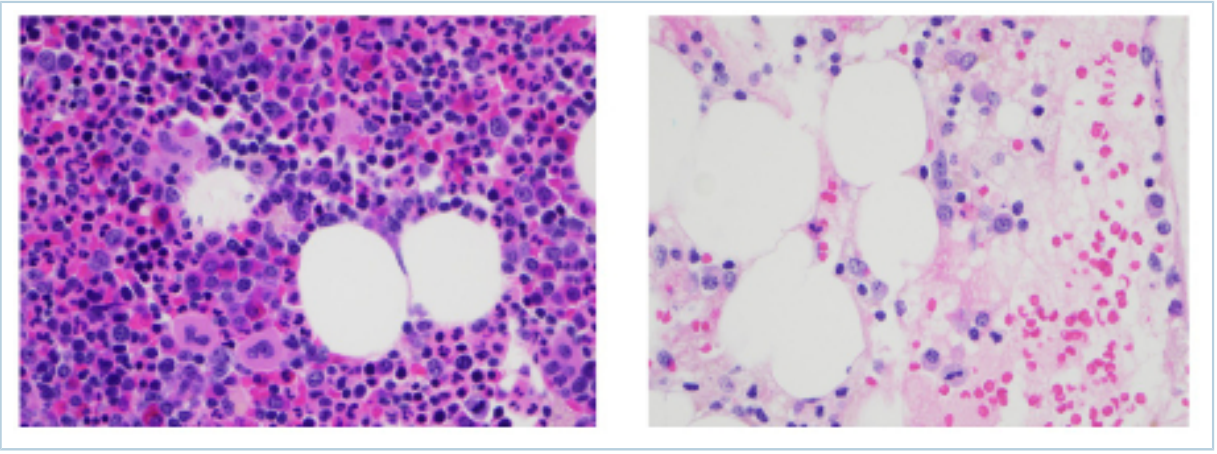
Bone marrow failure

Congenital and inherited bone marrow failure syndromes (IBMFS) most often present in childhood, although diagnosis in adulthood is increasing, secondary to awareness and greater testing.

- Fanconi's anaemia is primarily an autosomal recessive disorder (rare X-linked inheritance has been described) in which over 20 dysfunctional proteins result in decreased haematopoiesis and bone marrow failure.[3] 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.[4] [5] [6]
- Dyskeratosis congenita (DC) arises from genetic lesions that compromise telomere integrity, with resulting loss of cell self-renewal and regeneration.[7] Mutations in genes associated with telomere biology can be identified in the majority of patients with clinical features of classic DC.[8] [9] [10] Classic DC is defined by nail dystrophy, mucosal leukoplakia, and skin pigmentation changes, all ranging in severity from virtually non-existent to severe.[6] Other abnormalities include bone marrow failure, premature balding and grey hair, urethral strictures, excessive tear production, and pulmonary fibrosis.[11]
- Idiopathic (acquired) aplastic anaemia (IAA) is a rare acquired condition (2-6 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.[12] IAA is therefore a diagnosis of exclusion and has to be differentiated carefully from congenital and IBMFS.[13] 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.

- Other rare inherited single cell cytopenias, such as Diamond-Blackfan anaemia (DBA), Shwachman-Diamond syndrome (SDS), and amegakaryocytic thrombocytopenia (AMT), may evolve to pancytopenia.[6]
- Using whole exome sequencing, gene mutations seldom reported in inherited bone marrow failure have been identified in patients with bone marrow failure of suspected inherited origin but unresolved diagnosis.[14]



Aplastic anaemia: normocellular bone marrow is shown on the left; and empty marrow, typical of congenital or acquired aplastic anaemia, is shown on the right

Morris Edelman, MD and Peihong Hsu, MD

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), which are usually genetic in origin, or may be reactive to systemic conditions with a range of other clinical features (e.g., autoimmune disorders, T-cell lymphoma, referred to as macrophage activation syndrome). These distinctions may be difficult to discern in some instances.

Immune-mediated destruction of blood cells

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.[15] A significant number of people with Evans syndrome have underlying autoimmune lymphoproliferative syndrome.

Autoimmune lymphoproliferative syndrome (ALPS) is an inherited disorder resulting from mutations that inhibit apoptosis in the regulation of the immune response. Mild cases have been reported, suggesting that the incidence is significantly understated. ALPS is characterised by a usually benign lymphoproliferation (lymphadenopathy and splenomegaly) and autoimmunity, most often directed towards cells of the myeloid lineage (erythrocytes, granulocytes, and platelets),[16] although other targets are less commonly involved (e.g., autoimmune hepatitis).

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 cytomegalovirus infection
- Mycobacterial infection
- Infectious mononucleosis
- HIV has also been associated with pancytopenia secondary to underproduction of blood cells
- Felty syndrome (rheumatoid arthritis, splenomegaly, and neutropenia) may also be associated with pancytopenia.

Urgent considerations

(See **Differentials** for more details)

Unless the underlying cause is already apparent (and being appropriately managed), the presence of pancytopenia always warrants investigation by a haematologist.

Severe pancytopenia

In all cases of severe pancytopenia (symptomatic anaemia, WBC <0.5 x 10^9/L [<500/microlitre], and platelets <20 x 10^9/L [<20 x 10^3/microlitre]), investigation is mandatory within 24 to 48 hours. Supportive therapy with red blood cell and platelet transfusion, and broad-spectrum antibiotics to treat anaemia, bleeding, and/or infection may need to be initiated before the underlying cause has been ascertained.

Acute myeloid leukaemia

Occurs in all age groups but predominantly in older adults. Cytogenetic abnormalities are prognostically important and affect patient management. Clinical history plus most signs and symptoms usually reflect bone marrow failure. These include fatigue, dyspnoea, dizziness, bleeding, easy bruising, and recurrent infections. Most patients are treated with chemotherapy induction and consolidation regimens. Haematopoietic stem cell transplantation is also beneficial in select patients.

Acute lymphoblastic leukaemia

This is the most common acute leukaemia in childhood, but also occurs in adults. Clinical history plus most signs and symptoms usually reflect blood marrow failure. These include fatigue, dyspnoea, dizziness, bleeding, easy bruising, and recurrent infections. Physical examination may reveal pallor and ecchymoses, and lymphadenopathy. Neurological symptoms and/or signs may occur if central nervous system involvement is present. Treatment uses multi-agent dose-intense chemotherapy regimens in induction, consolidation, and maintenance phases.

Acquired aplastic anaemia

This rare condition affecting all age groups is characterised by pancytopenia with reduced or absent haematopoiesis in the bone marrow in the absence of a malignant infiltrate or fibrosis. Severe aplastic anaemia (SAA) is defined, using the modified Camitta criteria, as having a marrow cellularity <25% with at least 2 of the 3 following criteria:[17] [18] [19]

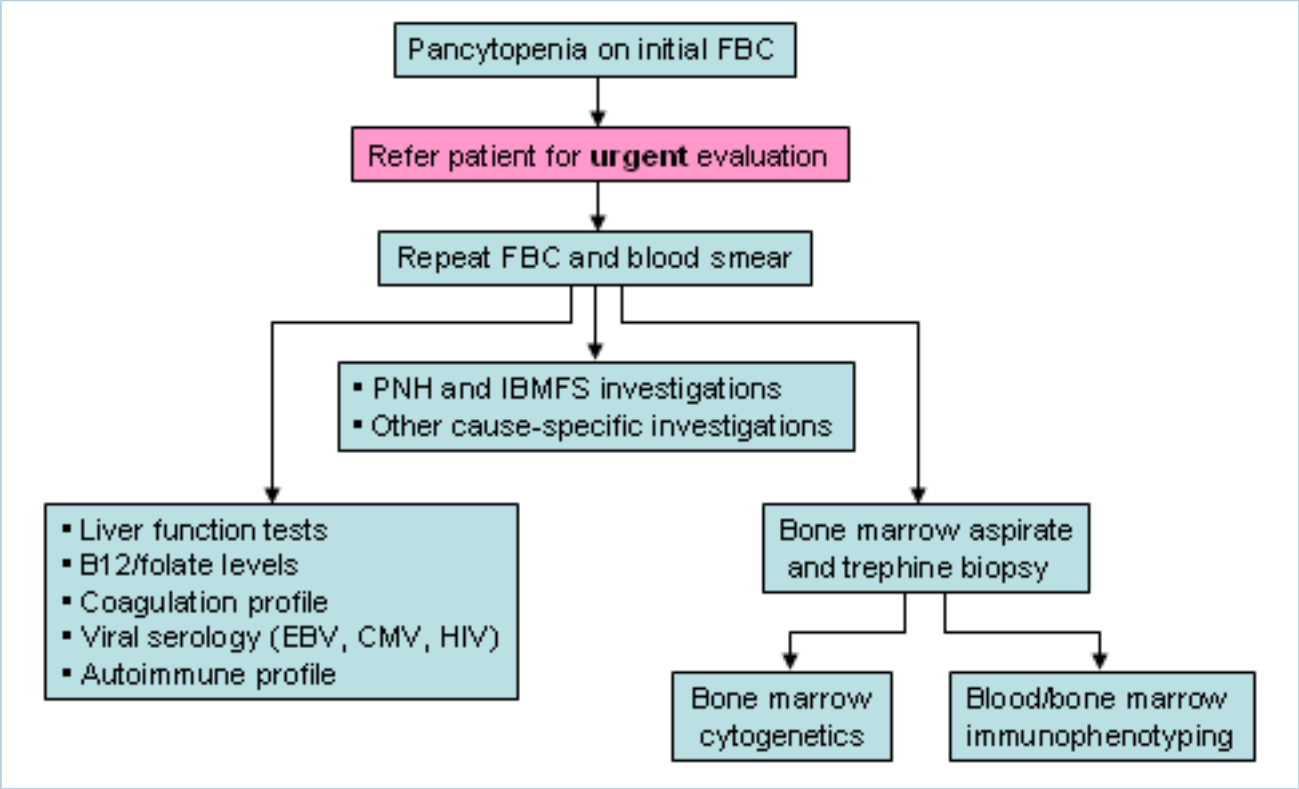
- neutrophils <0.5 x 10^9/L (<500/microlitre) (very severe aplastic anaemia [VSAA] <0.2 x 10^9/L [<200/microlitre])
- platelets <20 x 10^9/L (<20 x 10^3/microlitre)
- reticulocyte count <20 x 10^9/L (<20 x 10^3/microlitre).

Clinical history plus most signs and symptoms usually reflect bone marrow failure. These include fatigue, dyspnoea, dizziness, bleeding, easy bruising, and recurrent infections.

Approach

Unless the underlying cause is already apparent (and being appropriately managed), the presence of pancytopenia always warrants investigation by a haematologist.

The presence of severe pancytopenia (symptomatic anaemia, WBC <0.5 x 10^9/L [<500/microlitre], and platelets <20 x 10^9/L [<20 x 10^3/microlitre]) calls for urgent investigation (within 24-48 hours). A thorough history and physical examination are always required, preferably conducted by a haematologist. A full blood count and examination of peripheral blood film by a haematologist are essential. Bone marrow examination by aspirate and biopsy is almost always required.[20] [21]



Flow diagram for evaluation of pancytopenia. Abbreviations: PNH, paroxysmal nocturnal haemoglobinuria; IBMFS, inherited bone marrow failure syndromes

From the collection of Jeff K. Davies

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 anaemia, inherited bone marrow failure syndromes (IBMFS), early fetal loss, history of cancer, metabolic disorders, liver disease, or connective tissue disorders. A thorough drug history is essential.

