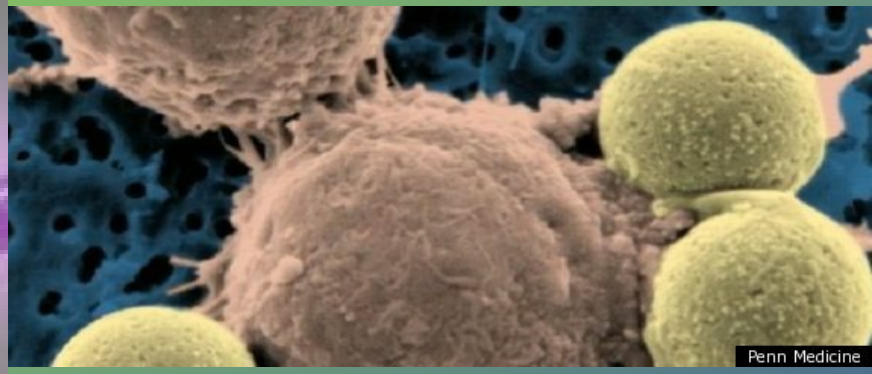


Dr. Mousa Qasim Hussein
Professor Internal Medicine

LEUKAEMIAS

are malignant disorders of the haematopoietic stem cell compartment, characteristically associated with increased numbers of white cells in the bone marrow and/or peripheral blood. The course of leukaemia may vary from a few days or weeks to many years, depending on the type

Epidemiology

- The incidence of leukaemia of all types in the population is approximately 10/100 000 per year, of which just under half are acute leukaemia.
- Males are affected more frequently than females, the ratio being about 3:2 in acute leukaemia, 2:1 in chronic lymphocytic leukaemia and 1.3:1 in chronic myeloid leukaemia.
- Acute lymphoblastic leukaemia shows a peak of incidence in the 1-5 age group.
- All forms of acute myeloid leukaemia have their lowest incidence in young adult life and there is a striking rise over the age of 50.
- Chronic leukaemias occur mainly in middle and old age .

Risk factors for leukaemia

The cause of the leukaemia is unknown in the majority of patients. Several factors, however, are associated with the development of leukaemia

Ionising radiation

•A significant increase in myeloid leukaemia followed the atomic bombing of Japanese cities
•An increase in leukaemia was observed after the use of radiotherapy for ankylosing spondylitis and diagnostic X-rays of the fetus in pregnancy

Cytotoxic drugs

•These, particularly alkylating agents, may induce myeloid leukaemia, usually after a latent period of several years
•Exposure to benzene in industry

Retroviruses

•One rare form of T-cell leukaemia/lymphoma appears to be associated with a retrovirus similar to the viruses causing leukaemia in cats and cattle

Genetic

•There is a greatly increased incidence of leukaemia in the identical twin of patients with leukaemia
•Increased incidence occurs in Down's syndrome and certain other genetic disorders

Immunological

•Immune deficiency states (e.g. hypogammaglobulinaemia) are associated with an increase in haematological malignancy

Terminology and classification

Leukaemias are traditionally classified into four main groups

- acute lymphoblastic leukaemia (ALL)
- acute myeloid leukaemia (AML)
- chronic lymphocytic leukaemia (CLL)
- chronic myeloid leukaemia (CML)

In acute leukaemia there is proliferation of primitive stem cells leading to an accumulation of blasts, predominantly in the bone marrow, which causes bone marrow failure.

In chronic leukaemia the malignant clone is able to differentiate, resulting in an accumulation of more mature cells.

Lymphocytic and lymphoblastic cells are those derived from the lymphoid stem cell (B cells and T cells).

Myeloid refers to the other lineages, i.e. precursors of red cells, granulocytes, monocytes and platelets

The diagnosis of leukaemia is usually suspected from an abnormal blood count, often a raised white count, and is confirmed by examination of the bone marrow. This includes:

1- the morphology of the abnormal cells,

2-analysis of cell surface markers (immunophenotyping)

3- clone-specific chromosome abnormalities and molecular changes.

The features in the bone marrow not only provide an accurate diagnosis but also give valuable prognostic information, allowing therapy to be tailored to the patient's disease.

ACUTE LEUKAEMIA

- There is a failure of cell maturation in acute leukaemia. Proliferation of cells which do not mature leads to an accumulation of useless cells which take up more and more marrow space at the expense of the normal haematopoietic elements. Eventually, this proliferation spills into the blood.
- Acute myeloid leukaemia is about four times more common than acute lymphoblastic leukaemia in adults.
- In children the proportions are reversed, the lymphoblastic variety being more common.