The symptoms and signs of pancytopenia relate to the blood cell lineages affected (red blood cells, white blood cells, and platelets). Mild pancytopenia is often symptomless and detected incidentally when a full blood count is performed for another reason, particularly in association with non-specific viral illnesses in children. Spontaneous mucosal bleeding (gums, gastrointestinal 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 anaemia (fatigue, shortness of breath, dependent oedema, chest pain in patients with ischaemic disease) and bacterial infection secondary to neutropenia (fever, mucositis, abscesses, rigors).

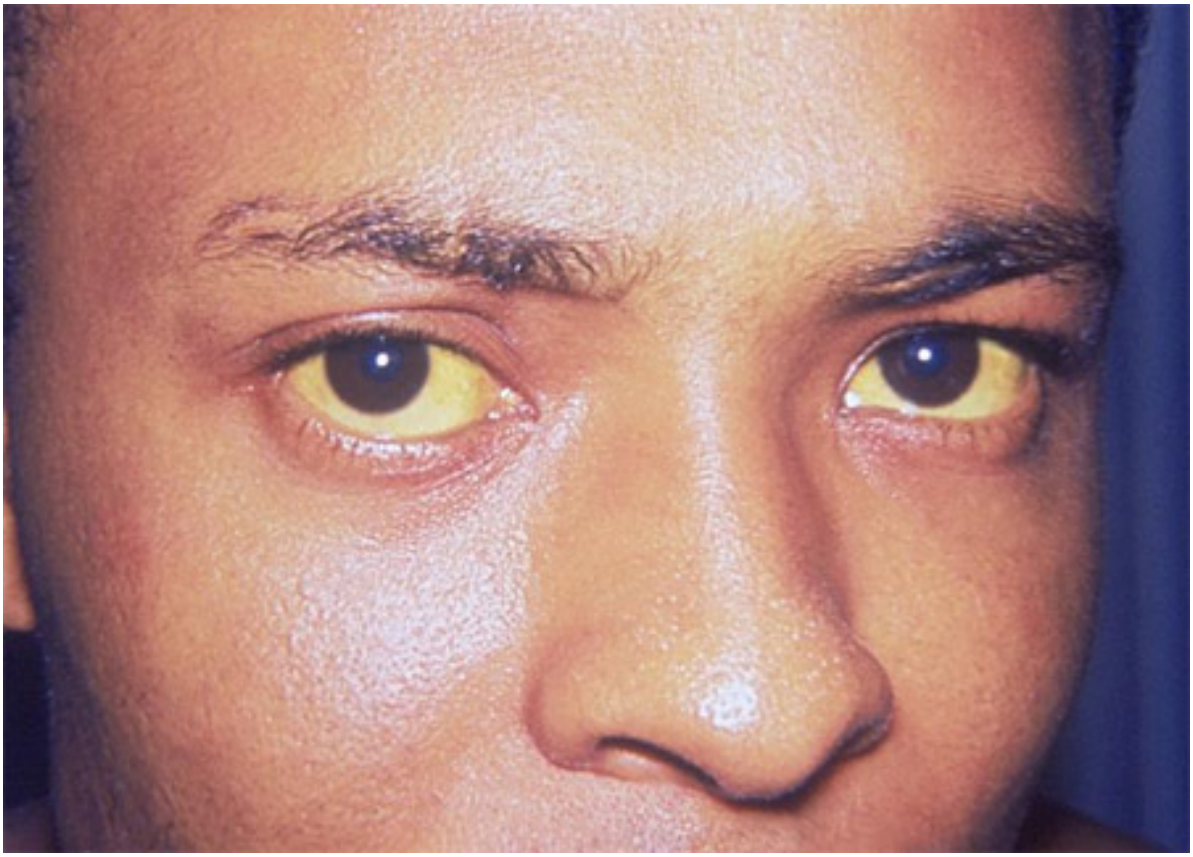
Physical examination

A thorough physical examination is required, preferably by a haematologist. Weight loss and/or anorexia are harbingers of underlying infection (either precedent to the pancytopenia or as a result of it) or malignancy. Spontaneous mucosal bleeding (gums, gastrointestinal 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 suggests systemic lupus erythematosus (SLE), and sore throat consideration of mononucleosis.

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

Eye examination

- Retinal haemorrhage (thrombocytopenia)
- Leukaemic infiltrates (acute leukaemia)
- Jaundiced sclera (paroxysmal nocturnal haemoglobinuria [PNH], hepatitis, cirrhosis)
- Epiphora (dyskeratosis congenita)

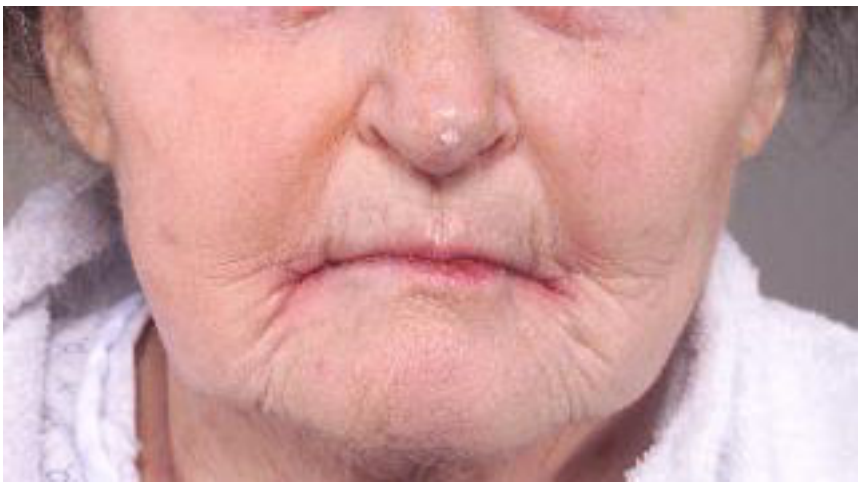


Icterus or jaundice

CDC. Dr Thomas F. Sellers/Emory University; used with permission

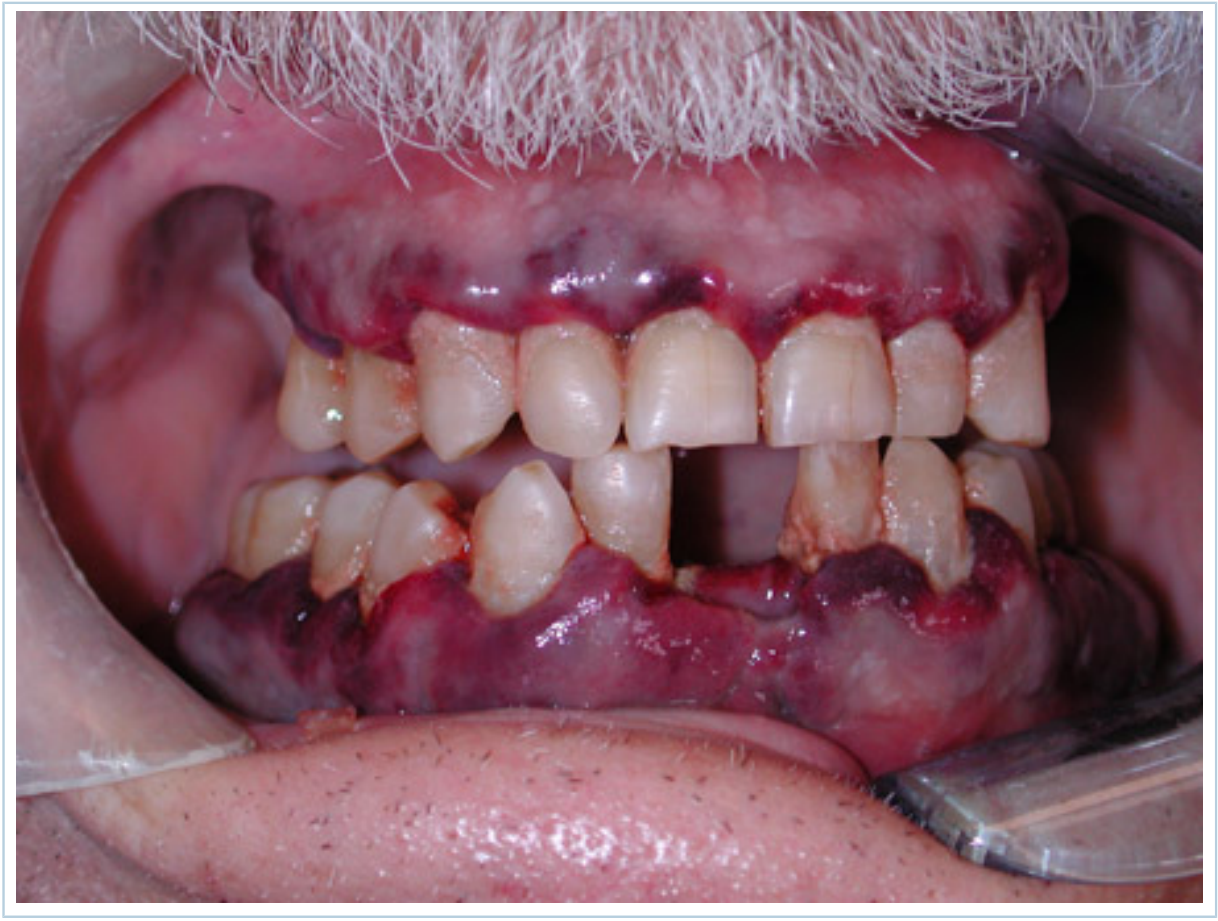
Oral examination

- Oral petechiae or haemorrhage (thrombocytopenia)
- Stomatitis or cheilitis (neutropenia, vitamin B12 deficiency)
- Gingival hyperplasia (leukaemia)
- Oral candidiasis or pharyngeal exudate (neutropenia, herpes family virus infections)