24.47 WHO classification of acute leukaemia

Acute myeloid leukaemia (AML) with recurrent genetic abnormalities

- AML with t(8;21), gene product AML-ETO
- AML with eosinophilia inv(16) or t(16;16), gene product CBFβ-MYH11
- Acute promyelocytic leukaemia t(15;17), gene product PML-RARA
- AML with t(9;11)(p22;q23), gene product MLLT3-MLL
- AML with t(6;9)(p23;q34), gene product DEK-NUP214
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2), gene product RPN1-EVI1

Acute myeloid leukaemia with myelodysplasia-related changes

- e.g. Following a myelodysplastic syndrome

Therapy-related myeloid neoplasms

- e.g. Alkylating agent or topoisomerase II inhibitor

Myeloid sarcoma

Myeloid proliferations related to Down's syndrome

Acute myeloid leukaemia not otherwise specified

- e.g. AML with or without differentiation, acute myelomonocytic leukaemia, erythroleukaemia, megakaryoblastic leukaemia, myeloid sarcoma

Acute lymphoblastic leukaemia (ALL)

- Precursor B ALL
- Precursor T ALL

ALL clinical features

Symptoms may appear insidiously or acutely.
Presenting features reflect the degree of marrow failure
And extramedullary spread.
Half of patients present with fever which is induced by
Pyrogenic cytokines e.g IL-1,IL-6 ,TNF released from
Leukemic cells .
Fever resolves writhen 72 hours after start therapy.
*fatigue ,lethargy are common manifestation of anaemia
In older patients.
*more than fourth of patients, especially younger children
May have bone pain, arthralgia because leukaemic
Infiltration to the periosteum.

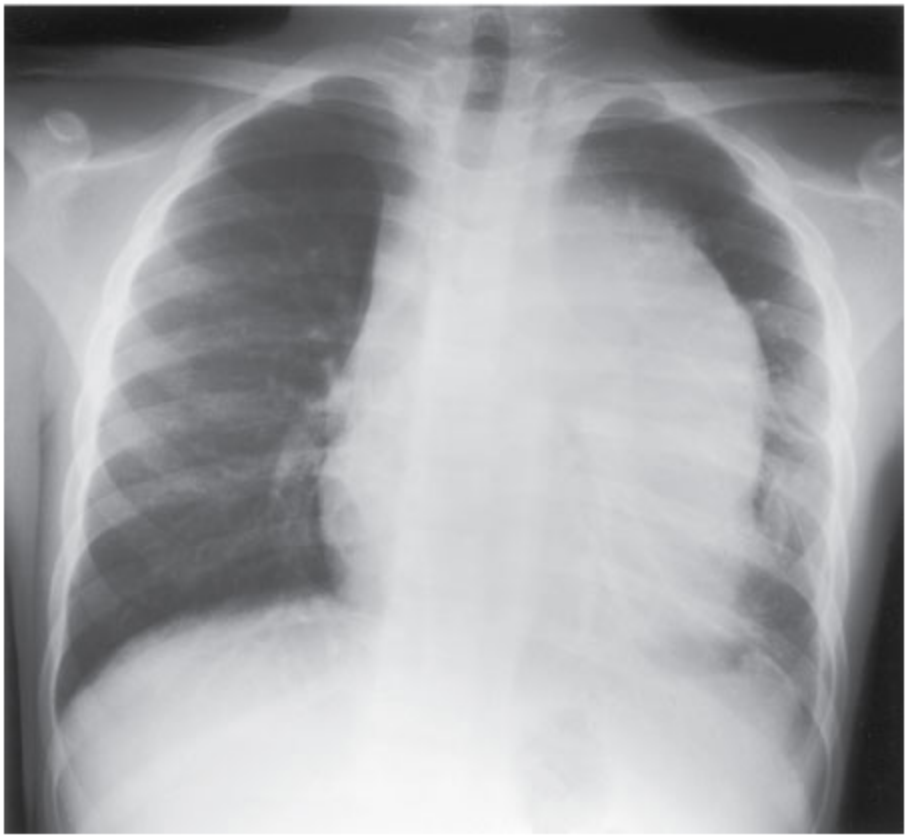
Arthralgia and bone pain less sever in adults.
Less common symptoms include headache, vomiting, Altered mental functions, oliguria and anuria.
Occasionlly patients present with life threatening infections Or bleeding (intracranial haematomas)

SIGNS :
*pallor ,petechiae , ecchymosis.
*liver, spleen and lymph nodes are the most common Extramedullary involvement.
*anterior mediastinal mass is present in 7-10% of childhood Cases and 15%of adult cases.

A bulky mass can compress the great vessels and Trachea and lead to superior vena caval syndrome Or superior mediastinal syndrome, patients with this Syndrome present with cough, dyspnea, orthopnea, Dysphagia, stridor , cyanosis, facial oedema and Increased intracranial pressure and sometimes Syncope.

compress the great vessels and trachea and possibly lead to the superior vena cava syndrome or the superior mediastinal syndrome.[68] Patients with this syndrome present with cough, dyspnea, orthopnea, dysphagia, stridor, cyanosis, facial edema, increased intracranial pressure, and sometimes syncope. Such patients tolerate anesthesia poorly.

Figure 91-3



Chest x-ray film of a 12-year-old black male with T cell ALL and an anterior mediastinal mass.

Painless enlargement of the scrotum can be a sign of a testicular leukemia or hydrocele, the latter resulting from

Signs and symptoms that signals the onset of AML include:

pallor, fatigue,weakness palpitations, and dyspnea on exertion.

The signs and symptoms reflect the development of anemia; however weakness, loss of sense of well-being, and fatigue on exertion can be out of proportion to the severity of anemia ..

Easy bruising, petechiae, epistaxis, gingival bleeding, conjunctival hemorrhages, and prolonged bleeding from skin injuries reflect thrombocytopenia and are frequent early manifestations of the disease.

Very infrequently, gastrointestinal, genitourinary, bronchopulmonary, or central nervous system (CNS) bleeding occurs at the onset of disease.

Pustules or other minor pyogenic infections of the skin and of minor cuts or wounds are most common

Anorexia and weight loss are frequent findings. Fever is present in many patients at the time of diagnosis.

Palpable splenomegaly or hepatomegaly occurs in approximately one third of patients .

Lymphadenopathy is extremely uncommon except in the monocytic variant of AML.

Investigations

Blood examination usually shows anaemia with a normal or raised MCV.

The leucocyte count may vary from as low as 1 × 10^9/1 to as high as 500 × 10^9/1 or more. In the majority of patients the count is below 100 × 10^9/1.

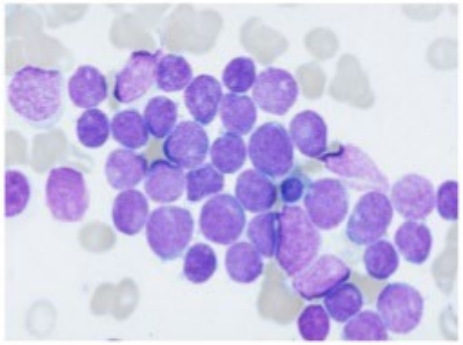
Severe thrombocytopenia is usual but not invariable.

blood film

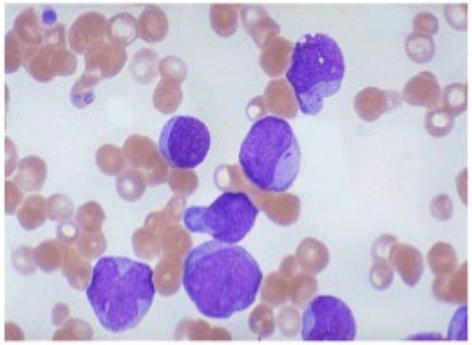
Frequently the blast cells are seen in the blood film., but sometimes they are infrequent or absent ,a bone marrow examination is necessary to confirm the diagnosis.

The bone marrow is the most valuable diagnostic investigation and will provide material for cytology cytogenetics and immunological phenotyping. A trephine biopsy should be taken if no marrow is obtained (dry tap). The marrow is usually hypercellular, with replacement of normal elements by leukaemic blast cells in varying degrees (but more than 20% of the cells). The presence of Auer rods in the cytoplasm of blast cells indicates a myeloblastic type of leukaemia.