Angular cheilitis

From the collection of Dr Wanda C. Gonsalves; patient consent obtained



Gingival enlargement, petechiae and bleeding in acute myeloid leukaemia

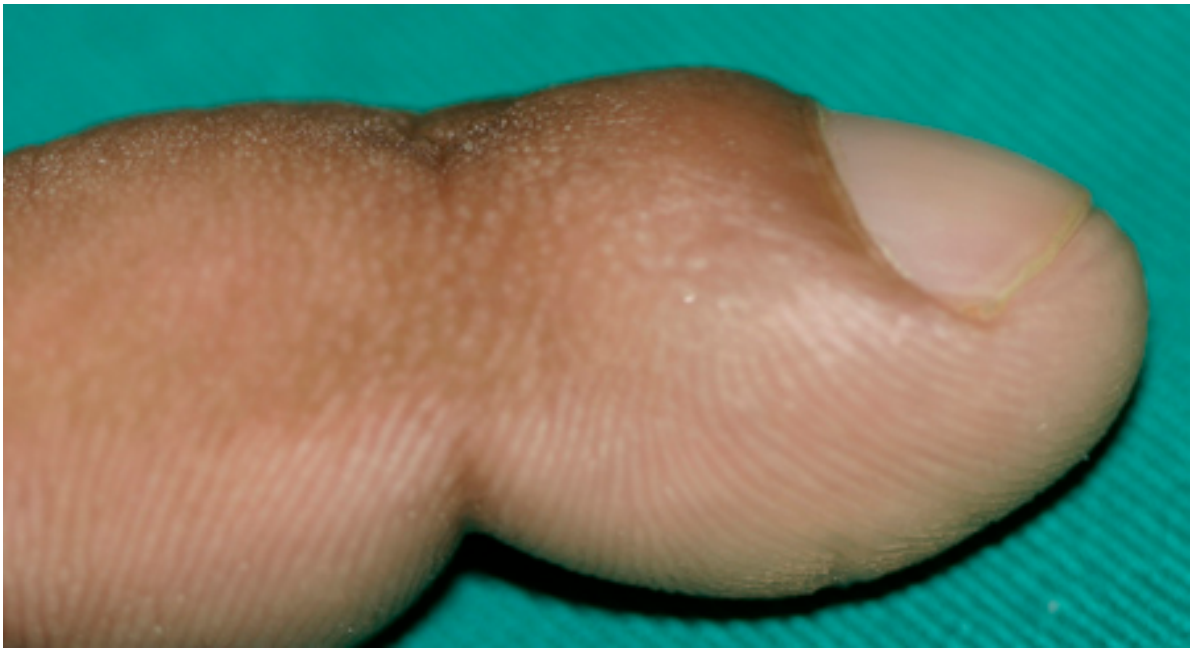
Collection of Giuseppina Campisi, DDS, MS and Giuseppe Pizzo, DDS

Cardiovascular examination

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

Respiratory examination

- Clubbing (lung cancer)
- Tachypnoea (sign of symptomatic anaemia)



Clubbing of nails showing loss of the classic Lovibond's angle

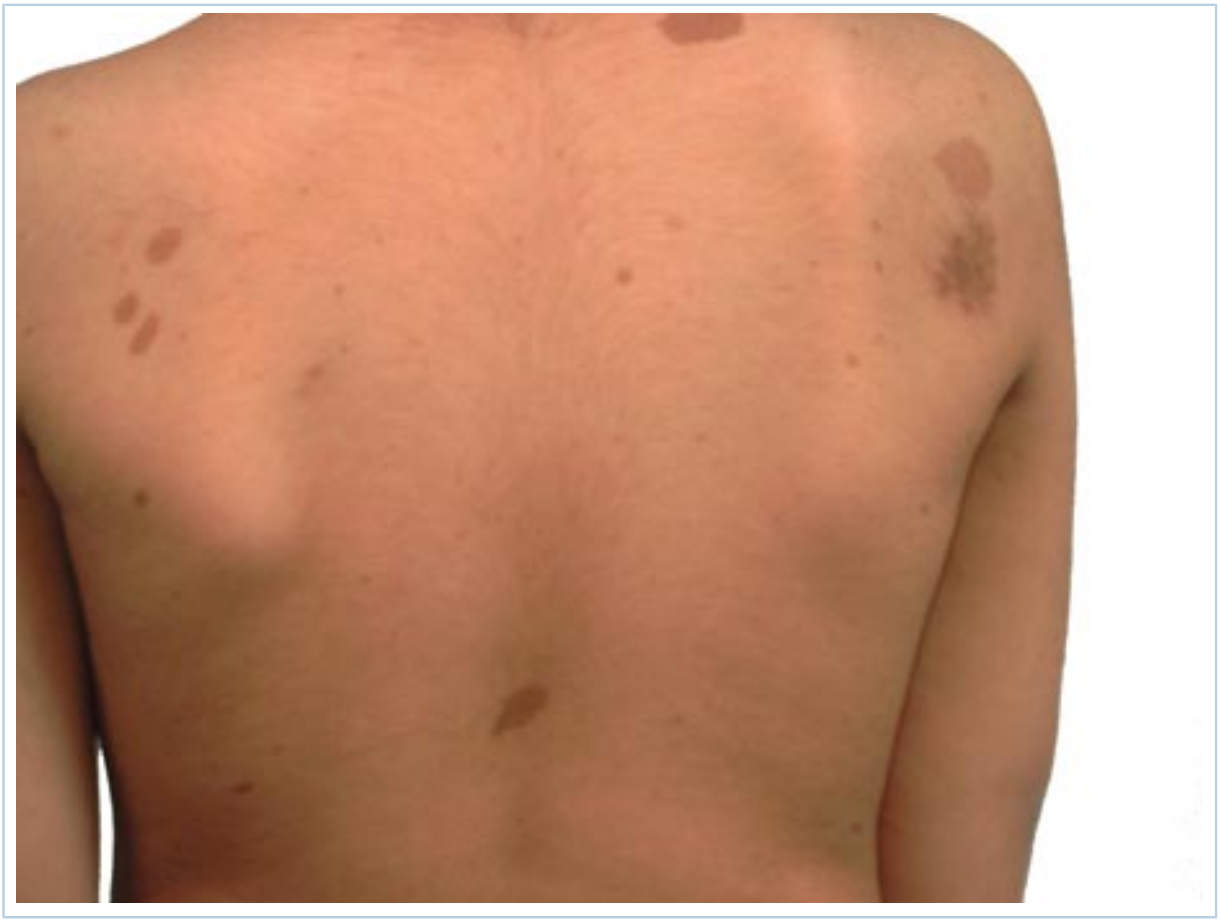
From the collection of Dr Murlidhar Rajagopalan

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's anaemia)



Café au lait spots on the back of a young boy

From the personal collection of Dr Vincent M. Riccardi; used with permission

Musculoskeletal examination

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

Signs associated with HIV disease

- Morbilliform rash early
- Kaposi's sarcoma, ulcerating nodules later

Inherited bone marrow failure syndromes (IBMFS) may have characteristic bony, renal, and other congenital abnormalities, or pulmonary or cutaneous abnormalities. A search for these should not be part of an initial work-up but, if found on images obtained for other reasons, should prompt further consideration of IBMFS as the aetiology of pancytopenia. The absence of physical anomalies does not rule out an IBMFS.

Laboratory

A full blood count and examination of peripheral blood film by a haematologist are essential. A standard battery of evaluative tests may include:

- Serum reticulocyte count
- Serum liver function tests 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's anaemia: diepoxybutane (DEB) test for chromosomal breakage in peripheral blood lymphocytes
- Lymphoproliferative disorders: immunophenotyping, cytogenetics, lymph node biopsy
- Multiple myeloma: immunoelectrophoresis
- Paroxysmal nocturnal haemoglobinuria (PNH): peripheral blood immunophenotyping for deficiency of phosphatidylinositol-glycan-linked molecules on peripheral blood cells (e.g., CD16, CD55, CD59)
- Cytomegalovirus 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 enzyme-linked immunosorbent assay (ELISA)
- Rare genetic and metabolic disease: leukocyte glucocerebrosides

Further specific tests include:

- Serum prostate-specific antigen in suspect cases of prostatic malignancy
- Telomere length
- Genetic analysis involving tests for individual disorders based upon clinical suspicion, or newer panels (many currently in development) to evaluate for mutations and deletions. Germline mutations may be absent in peripheral blood lymphocytes due to mosaicism; consider skin fibroblasts for genetic analysis if there is a strong suspicion of a germline mutation.[22]

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 examination 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, haemophagocytosis, and infection [e.g., Leishman-Donovan bodies])
- Immunophenotype (acute and chronic leukaemias, lymphoproliferative disorders)
- Cytogenetics (myelodysplasia [MDS], acute and chronic leukaemias, lymphoproliferative disorders).

Bone marrow trephine biopsy permits specific examination of cellularity:

- Normal or increased in MDS, acute and chronic leukaemia, myeloma with plasma cells, carcinomatosis marrow infiltration, peripheral destruction/sequestration conditions, early HIV disease, and megaloblastic anaemia
- Decreased after chemotherapy, acute infection/sepsis, advanced HIV disease, hypoplastic myelodysplastic syndrome, congenital/inherited BMFS, idiopathic aplastic anaemia, SLE, and PNH.

Trephine biopsy also permits examination of histology and evaluation for:

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

In the developed world, it has been proposed that the most likely aetiology of new onset pancytopenia, when investigated with bone marrow evaluation, is acute lymphoblastic leukaemia in children and acute myeloid leukaemia/myelodysplastic syndrome in adults.[23] In some other parts of the world (e.g., India), hypersplenism and infection may be the most frequent aetiologies of pancytopenia.[24]

Radiology

Abdominal ultrasound scan or computed tomography scan of the abdomen is indicated to evaluate for splenomegaly. Chest radiograph may reveal tumour 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. Inherited bone marrow failure syndromes may have characteristic bony, renal, or pulmonary abnormalities. A search for these should not be part of an initial work-up but, if found on images obtained for other reasons, should prompt further consideration of IBMFS as the aetiology of pancytopenia.

Differentials overview

Common
Chemotherapy
Radiotherapy
Vitamin B12 deficiency
Folic acid deficiency
Bone marrow infiltration by non-haematological malignancy
Non-Hodgkin's lymphoma
Hairy cell leukaemia
Chronic lymphocytic leukaemia
Myelodysplasia
Cirrhosis
Seronegative (idiopathic) hepatitis (likely autoimmune)
Hepatitis B
Hepatitis C
Autoimmune hepatitis
HIV
Cytomegalovirus infection
Mycobacterial infection

Uncommon
Acute myeloid leukaemia
Acute lymphocytic leukaemia (ALL)
Multiple myeloma

Uncommon
Myelofibrosis
Lysosomal storage disorders
Anorexia nervosa
Graft-versus-host disease (GVHD)
Heavy metal (arsenic) poisoning
Parvovirus infection in sickle cell anaemia (and other haemolytic anaemias)
Dyskeratosis congenita (DC)
Paroxysmal nocturnal haemoglobinuria (PNH)
Idiopathic aplastic anaemia
Fanconi's anaemia
Other rare inherited cytopenias (e.g., Diamond-Blackfan anaemia, Shwachman-Diamond syndrome, amegakaryocytic thrombocytopenia)
Idiopathic portal hypertension
Chronic myeloid leukaemia
Brucellosis
Leishmaniasis
Haemophagocytosis syndromes
Drug-induced immune pancytopenia
Evans syndrome with associated neutropenia
Autoimmune lymphoproliferative syndrome (ALPS)
Systemic lupus erythematosus
Rheumatoid arthritis
Infectious mononucleosis

Uncommon

Felty syndrome

Differentials

Common

◊ Chemotherapy

History	Exam	1st Test	Other tests
transient pancytopenia associated with chemotherapeutic agents	nausea and vomiting, hair loss, easy bruising, bleeding, pallor, fever, rigors	»**peripheral blood:** irregular size and shape of red blood cells (anisocytosis and poikilocytosis), basophilic stippling	»**bone marrow aspirate:** variable hypoplasia Order if extended delay in recovery (which may suggest a relapse). »**bone marrow biopsy:** hypoplasia, megaloblastosis Order if extended delay in recovery (which may suggest a relapse).