Investigations

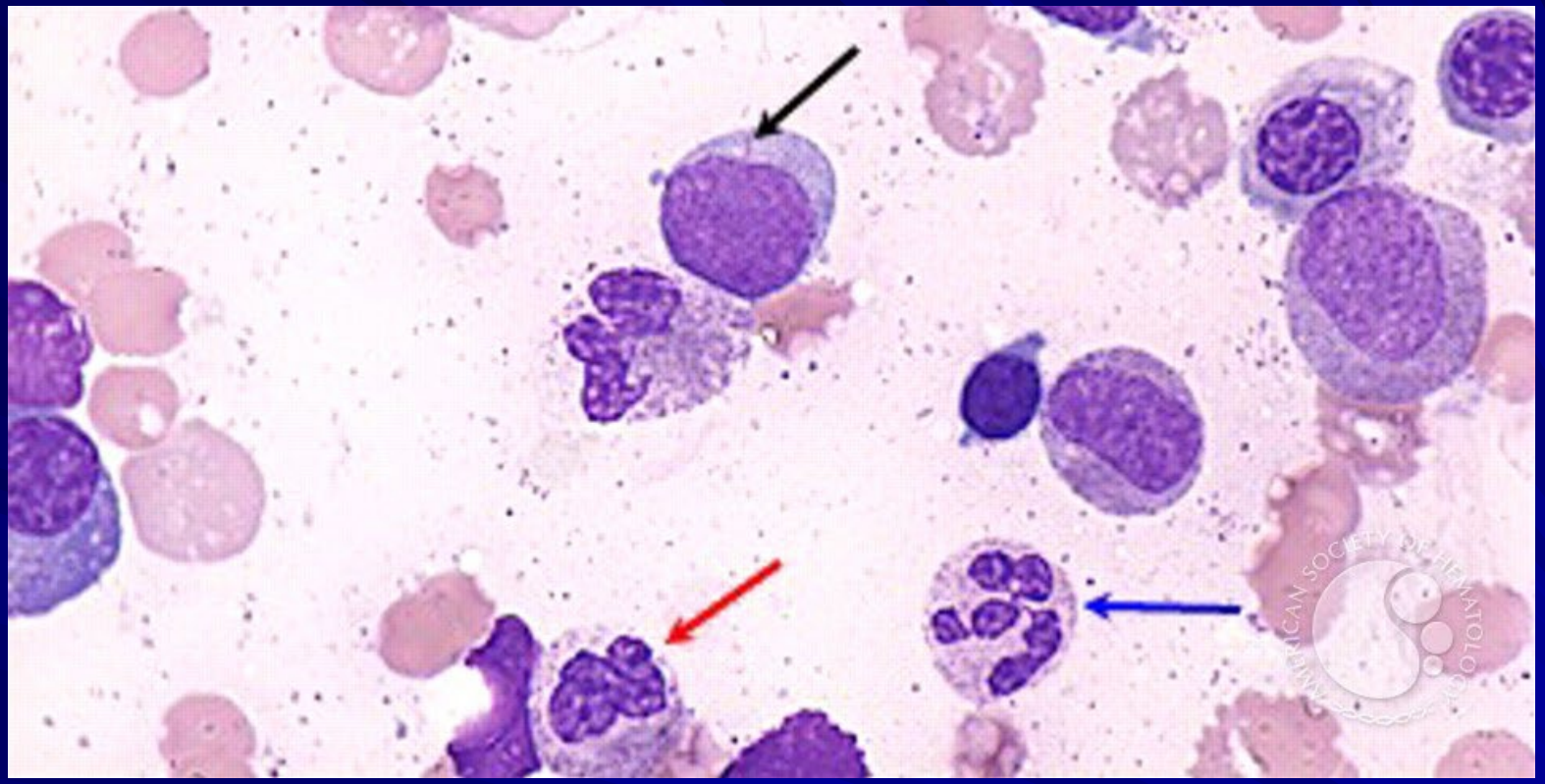


Acute lymphoblastic leukemia



Acute myeloid leukemia

the lymphoblasts are small and the nuclear and cytoplasmic characteristics appear uniform with scant blue cytoplasm, regular nuclear shape,

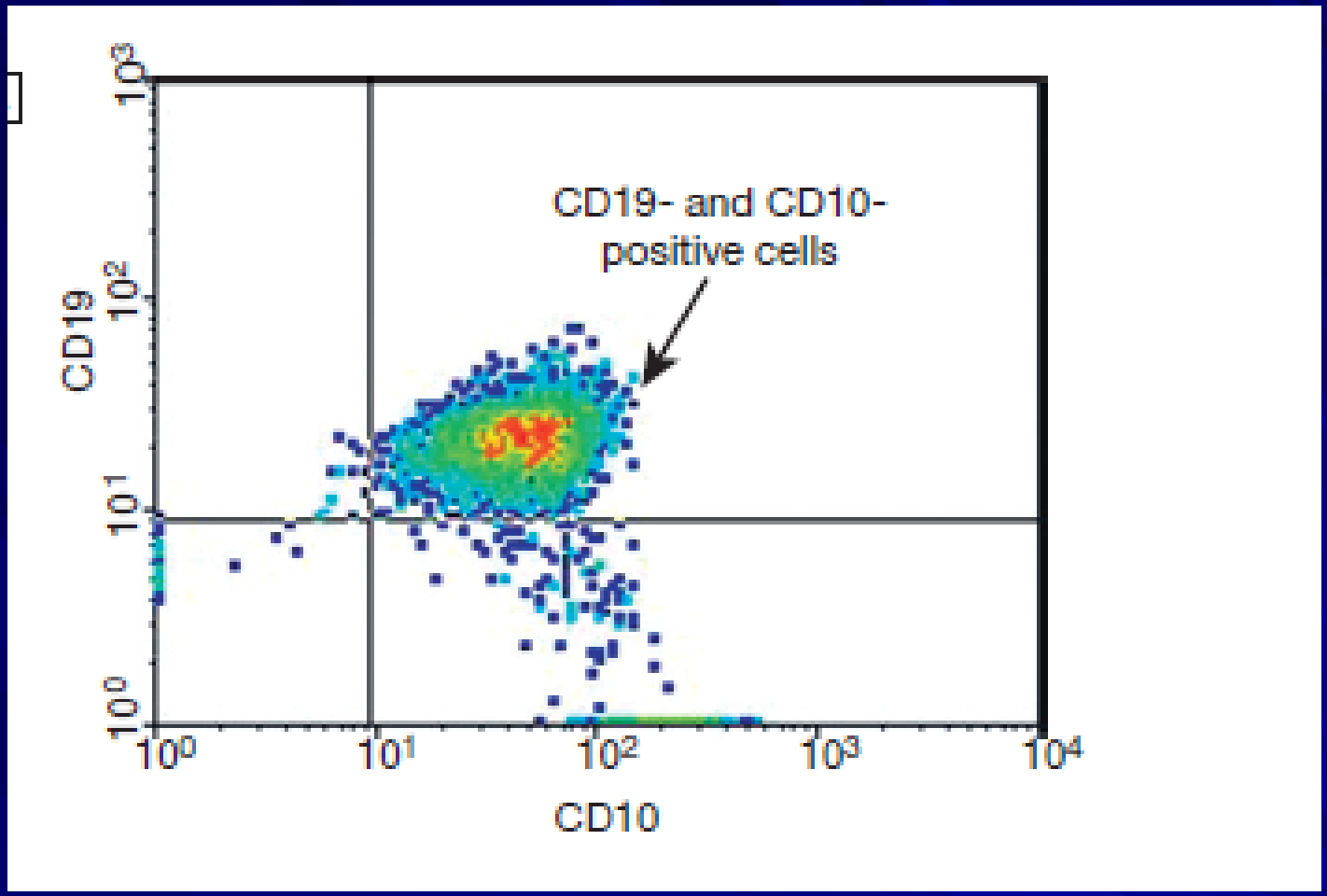


Bone marrow aspirate from this patient with AML shows a blast with an Auer rod (black arrow) as well as neutrophils with hypersegmented (blue arrow) and a hyposegmented (red arrow) nuclei.

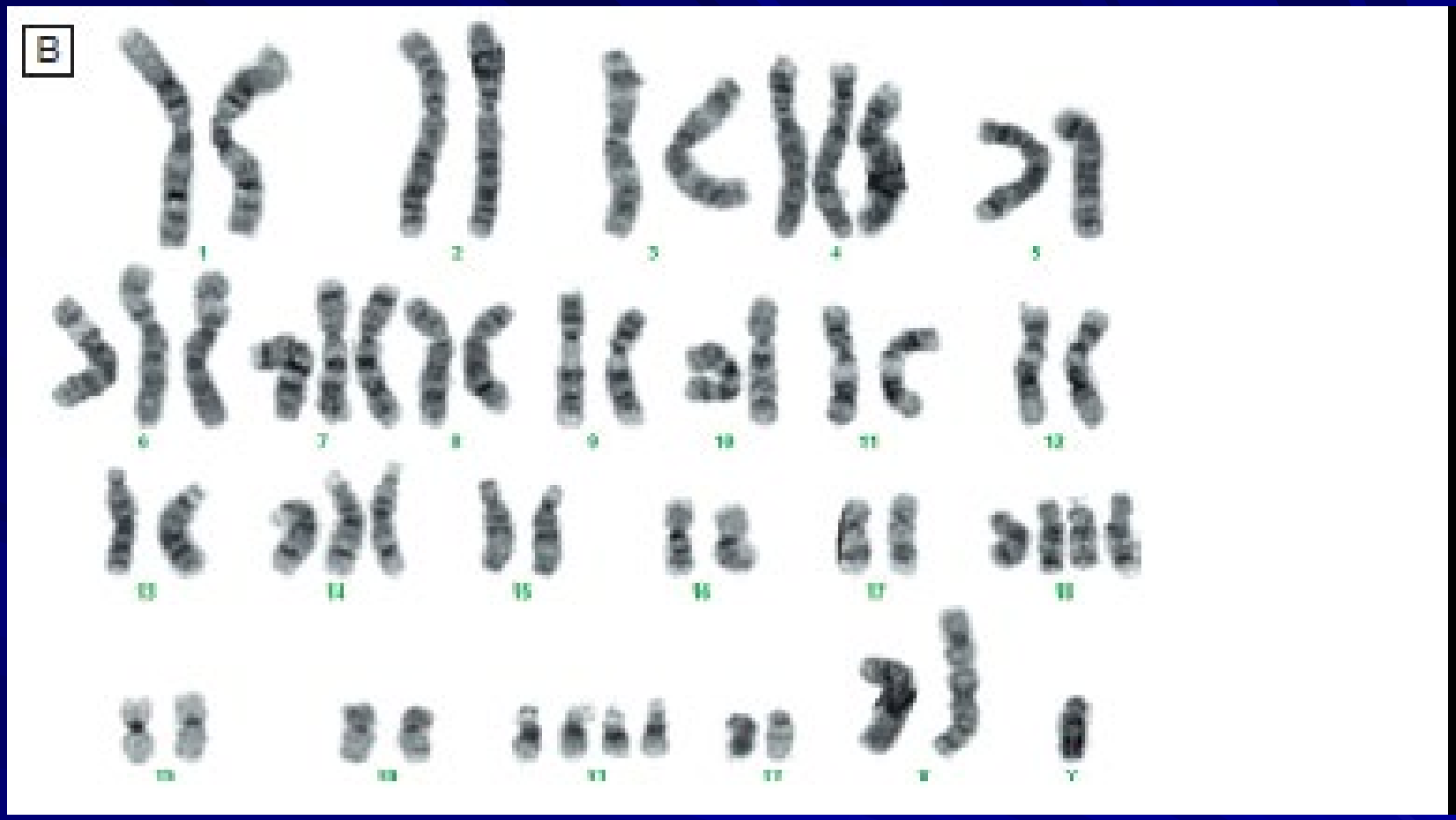
Investigations

Immunophenotyping

- **identify antigens present on the blast cells**
- **determine whether the leukaemia is lymphoid or myeloid(**especially important when cytochemical markers are negative or equivocal. E.g : AML-MO)
- **differentiate T-ALL and B-ALL**



Flow cytometric analysis of blasts labelled with the fluorescent antibodies anti-CD19 (y axis) and anti-CD10 (x axis). ALL blasts are positive for both CD19 and CD10 (arrow).