◊ Radiotherapy

History	Exam	1st Test	Other tests
transient pancytopenia associated with radiotherapy	nausea and vomiting, hair loss, easy bruising, bleeding, pallor, fever, rigors	»**peripheral blood:** irregular size and shape of red blood cells (anisocytosis and poikilocytosis), basophilic stippling	»**bone marrow aspirate:** variable hypoplasia Order if extended delay in recovery (which may suggest a relapse). »**bone marrow biopsy:** hypoplasia, megaloblastosis Order if extended delay in recovery (which may suggest a relapse).

◊ Vitamin B12 deficiency

History	Exam	1st Test	Other tests
may be a history of autoimmune disorders, vegan diet, total or partial gastrectomy, ileal resection, or	glossitis and angular stomatitis, easy bruising or spontaneous bleeding (rare), peripheral	»**peripheral blood film:** oval macrocytic red blood cells (RBCs), irregular size and shape of RBCs (anisocytosis	»**intrinsic factor antibody:** may be positive order if pernicious anaemia is suspected

Common

◊ Vitamin B12 deficiency

History	Exam	1st Test	Other tests
coeliac disease; gradual onset of fatigue	sensory loss, balance and gait disturbance	and poikilocytosis), hypersegmented granulocytes (>5 lobes) RBC mean volume usually normal at presentation due to gross anisocytosis. »**serum reticulocyte count:** usually low »**serum B12:** low in B12 deficiency »**bone marrow aspirate:** hypercellular, megaloblastic erythroblasts, giant metamyelocytes »**serum LDH:** moderately raised »**serum bilirubin:** moderately raised, mostly indirect	

◊ Folic acid deficiency

History	Exam	1st Test	Other tests
may be a history of diet poor in green vegetables, ileal resection, pregnancy with hyperemesis; gradual onset of fatigue	glossitis and angular stomatitis, easy bruising or spontaneous bleeding (rare), peripheral sensory loss, balance and gait disturbance	»**peripheral blood film:** oval macrocytic red blood cells (RBCs), irregular size and shape of RBCs (anisocytosis and poikilocytosis), hypersegmented granulocytes (>5 lobes) RBC mean volume usually normal at presentation due to gross anisocytosis. »**serum reticulocyte count:** usually low »**serum RBC folate:** low in folate deficiency	

Common

◊ Folic acid deficiency

History	Exam	1st Test	Other tests
		»**bone marrow aspirate:** hypercellular, megaloblastic erythroblasts, giant metamyelocytes »**serum LDH:** moderately raised »**serum bilirubin:** moderately raised, mostly indirect	

Bone marrow infiltration by non-haematological malignancy

History	Exam	1st Test	Other tests
may be a history of breast, prostate, lung, thyroid, kidney, gastrointestinal malignancy or metastatic melanoma in adults; neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma, retinoblastoma in children; weight loss, anorexia, fatigue	cachexia, finger clubbing, breast lump, lymphadenopathy, enlarged irregular prostate, abdominal mass	»**peripheral blood film:** leuko-erythroblastic cell forms »**bone marrow aspirate:** clumps of tumour cells Aspirate may be dry (non-diagnostic) or normal when infiltration is detectable on the trephine roll or trephine biopsy.[25] »**chest x-ray:** mass (lung cancer) »**serum liver function tests:** elevated alanine aminotransferase and aspartate aminotransferase (hepatic metastases) »**serum coagulation profile:** prolonged prothrombin time and partial thromboplastin time »**serum fibrinogen and D-dimer:** diminished fibrinogen and elevated D-	»**CT of abdomen:** may reveal abdominal or renal mass »**serum prostatic-specific antigen:** elevated in prostate cancer »**thyroid ultrasound:** irregular mass or nodule »**breast imaging:** mass or calcifications

Common

Bone marrow infiltration by non-haematological malignancy

History	Exam	1st Test	Other tests
		dimer (indicative of chronic disseminated intravascular coagulation) Common in mucin-secreting adenocarcinoma (e.g., prostate).	

Non-Hodgkin's lymphoma

History	Exam	1st Test	Other tests
gradual onset of fatigue, weight loss, lymphadenopathy, fever, rigors, respiratory distress, abdominal distention	cachexia, lymphadenopathy, hepatosplenomegaly	»**peripheral blood film:** variable; may show circulating lymphoma cells »**bone marrow aspirate:** increased proportion of lymphoid cells »**immunophenotyping (of peripheral blood or bone marrow):** clonal population of lymphoid cells »**lymph node biopsy:** lymphoproliferative disorder	

Hairy cell leukaemia

History	Exam	1st Test	Other tests
gradual onset of fatigue, weight loss, lymphadenopathy, fever, rigors, respiratory distress, abdominal distention	cachexia, lymphadenopathy, hepatosplenomegaly	»**peripheral blood film:** presence of hairy cells Absent monocytes suggests hairy cell leukaemia, circulating lymphoid cells may have characteristic morphology.[28]	

Common

Hairy cell leukaemia

History	Exam	1st Test	Other tests
		»**bone marrow aspirate:** increased proportion of lymphoid cells »**immunophenotyping (of peripheral blood or bone marrow):** clonal population of lymphoid cells	

Chronic lymphocytic leukaemia

History	Exam	1st Test	Other tests
gradual onset of fatigue, weight loss, lymphadenopathy, fever, rigors, respiratory distress, abdominal distention	cachexia, lymphadenopathy, hepatosplenomegaly	»**peripheral blood film:** circulating leukaemia cells »**bone marrow aspirate:** increased proportion of lymphoid cells »**immunophenotyping (of peripheral blood or bone marrow):** clonal population of lymphoid cells	»**lymph node biopsy:** lymphoproliferative disorder

Myelodysplasia

History	Exam	1st Test	Other tests
incidental presentation common, gradual onset of fatigue, shortness of breath, recurrent infection, easy bruising, spontaneous mucosal bleeding, abdominal fullness	pallor, oedema, purpura, or petechiae	»**peripheral blood film:** may have irregular or macrocytic red blood cells, dysplastic granulocytes, platelets may be large and hypogranular »**serum reticulocyte count:** usually low, may be normal or raised »**bone marrow aspirate:** usually hypercellular, rarely, hypocellular	»**cytogenetics:** may be abnormal Cytogenetic abnormalities can be detected in 40% to 70% of de novo MDS cases, and 95% of secondary MDS cases.[29]

Common

Myelodysplasia

History	Exam	1st Test	Other tests
		(hypocellular myelodysplasia [MDS]), dysplastic changes	

◊ Cirrhosis

History	Exam	1st Test	Other tests
liver disease secondary to viral, autoimmune, or alcoholic hepatitis	pallor, jaundiced sclerae, abdominal distension, ascites, hepatosplenomegaly	»**peripheral blood film:** macrocytes, target cells, stomatocytes, acanthocytes »**reticulocyte count:** elevated or normal »**serum liver function tests:** elevated	»**bone marrow aspirate:** hypercellular, erythroid hyperplasia

◊ Seronegative (idiopathic) hepatitis (likely autoimmune)

History	Exam	1st Test	Other tests
no antecedent history	pallor, jaundice	»**peripheral blood film:** macrocytes, target cells, stomatocytes, acanthocytes »**reticulocyte count:** elevated or normal »**serum liver function tests:** elevated »**viral hepatitis serology:** absence of anti-hepatitis B or C virus antibodies	»**bone marrow aspirate:** hypercellular, erythroid hyperplasia

◊ Hepatitis B

History	Exam	1st Test	Other tests
intravenous drug use	pallor, jaundice, abdominal	»**peripheral blood film:** macrocytes, target	»**bone marrow aspirate:** hypercellular, erythroid hyperplasia

Common

◊ Hepatitis B

History	Exam	1st Test	Other tests
	pain, ascites, hepatosplenomegaly	cells, stomatocytes, acanthocytes »**reticulocyte count:** elevated or normal »**serum liver function tests:** elevated »**serum HBsAg:** positive	

◊ Hepatitis C

History	Exam	1st Test	Other tests
intravenous drug use or transfusion, fatigue, myalgia, arthralgia	pallor, jaundice, ascites, spider haemangiomata	»**peripheral blood film:** macrocytes, target cells, stomatocytes, acanthocytes »**reticulocyte count:** elevated or normal »**serum liver function tests:** elevated »**serum anti-hepatitis C virus (HCV):** presence of HCV antibodies	»**bone marrow aspirate:** hypercellular, erythroid hyperplasia

◊ Autoimmune hepatitis

History	Exam	1st Test	Other tests
fatigue, malaise, anorexia, nausea, pruritus	pallor, jaundice, ascites, hepatosplenomegaly, encephalopathy	»**peripheral blood film:** macrocytes, target cells, stomatocytes, acanthocytes »**reticulocyte count:** elevated or normal »**serum liver function tests:** elevated »**autoantibody screen:** positive	»**bone marrow aspirate:** hypercellular, erythroid hyperplasia

Common

◊ HIV

History	Exam	1st Test	Other tests
HIV disease or risk factors, influenza-like illness (acute seroconversion), fatigue, easy bruising, spontaneous bleeding, fever, rigors (chronic HIV disease)	cachexia, generalised lymphadenopathy, HIV-associated skin lesions (oral hairy leukoplakia, molluscum contagiosum, Kaposi's sarcoma)	»**peripheral blood film:** atypical lymphocytes (acute seroconversion), rouleaux, dysplastic neutrophils »**reticulocyte count:** reduced »**HIV serology:** positive »**bone marrow aspirate:** hypercellular (acute seroconversion), hypocellular, dyserythropoiesis	»**protein electrophoresis:** polyclonal hypergammaglobulinaemia

◊ Cytomegalovirus infection

History	Exam	1st Test	Other tests
fever, malaise, arthralgia, tender lymphadenopathy, pharyngitis	fever, generalised tender lymphadenopathy, pharyngeal exudates, mild splenomegaly, abdominal tenderness	»**peripheral blood film:** atypical lymphocytes, spherocytes if co-existing haemolysis »**cytomegalovirus-specific IgM and IgG:** positive »**bone marrow aspirate:** cellularity usually increased, haemophagocytosis may be prominent »**bone marrow trephine biopsy:** cellularity usually increased	

◊ Mycobacterial infection

History	Exam	1st Test	Other tests
HIV disease or other chronic immunosuppression,	cachexia, lymphadenopathy	»**peripheral blood film:** rouleaux »**reticulocyte count:** reduced	

Common

◊ Mycobacterial infection

History	Exam	1st Test	Other tests
fever, weight loss, skin lesions, cough		»**bone marrow aspirate:** reduced cellularity, haemophagocytosis »**bone marrow trephine biopsy:** reduced cellularity, granulomas, fibrosis »**bone marrow culture:** positive for organism	