Chromosome analysis (karyotype) of blasts showing additional chromosomes X, 4, 6, 7, 14, 18 and 21.

Investigations

COMMON CHROMOSOME ABNORMALITIES ASSOCIATED WITH ACUTE LEUKEMIA

- t(8;21) AML with maturation (M2)
- t(15;17) AML-M3(APML)
- Inv 16 AML-M4
- t(9;22) Chronic granulocytic leukemia
- t(8;14) B-ALL

Others Invx

Biochemical screening

- leucocyte count very high - renal impairment and hyperuricaemia

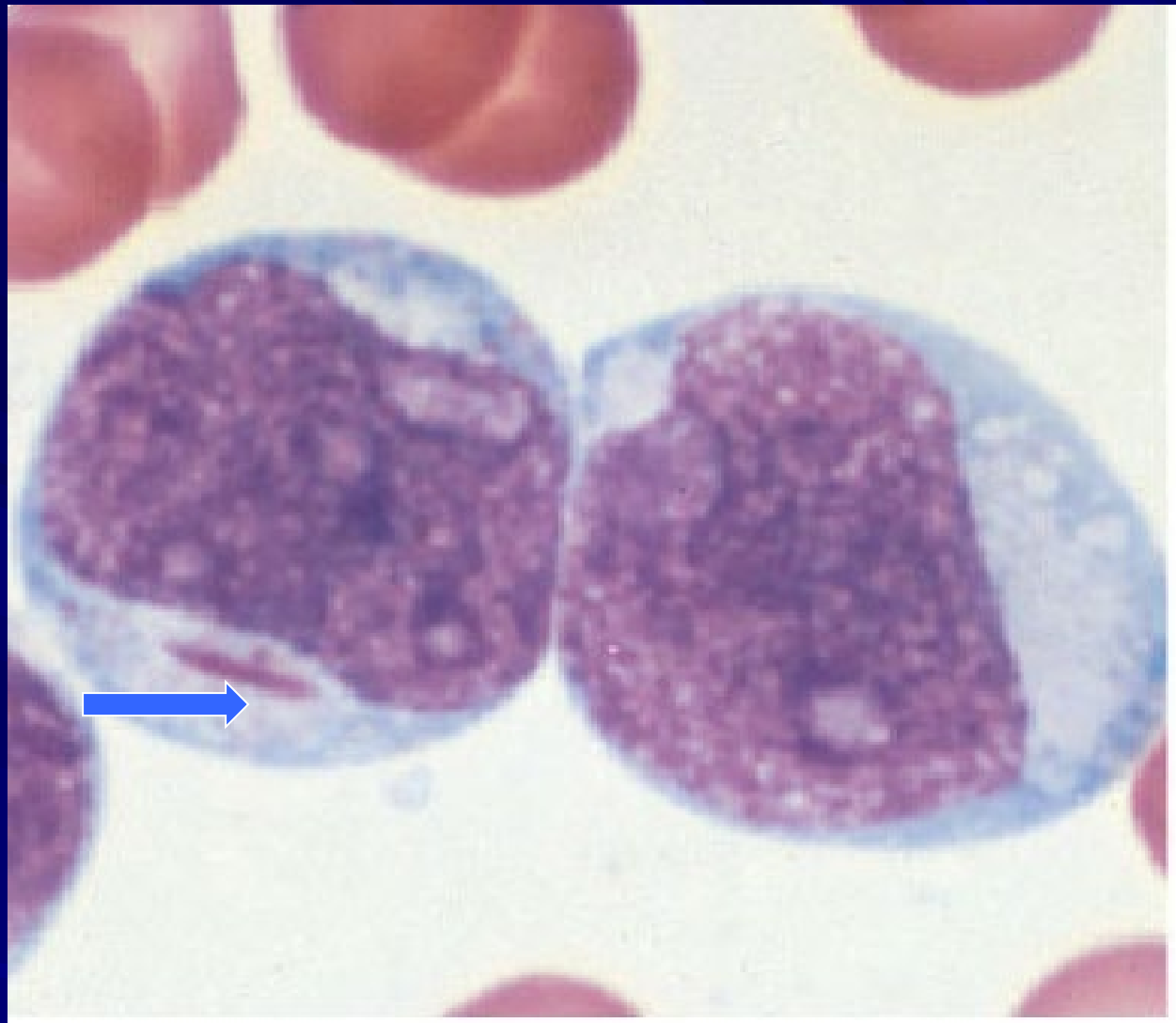
Chest radiography

- mediastinal mass - present in up to 70% of patients with T -ALL

In childhood ALL bone lesions may also seen.

Others Invx

- ***.Lumbar puncture***
  - **initial staging inv. to detect leukaemic cells in the cerebrospinal fluid, indicating involvement of the CNS**
  - Done in acute lymphoblastic leukemia



Source: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: *Williams Hematology*, 7th Edition: http://www.accessmedicine.com

Management

The first decision must be whether or not to give specific treatment. This is generally aggressive, has a number of side-effects, and may not be appropriate for the very elderly or patients with other serious disorders In these patients, supportive treatment can effect considerable improvement in well-being..