Uncommon

Acute myeloid leukaemia

History	Exam	1st Test	Other tests
more common in older adults (but could be any age); rapid onset of fatigue, shortness of breath, fever, rigors	lymphadenopathy, hepatosplenomegaly, mucosal bleeding	»**peripheral blood film:** blasts on blood film, presence of Auer's rods »**serum prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, D-dimer:** may be abnormal; suspect disseminated intravascular coagulation »**bone marrow aspiration:** usually hypercellular with blasts, rarely hypocellular Acute promyelocytic leukaemia most commonly presents with pancytopenia.[26] Diagnosis of acute leukaemia can be made with less than 20% blasts in the bone marrow in	

Uncommon

Acute myeloid leukaemia

History	Exam	1st Test	Other tests
		erythroleukaemia or when a characteristic chromosomal abnormality is detected.[27] Rarely, the bone marrow may be hypocellular. Immunophenotyping is essential to differentiate hypoplastic acute leukaemia from aplastic anaemia. »**bone marrow biopsy:** presence of blasts, infiltration, Auer's rods »**immunophenotyping:** detection of clonal population of blasts »**cytogenetics:** identification or non-random chromosomal abnormalities	

Acute lymphocytic leukaemia (ALL)

History	Exam	1st Test	Other tests
rapid onset of fatigue, shortness of breath, fever, rigors	fever, lymphadenopathy, hepatosplenomegaly, gum infiltration, pallor, petechiae, purpura; papilloedema, nuchal rigidity, and meningismus	»**peripheral blood film:** blasts may or may not be present »**bone marrow aspirate:** hypercellular with blasts; occasionally hypocellular (childhood ALL)	»**immunophenotyping (of peripheral blood or bone marrow):** detection of clonal population of blasts »**cytogenetics:** identification of non-random chromosomal abnormalities

Uncommon

Multiple myeloma

History	Exam	1st Test	Other tests
gradual onset of fatigue, weight loss, fever, rigors, back pain, constipation (due to hypercalcaemia), bone pain	pallor, vertebral collapse; less commonly hyperviscosity syndrome (purpura, visual defects, confusion, neuropathy)	»**peripheral blood film:** rouleaux, circulating plasma cells may rarely be present »**bone marrow aspirate:** plasma cell infiltrate, abnormal plasma cells, plasmablasts »**immunophenotyping (of peripheral blood or bone marrow):** plasma cells exhibit restriction of kappa or lambda light chain expression »**serum and urine electrophoresis:** monoclonal serum protein and urinary Bence Jones proteins (light chains) detected	»**radiological skeletal survey:** lytic lesions and/or osteopenia

Myelofibrosis

History	Exam	1st Test	Other tests
gradual onset of fatigue, weight loss, fever, night sweats, left upper quadrant discomfort	cachexia, pallor, splenomegaly, hepatomegaly	»**peripheral blood film:** leuko-erythroblastic, teardrop-shaped red blood cells »**bone marrow aspirate:** hypercellular and fibrotic, often dry tap and non-diagnostic	»**serum and red blood cell folate:** usually diminished »**serum B12:** usually elevated

◊ Lysosomal storage disorders

History	Exam	1st Test	Other tests
gradual onset of fatigue, fever, rigors, bone pain, abdominal discomfort, fractures, spontaneous bruising, or mucosal bleeding	pallor, splenomegaly or hepatosplenomegaly, purpura and petechiae	»**leukocyte glucocerebroside activity:** reduced or absent »**peripheral blood film:** pancytopenia	»**bleeding time:** prolonged

Uncommon

◊ Lysosomal storage disorders

History	Exam	1st Test	Other tests
		»**reticulocyte count:** may be high, normal, or reduced »**bone marrow aspirate:** may reveal Gaucher's cells	

◊ Anorexia nervosa

History	Exam	1st Test	Other tests
may be a prior history of eating disorder, distorted body image and self-harming behaviour, amenorrhoea	decreased body mass index, parotid swelling, lanugo hair, bradycardia, hypotension	»**peripheral blood film:** red cell acanthocytes, poikilocytosis and basophilic stippling »**reticulocyte count:** low »**bone marrow aspirate:** hypocellular, reduced haematopoietic cells, may show gelatinous transformation »**bone marrow trephine biopsy:** hypocellular without infiltration or fibrosis »**diepoxybutane test:** normal	

Graft-versus-host disease (GVHD)

History	Exam	1st Test	Other tests
non-irradiated cellular product transfusion in immunocompromised patient, fatigue, spontaneous bruising and/or mucosal bleeding, fever, diarrhoea	rash (particularly hands and feet), jaundice, pallor, purpura, petechiae	»**peripheral blood film:** no specific features »**reticulocyte count:** low »**bone marrow aspirate:** hypocellular, reduced haematopoietic cells, increased	

Uncommon

Graft-versus-host disease (GVHD)

History	Exam	1st Test	Other tests
		macrophages, erythrophagocytosis »**bone marrow trephine biopsy:** hypocellular without infiltration or fibrosis, increased macrophages »**skin, liver, upper gastrointestinal biopsy:** characteristic appearances of acute GVHD »**HLA typing of peripheral blood lymphocytes:** chimerism Definitive diagnostic test.	

◊ Heavy metal (arsenic) poisoning

History	Exam	1st Test	Other tests
environmental exposure (wood, glass production, semiconductor industry, smelting, pesticides), headaches, abdominal pain	pallor, jaundice, signs of portal hypertension may be present	»**peripheral blood film:** basophilic stippling »**bone marrow aspirate:** hypocellular without infiltrate or fibrosis, decreased haematopoietic cells, dyserythropoiesis »**bone marrow trephine biopsy:** hypocellular without infiltration or fibrosis dyserythropoiesis »**diepoxybutane test:** normal »**screening for paroxysmal nocturnal haemoglobinuria clone:** negative	

Uncommon

◊ Heavy metal (arsenic) poisoning

History	Exam	1st Test	Other tests
		»**arsenic level (serum, urine, hair, nails):** elevated Serum and urine levels only indicative of recent exposure. Hair/nail arsenic levels indicative of exposure over prior 6 to 9 months.	

◊ Parvovirus infection in sickle cell anaemia (and other haemolytic anaemias)

History	Exam	1st Test	Other tests
weakness, and lethargy secondary to associated aplastic crisis	pallor, rash	»**FBC:** drop in haemoglobin concentration of >30 percent secondary to complete arrest of erythropoiesis »**reticulocyte count:** decrease or absence of measurable reticulocytes »**bone marrow biopsy:** remarkable for severe aplasia	

◊ Dyskeratosis congenita (DC)

History	Exam	1st Test	Other tests
presents in the third or fourth decade of life, fatigue, spontaneous bruising and mucosal bleeding, fever, rigors (less common), chronic tearing, difficulty with urination	nail and skin atrophy, blocked tear ducts, urethral meatal stenosis, reticulated skin pigmentation, pallor, purpura, petechiae	»**peripheral blood film:** red cells usually macrocytic »**reticulocyte count:** low or absent »**bone marrow aspirate:** hypocellular, reduced haematopoietic cells, dyserythropoiesis common	»**genetic studies:** may identify 1 of several genetic mutations Dyskeratosis congenita is genetically heterogeneous and in many cases the genetic lesion has not been identified. Aplasia only occurs in

Uncommon

◊ Dyskeratosis congenita (DC)

History	Exam	1st Test	Other tests
		»**bone marrow trephine biopsy:** hypocellular without infiltration or fibrosis »**diepoxybutane test:** normal (peripheral blood lymphocytes) »**screening for paroxysmal nocturnal haemoglobinuria (PNH) clone:** may be present Presence of a PNH clone is established by demonstration of glycosyl phosphatidylinositol (GPI)-linked protein deficiencies on red blood cell and neutrophil surfaces by multiparameter flow cytometry.[30] »**peripheral blood and/or bone marrow immunophenotyping:** normal »**blood and/or bone marrow cytogenetics:** clonal abnormalities present in some patients	X-linked and autosomal recessive forms of DC. In kindreds where the genetic lesion is known, screening of potential related haematopoietic stem cell donors is useful.[13] »**telomere length:** abnormally short; length in lymphocytes and granulocytes <1 percentile for age

◊ Paroxysmal nocturnal haemoglobinuria (PNH)

History	Exam	1st Test	Other tests
previous venous thrombosis, fatigue, intermittent abdominal pain and dark urine, blood in stool	pallor, jaundice, portal hypertension	»**peripheral blood film:** polychromasia »**reticulocyte count:** relative reticulocytosis »**bone marrow aspirate:** hypocellular, reduced	»**diepoxybutane test:** normal »**screening for PNH clone:** positive Presence of a PNH clone is established

Uncommon

◊ Paroxysmal nocturnal haemoglobinuria (PNH)

History	Exam	1st Test	Other tests
		haematopoietic cells, mast cells may be increased	by demonstration of glycosyl phosphatidylinositol (GPI)-linked protein deficiencies on red blood cell and neutrophil surfaces by flow cytometry.[30]

Idiopathic aplastic anaemia

History	Exam	1st Test	Other tests
prior non-A, B, or C hepatitis, exposure to drugs; rapid onset of fatigue, fever, rigors, spontaneous bruising, mucosal bleeding	pallor, oedema, purpura, petechiae, stomatitis	»**peripheral blood film:** normocytic or mildly macrocytic red blood cells, no immature precursors present »**serum reticulocyte count:** low or absent »**bone marrow aspirate:** hypocellular, mild dyserythropoiesis common »**bone marrow trephine biopsy:** hypocellular without fibrosis or infiltrate »**diepoxybutane (DEB) test (peripheral blood lymphocytes):** normal DEB test for chromosomal breakage should be performed on all patients under the age of 50 years to exclude Fanconi's anaemia, and on all patients who are being considered for	»**genetic testing:** may identify genetic abnormality Complete evaluation for all genetic causes of inherited bone marrow failure syndromes may be done, if available.

DIAGNOSIS

Uncommon

Idiopathic aplastic anaemia

History	Exam	1st Test	Other tests
		haematopoietic stem cell transplantation.[31] »**screening for paroxysmal nocturnal haemoglobinuria (PNH) clone:** may be detectable in up to 30% of patients Presence of a PNH clone is established by demonstration of glycosyl phosphatidylinositol (GPI)-linked protein deficiencies on red blood cell and neutrophil surfaces by flow cytometry.[30] »**peripheral blood, bone marrow immunophenotyping:** normal »**peripheral blood, bone marrow cytogenetics:** abnormal clones present in a minority of patients	

◊ Fanconi's anaemia

History	Exam	1st Test	Other tests
thrombocytopenia, leukopenia preceding pancytopenia, prior cardiac or genitourinary abnormalities, fatigue, spontaneous bruising and mucosal bleeding, fever, rigors; may have long history of abnormal findings	short stature, structural abnormalities of upper and lower limbs, eyes, ears, gonads; hyperpigmentation, café au lait spots, purpura, petechiae	»**peripheral blood film:** red blood cells usually macrocytic »**reticulocyte count:** low or absent »**bone marrow aspirate:** hypocellular dyserythropoiesis »**diepoxybutane test (peripheral**	»**genetic testing:** may identify genetic abnormality

Uncommon

◊ Fanconi's anaemia

History	Exam	1st Test	Other tests
		blood lymphocytes): increased chromosomal breakage	

◊ Other rare inherited cytopenias (e.g., Diamond-Blackfan anaemia, Shwachman-Diamond syndrome, amegakaryocytic thrombocytopenia)

History	Exam	1st Test	Other tests
anaemia and/or thrombocytopenia, leukopenia preceding pancytopenia, prior congenital anomalies characteristic of any of these syndromes (e.g., cardiac, skeletal, genitourinary, orofacial); fatigue, spontaneous bruising and mucosal bleeding, fever, rigors; may have a long history of abnormal findings in particular single cell cytopenias	short stature, characteristic structural abnormalities of upper and lower limbs, eyes, and ears; pallor, purpura, petechiae	»**peripheral blood film:** red blood cells usually macrocytic »**reticulocyte count:** low or absent »**bone marrow aspirate:** hypocellular dyserythropoiesis »**fetal haemoglobin and erythrocyte adenosine deaminase activity (Diamond-Blackfan anaemia):** elevated »**pancreatic enzymes:** abnormal (in particular stool elastase; Shwachman-Diamond syndrome)	»**genetic testing:** may identify genetic abnormality Panels that encompass all known syndromes are being developed and improved to evaluate for mutations and deletions.

◊ Idiopathic portal hypertension

History	Exam	1st Test	Other tests
gastrointestinal bleeding secondary to oesophageal varices, no history of liver disease	pallor, ascites, splenomegaly, hepatomegaly, oedema	»**peripheral blood film:** no specific features »**reticulocyte count:** elevated or normal »**serum liver function tests:** normal or mildly elevated	»**bone marrow aspirate:** hypercellular, erythroid hyperplasia »**bone marrow trephine biopsy:** hypercellular, erythroid hyperplasia

Uncommon

Chronic myeloid leukaemia

History	Exam	1st Test	Other tests
fever, chills, malaise, weight loss, anorexia	splenomegaly	»**peripheral blood film:** myeloid maturing cells, elevated basophils, eosinophils »**cytogenetics:** Philadelphia chromosome positive »**bone marrow biopsy:** granulocytic hyperplasia	

◊ Brucellosis

History	Exam	1st Test	Other tests
travel to high risk areas (e.g., the Mediterranean Basin [Portugal, Spain, Southern France, Italy, Greece, Turkey, North Africa], Mexico, South and Central America, Eastern Europe, Asia, Africa, the Caribbean, the Middle East);[32] fever; myalgia	splenomegaly, hepatomegaly, pallor, purpura, petechiae	»**peripheral blood film:** no specific features »**bone marrow aspirate:** trilineage hypercellularity, haematophagocytosis »**blood and bone marrow cultures:** positive for organism	

◊ Leishmaniasis

History	Exam	1st Test	Other tests
fever, lymphadenopathy, skin discoloration	lymphadenopathy, splenomegaly, hepatomegaly, pallor, purpura, petechiae	»**peripheral blood film:** rouleaux; organisms rarely seen in peripheral blood film »**bone marrow aspirate:** trilineage hypercellularity; organisms may be seen within macrophages (Leishman-Donovan bodies) »**bone marrow trephine biopsy:** trilineage hypercellularity,	

Uncommon

◊ Leishmaniasis

History	Exam	1st Test	Other tests
		haematophagocytosis, small granulomata »**immunochromatographic or polymerase chain reaction-based tests on peripheral blood or bone marrow aspirate:** positive for organism	

◊ Haemophagocytosis syndromes

History	Exam	1st Test	Other tests
may be primary (e.g., haemophagocytic lymphohistiocytosis) or secondary to a systemic disorder (e.g., T-cell lymphoma), malaise, fatigue, erythematous skin rash, abdominal discomfort	fever, lymphadenopathy, hepatosplenomegaly, neurological findings in familial disorder (e.g., irritability, neck stiffness, hypotonia, hypertonia, convulsions, cranial nerve palsies, ataxia, haemiplegia, quadriplegia, blindness, coma)	»**peripheral blood film:** no specific features »**bone marrow aspirate:** trilineage hypercellularity, haematophagocytosis »**blood and bone marrow cultures:** positive for organism	»**autoimmune screen:** positive antinuclear antibodies (ANA) and anti-ds DNA Positive ANA and anti-ds DNA in systemic lupus erythematosus-related cases.[33] »**serum ferritin:** 22,470 picomol/L (>10,000 microgram/L or 10,000 ng/mL) A ferritin level over 22,470 picomol/L (10,000 microgram/L or 10,000 ng/mL) is 90% sensitive and 96% specific for haemophagocytic lymphohistiocytosis in children.[34] »**molecular genetic testing:** specific karyotype present 5 disease subtypes (FHL1 to FHL5) are described; four genes have been identified and characterised:

Uncommon

◊ Haemophagocytosis syndromes

History	Exam	1st Test	Other tests
			FHL1 (unknown gene), PRF1 (FHL2), UNC13D (FHL3), and STX11 (FHL4).[35]

◊ Drug-induced immune pancytopenia

History	Exam	1st Test	Other tests
drug ingestion (e.g., phenacetin, para-amino salicylic acid, rifampicin, sulfonamides), rapid onset of fatigue, easy bruising, spontaneous bleeding	pallor, purpura, petechiae, rarely mild splenomegaly, mild jaundice	»**platelet-specific antibodies:** positive »**peripheral blood film:** no specific features »**reticulocyte count:** elevated »**bone marrow aspirate:** hypercellular »**bone marrow trephine biopsy:** hypercellular	

◊ Evans syndrome with associated neutropenia

History	Exam	1st Test	Other tests
fatigue, dark urine, jaundice, easy bruising, spontaneous mucosal bleeding	pallor, purpura, petechiae; lymphadenopathy and hepatosplenomegaly, which may be subtle with a duration >6 months	»**peripheral blood film:** polychromasia, spherocytes »**reticulocyte count:** elevated »**direct antiglobulin test:** positive »**platelet, neutrophil-specific antibodies:** positive »**bone marrow aspirate:** normal or trilineage hypercellularity »**bone marrow trephine biopsy:** normal or trilineage hypercellularity	»**further tests for autoimmune lymphoproliferative syndrome (ALPS):** may be increased double-negative T cells; defective lymphocyte apoptosis; known ALPS-related germ-line pathological mutation or positive results from other functional assays A significant number of people with Evans syndrome have underlying ALPS.[16] [36] [37]

Uncommon

◊ Autoimmune lymphoproliferative syndrome (ALPS)

History	Exam	1st Test	Other tests
bicytopenia or pancytopenia, other organs (e.g., the liver) may cause symptoms, may be a family history; in children with autoimmune bicytopenia or pancytopenia (Evans syndrome), a diagnostic work-up for ALPS is strongly suggested[16] [36]	splenomegaly and/or lymphadenopathy for >6 months, which may be subtle	»**T-cell analysis:** increased double-negative T cells »**lymphocyte apoptosis:** may be defective »**genetic analysis:** ALPS-related germ-line mutation may be detected	

◊ Systemic lupus erythematosus

History	Exam	1st Test	Other tests
established connective tissue disorder, joint pain, swelling, fatigue, easy bruising	synovitis, joint deformity, malar rash, splenomegaly	»**peripheral blood film:** rouleaux »**autoimmune screen:** positive antinuclear antibodies and anti-DNA »**ultrasound of the abdomen:** splenomegaly »**bone marrow aspirate:** hypocellular, dysplastic changes, haematophagocytosis »**bone marrow trephine biopsy:** hypocellular, benign lymphoid aggregates, bone marrow fibrosis[38]	

◊ Rheumatoid arthritis

History	Exam	1st Test	Other tests
established connective tissue disorder, joint pain, swelling, fatigue, easy bruising	synovitis, joint deformity	»**peripheral blood film:** rouleaux	

Uncommon

◊ Rheumatoid arthritis

History	Exam	1st Test	Other tests
		»**autoimmune screen:** positive rheumatoid factor »**bone marrow aspirate:** hypocellular, dysplastic changes, haematophagocytosis »**bone marrow trephine biopsy:** hypocellular, benign lymphoid aggregates »**ultrasound of the abdomen:** splenomegaly	

◊ Infectious mononucleosis

History	Exam	1st Test	Other tests
malaise, headache, low-grade fever	tonsillitis, pharyngitis, cervical lymphadenopathy, nodal tenderness	»**serum monospot:** positive »**peripheral blood film:** atypical lymphocytes »**Epstein-Barr nuclear antibody:** present »**blood serology (specific IgM and IgG titres) for viral capsid antigen:** positive	

◊ Felty syndrome

History	Exam	1st Test	Other tests
rheumatoid arthritis, typically precedes other findings, may be long-standing (>10 years' duration)	splenomegaly	»**bone marrow biopsy:** myeloid hyperplasia with excess of immature forms »**autoimmune screen:** positive rheumatoid factor	

Uncommon

◊ Felty syndrome

History	Exam	1st Test	Other tests
		»**ultrasound of the abdomen:** splenomegaly	

Guidelines

Europe

Diagnosis and management of aplastic anaemia (https://b-s-h.org.uk/guidelines/guidelines/)

Published by: British Society for Haematology
Last published: 2017

International

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia (https://ashpublications.org/blood/article/127/20/2391/35255/The-2016-revision-to-the-World-Health-Organization)

Published by: World Health Organization
Last published: 2016

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Images

Classification	Congenital/inherited	Acquired	Acquired
Mechanism	**Decreased bone marrow production**	**Decreased bone marrow production**	**Increased destruction/sequestration**
Common	Gaucher's disease (marrow infiltration, splenomegaly) Fanconi's anaemia (bone marrow failure)	Cytotoxic chemotherapy Radiotherapy Megaloblastic anaemia Bone marrow infiltration Myelodysplasia Myelofibrosis Idiopathic aplastic anaemia	Liver disease Portal hypertension
		Connective tissue disorders (rheumatoid arthritis, SLE) Acute viral infections (CMV, EBV, HIV) HIV disease Mycobacterial infection	
Uncommon	Various childhood, metabolic, and complex multisystem disorders and inherited bone marrow failure syndromes (e.g., dyskeratosis congenita, congenital amegakaryocytic thrombocytopenia, Shwachman syndrome)	Paroxysmal nocturnal haemoglobinuria Anorexia nervosa Transfusion-associated GVHD Heavy-metal poisoning Infection (parvovirus B19 infection, HHV6 or CMV in transplant recipients, legionnaires' disease)	Hypersplenism secondary to myelo/lymphoproliferative disorders Haemophagocytic syndromes Drug-induced immune pancytopenia Evans syndrome with tricytopenia Infection (brucellosis, visceral leishmaniasis)

Figure 1: Table of aetiologies for pancytopenia (SLE: systemic lupus erythematosus, CMV: cytomegalovirus, EBV: Epstein-Barr virus, GVHD: graft-versus-host disease)