Specific therapy

Ideally, whenever possible, patients with acute leukaemia should be treated within a clinical trial. If a decision to embark on specific therapy has been taken, the patient should be prepared properly . It is unwise to attempt aggressive management of acute leukaemia unless adequate services are available for the provision of supportive therapy.

Preparation for specific therapy in acute leukaemia

- Existing infections identified and treated (e.g. urinary tract infection, oral candidiasis, dental, gingival and skin infections)
- Anaemia corrected by red cell concentrate transfusion
- Thrombocytopenic bleeding controlled by platelet transfusions
- If possible, central venous catheter (e.g. Hickman line) inserted to facilitate access to the circulation for delivery of chemotherapy, fluids, blood products and other supportive drugs
- Tumour lysis risk assessed and prevention started: fluids with allopurinol or rasburicase
- Therapeutic regimen carefully explained to the patient and informed consent obtained
- Consideration of entry into clinical trial

Specific therapy

Acute myeloid leukaemia (AML) AML is predominantly a disease of those in old age and many patients are frail. Treatment has become more complex in the recent years and is increasingly tailor-made for AML subgroups defined by genetic abnormalities or persistence of measurable residual disease (MRD).

The first decision must be whether or not to give specific treatment to attempt to achieve remission. The most effective remission induction therapy is based around intensive combination chemotherapy.

This is generally aggressive, has numerous side-effects and may not be appropriate for the very old or patients with serious comorbidities. In these patients, supportive treatment can effect considerable improvement in well-being, but there remains considerable unmet need.

Low-intensity chemotherapy, such as low-dose cytosine arabinoside or azacitidine, is frequently used in older and frailer patients, but this induces remission in less than 20% of patients.

There are currently three phases of specific treatment for AML:

-Remission induction.

In this phase, a fraction of the tumour is killed by combinations of chemotherapy drugs. The standard of care for remission induction in AML is daunorubicin with cytosine arabinoside given for 7–10 days in two cycles.

Patients with a good or standard risk karyotype, including normal karyotype, benefit from the addition of the antibody-drug conjugate gemtuzumab ozagomicin which targets CD33 on the AML cell and delivers the DNA damaging drug calicheamicin directly into the cell , while
AML with the FLT3-ITD mutation benefits from the addition of the FLT3 inhibitor midostaurin.

The patient goes through a period of severe bone marrow hypoplasia lasting 3–4 weeks and requires intensive support and inpatient care from a specially trained multidisciplinary team.
The aim is to achieve remission, a state in which the blood counts return to normal and the marrow blast count is less than 5%.
Quality of life is highly dependent on achieving remission,

Remission consolidation. If remission has been achieved, residual disease is attacked by therapy during the consolidation phase.
This consists of a number of courses of chemotherapy, most commonly 1–2 courses of high-dose cytosine arabinoside, again resulting in periods of marrow hypoplasia.

In poor-prognosis AML, defined by poor risk cytogenetic/molecular genetic abnormalities or persistent MRD, this may include allogeneic HSCT

Remission maintenance. Maintenance therapy has only recently become an effective tool for some patients with AML compared to its long-established role in ALL.

Acute promyelocytic leukaemia (APML)

A subtype of AML, called acute promyelocytic leukaemia (APML), is characterised by a block in differentiation of malignant promyelocytes. These cells accumulate and lead to bone marrow failure and a tendency to severe bleeding, including into the CNS, because of enhanced fibrinolysis and DIC induced by the procoagulant proteins in the malignant cells, e.g. tPA and uPA.

APML carries the best prognosis of all AML if the patient survives the initial bleeding risk.

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The prognosis is excellent with 90% cure rate for patients receiving treatment. However, the early death rate from bleeding remains problematic and intensive supportive care and immediate introduction of ATRA therapy
is vital to prevent this.

Acute lymphoblastic leukaemia (ALL) This is predominantly a disease of childhood with a mean age of 2–4 years. However, it also occurs in adulthood where it is more difficult to treat and carries a poorer prognosis.

Once again there are three phases of therapy with treatment tailor-made to risk groups based on genetic abnormaliites and levels of MRD:

Remission induction – As with AML the aim is to achieve remission using a combination of chemotherapy drugs given over a 4-week period. The drugs commonly used are dexamethasone, vincristine, anthracyclines, methotrexate, mercaptopurine and asparaginase.

Induction therapy in ALL is often less damaging and better tolerated than AML, however, the high dosage of steroids coupled with neutropenia carries a high risk of infections, including fungal infections.

Remission consolidation – The consolidation phase builds on the remission by further decreasing the leukaemic burden. The intensity of consolidation depends on the level of MRD at the end of remission induction and includes blocks of chemotherapy drugs.
Allogeneic HSCT is used as consolidation for fit adults with ALL and a suitable donor, but rarely in children unless they relapse.

Remission maintenance – If the patient is still in remission after the consolidation phase for ALL, a period of maintenance therapy is given, with the individual as an outpatient and treatment consisting of a repeating cycle of drug administration. This may extend for up to 3 years if relapse does not occur.