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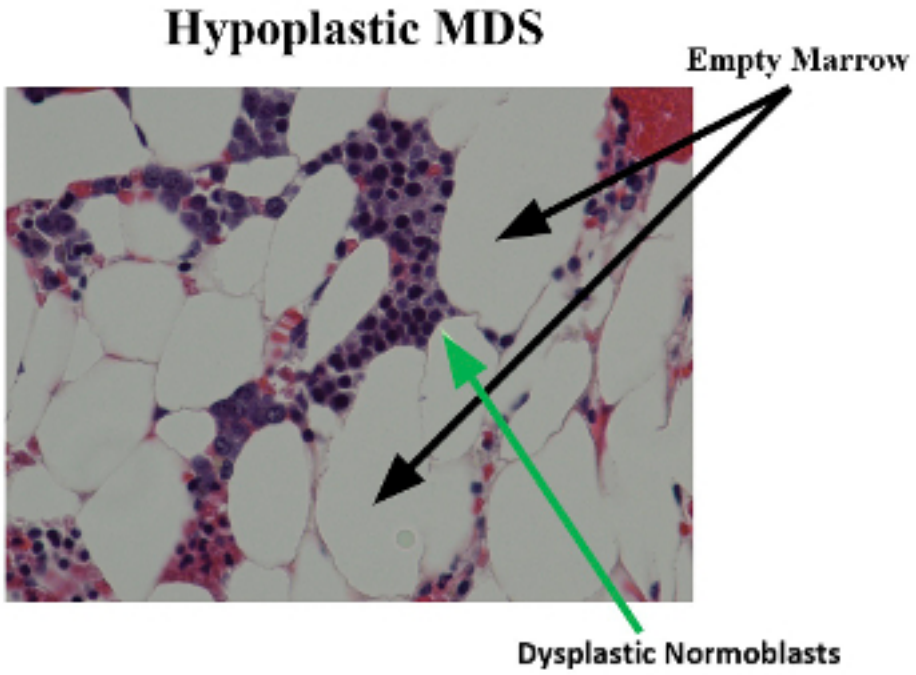

Figure 2: Hypoplastic myelodysplastic syndrome with dysplastic normoblasts

Morris Edelman, MD and Peihong Hsu, MD

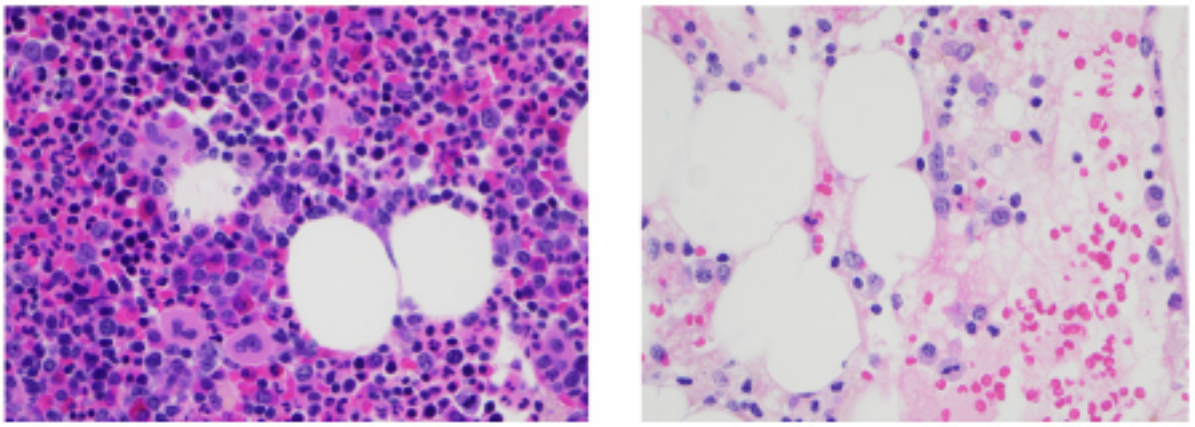

Figure 3: Aplastic anaemia: normocellular bone marrow is shown on the left; and empty marrow, typical of congenital or acquired aplastic anaemia, is shown on the right

Morris Edelman, MD and Peihong Hsu, MD

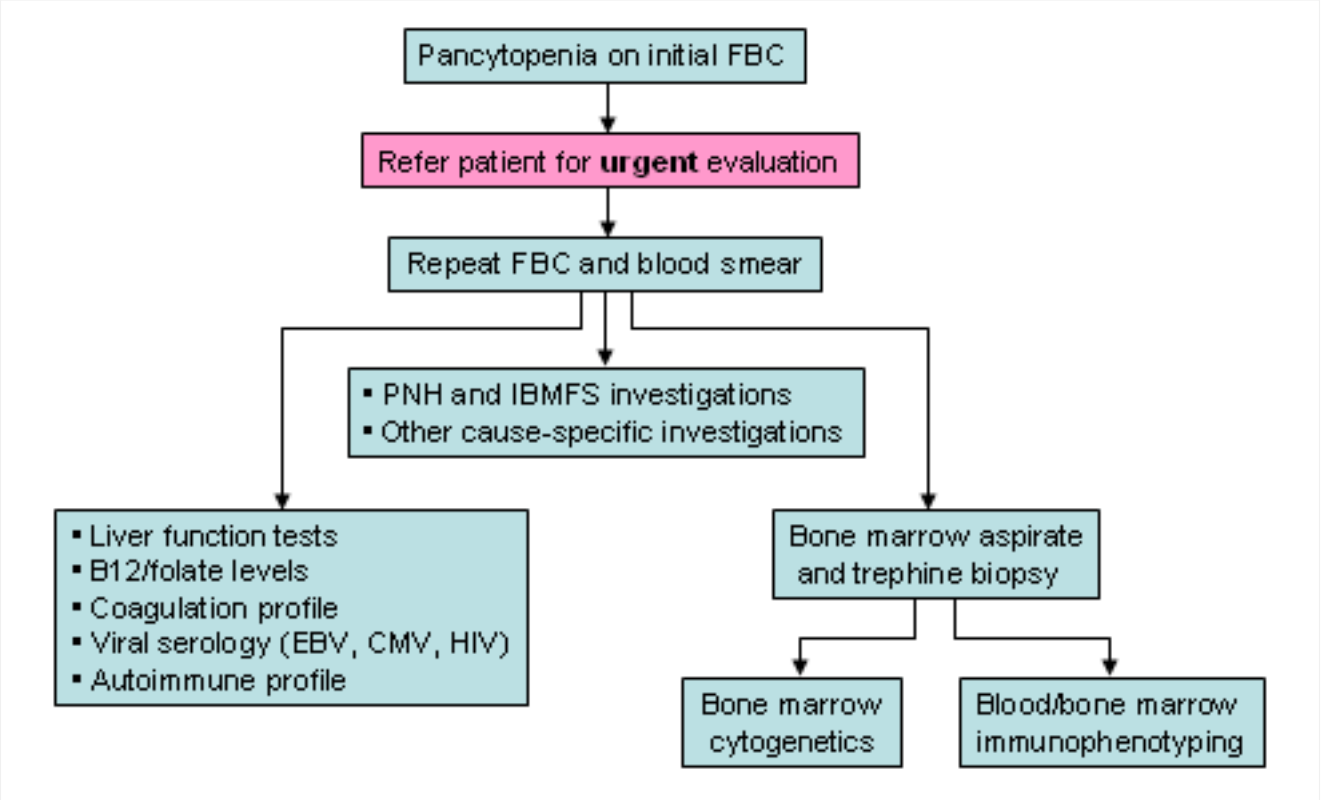

Figure 4: Flow diagram for evaluation of pancytopenia. Abbreviations: PNH, paroxysmal nocturnal haemoglobinuria; IBMFS, inherited bone marrow failure syndromes

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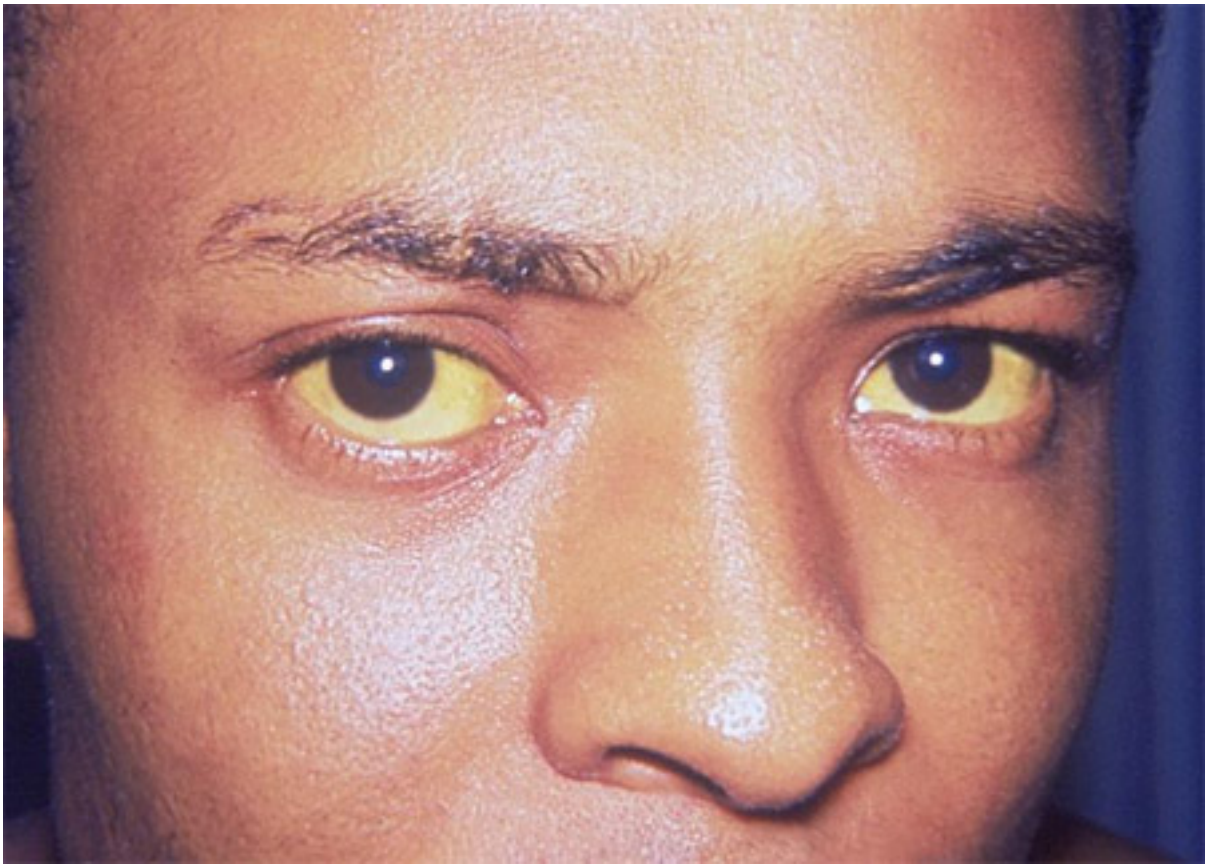