In ALL prophylactic treatment to the central nervous system is required, as this is a sanctuary site where standard therapy does not penetrate. This usually consists of a combination of cranial irradiation, intrathecal chemotherapy and high-dose methotrexate, which crosses the blood–brain barrier.Such therapy is integrated into the induction, remission and consolidation phases of therapy

Drugs commonly used in the treatment of acute leukaemia

Acute lymphoblastic lekaemia

phase

Induction

Vincristine (IV)
Prednisolone (oral)
L-Asparaginase (IM)
Daunorubicin (IV)
Methotrexate (intrathecal)
Imatinib (oral)*

Acute myeloid leukaemia

Daunorubicin (IV)
Cytarabine (IV)
Etoposide (IV and oral)
Gentuzumab ozogamicin (IV)
All-*trans retinoic acid* (ATRA) (oral)
Arsenic trioxide (ATO)

ALL

Consolidation

Daunorubicin (IV)
Cytarabine (IV)
Etoposide (IV)
Methotrexate (IV)
Imatinib (oral)*

Maintenance

Prednisolone (oral)
Vincristine (IV)
Mercaptopurine (oral)
Methotrexate (oral)
Imatinib (oral)*

Relapse

Fludarabine
Cytarabine
Idarubicin

AML

Cytarabine (IV)
Amsacrine (IV)
Mitoxantrone (IV)

Fludarabine
Cytarabine
Arsenic trioxide (ATO)
Idarubicin

*If Philadelphia chromosome-positive.

Supportive therapy

Aggressive and potentially curative therapy which involves period of sever bone marrow failure would not be possible without adequate and skilled supportive care the following problems commonly arise.

Anaemia. Anaemia is treated with red cell concentrate transfusions.
*Bleeding. Thrombocytopenic bleeding requires plateletb*transfusions, unless the bleeding is trivial. Prophylactic platelet transfusion should be given to maintain the platelet count above 10 × 109/L. Coagulation abnormalities occur and need accurate diagnosis and treatment

Infection So-called neutropenic sepsis is a major complication of acute leukaemia and its treatment.
Every leukaemia centre will have a written definition and management policy for this common event.
UK NICE guidelines define neutropenic sepsis as fever (>38°C) lasting over 1 hour in a neutropenic patient (neutrophils <0.5 × 109/l) or with other signs or symptoms of significant sepsis . Parenteral broad-spectrum antibiotic therapy is essential. Empirical therapy is given according to the perceived severity of the sepsis illness and local bacteriological resistance patterns.

The organisms most commonly associated with severe neutropenic sepsis are Gram-positive bacteria, such as Staphylococcus aureus and Staphylococcus epidermidis, which are present on the skin and gain entry via cannulae and central lines. Gram-negative infections often originate from the gastrointestinal tract, which is affected by chemotherapy-induced mucositis; organisms such as Escherichia coli, Pseudomonas and Klebsiella spp. are likely to cause rapid clinical deterioration and must be covered with initially empirical antibiotic therapy.

Oral and pharyngeal Candida infection is common. Fluconazole is effective for the treatment of established local infection and for prophylaxis against systemic candidaemia.

Prophylaxis against other systemic fungal infections including Aspergillus, for example itraconazole or posaconazole, is usual practice during high-risk intensive chemotherapy.

For systemic fungal infection with Candida oraspergillosis, intravenous liposomal amphotericin, caspofungin or voriconazole is required for up to 3 weeks. In systemic Candida infection intravenous catheters should be removed.

Reactivation of herpes simplex infection occurs frequently around the lips and nose during ablative therapy for acute leukaemia, and is treated with aciclovir. This may also be prescribed prophylactically to patients with a history of cold sores or elevated antibody titres to herpes simplex. Herpes zoster manifesting as chickenpox or, after reactivation, as shingles should be treated in the early stage
with high-dose aciclovir, as it can be fatal in immunocompromised patients.

- **Psychological problems**

  Psychological support is a key aspect of care. Patients should be kept informed, and their questions answered and fears allayed as far as possible. A multidisciplinary approach to patient care involves input from many services, including psychology.

  Key members of the team include haematology specialist nurses, who are often the central point of contact for patients and families throughout theillness.

Prognosis

Without treatment the median survival of patient with acute leukaemia is About 5weeks.

This may be extended to number of months with supportive treatment.

Patient who achieve remission with specific therapy have a better outlook.

About 80% of adult patients under 60 years of age with ALL or AML achieve remission.

The level of detectable leukaemia cells after induction therapy, called measurable residual disease (MRD), can be a powerful prognostic tool and is now used routinely in some forms of acute leukaemia
(e.g. ALL and AML with NPM1 mutation) to determine subsequent consolidation therapy

Advances in treatment have led to steady improvement in survival from acute leukaemia. Some 90% of children with ALL are cured and about 50% of adults aged less than 60 years are cured from AML. As discussed above, APML has a 90% cure rate. Prognosis remains poor in most other groups of patients with acute leukaemias, especially in old age.

THANK YOU