Figure 5: Icterus or jaundice

CDC. Dr Thomas F. Sellers/Emory University; used with permission

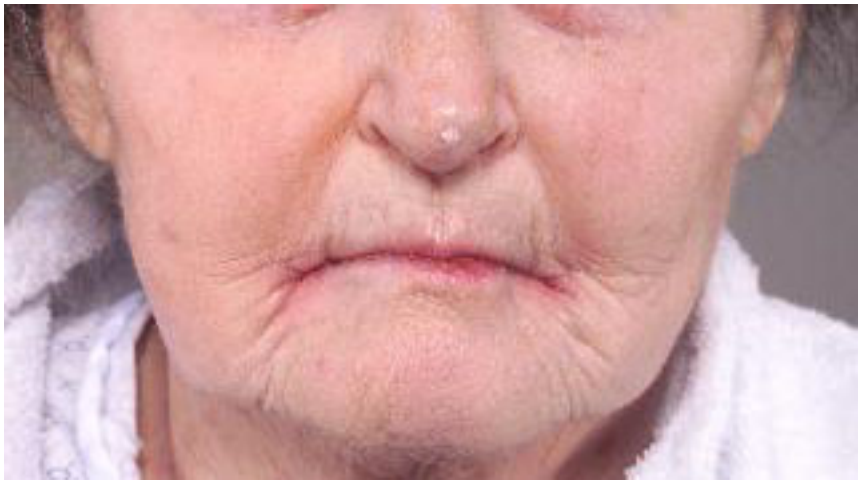

Figure 6: Angular cheilitis

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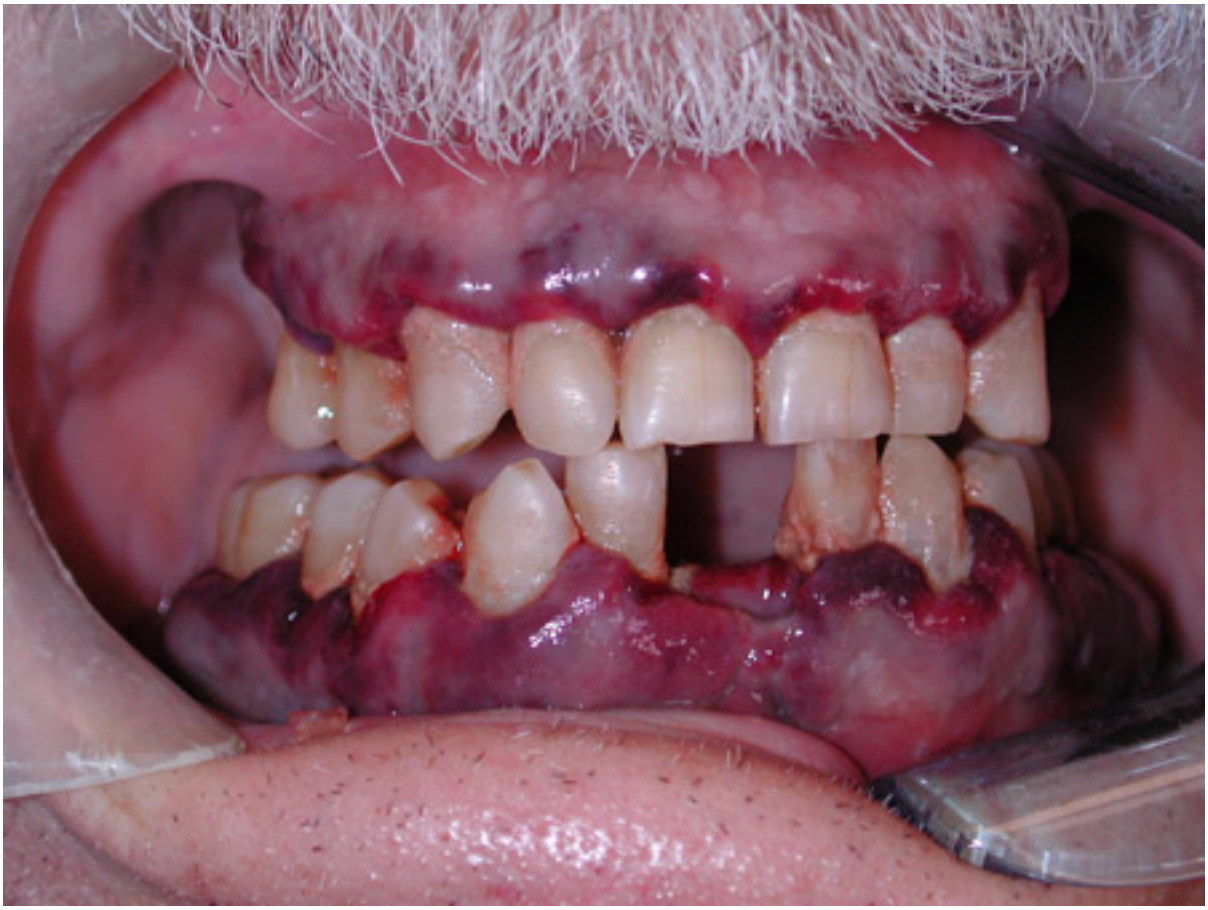

Figure 7: Gingival enlargement, petechiae and bleeding in acute myeloid leukaemia

Collection of Giuseppina Campisi, DDS, MS and Giuseppe Pizzo, DDS

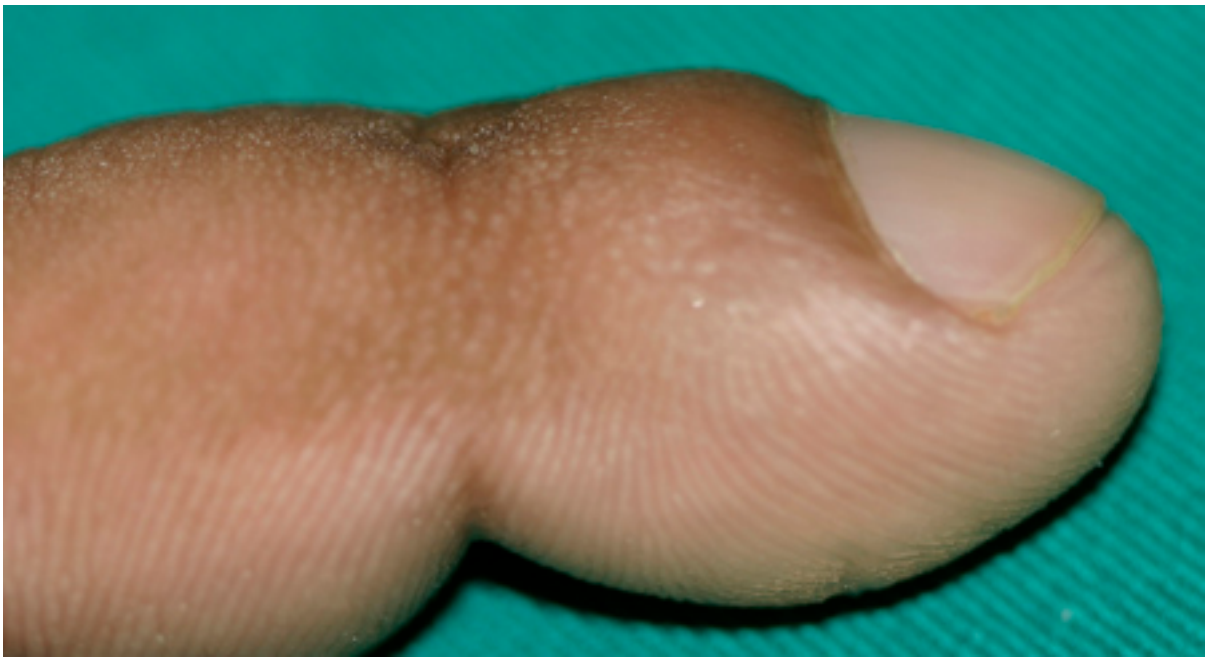

Figure 8: Clubbing of nails showing loss of the classic Lovibond's angle

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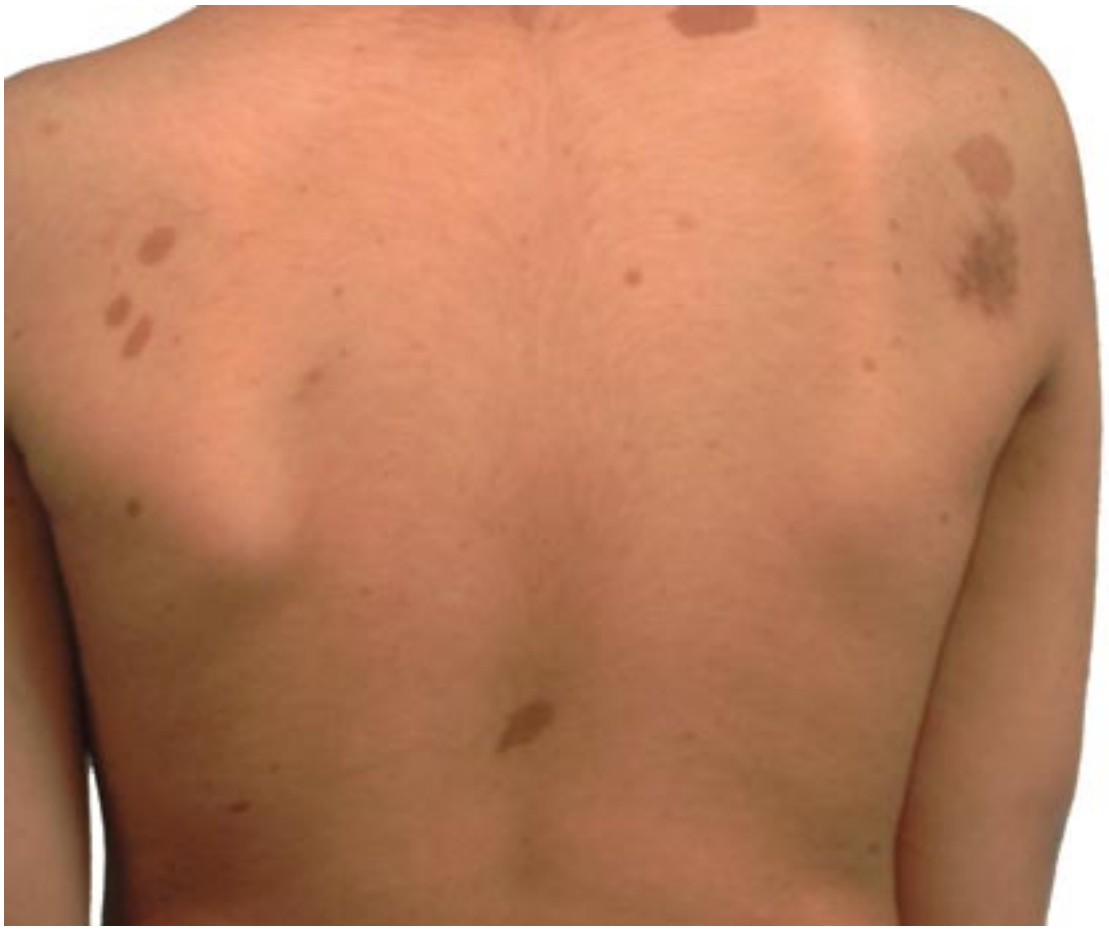

Figure 9: Café au lait spots on the back of a young boy

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Figure 1 – BMJ Best Practice Numeral Style

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