University of Basrah
Al-Zahraa Medical College

Ministry of Higher education
and Scientific Research

Block: Child Health.

Lecture: Hemato-onchology.

Lecturer: *Dr Ihsan Mardan Al-Badran* MBChB, MSc, FIBMS (Hematopathologist)

Block staff:

Dr. Jawad Ramadan (supervisor)
Dr. Rehab abdulwehab (leader)
Dr. Ahmad Jaafer (co-leader)
Dr. Ihsan Mardan
Dr. Dhaigam Emad
Dr. Ahmad Ibrahim
Dr. Huda Kareem
Dr Murtadha Abdul Hassan
Dr . Rasha Kahtaan
Dr Aymen Mohammed

Nelson Textbook of Pediatrics, 21th edition.
Nelson Essentials of Pediatrics, 7th Edition 2015
Pediatric Decision-Making Strategies
Illustrated Textbook of Pediatrics
Short Atlas in Pediatrics

LEUKEMIAS

- A group of malignant diseases in which **genetic abnormalities** in a hematopoietic cell give rise to **an unregulated clonal proliferation** of cells.

- The progeny of these cells have a **growth advantage** over normal cellular elements because of their increased rate of proliferation and a decreased rate of spontaneous apoptosis.

- The leukemias are the **most common malignant** neoplasms in childhood, accounting for approximately **31%** of all malignancies that occur in children younger than 15 years old.

- **Acute lymphoblastic leukemia** (ALL) accounts for approximately 77% of cases of childhood leukemia, **acute myelogenous leukemia** (AML) for approximately 11%, **chronic myelogenous leukemia** (CML) for 2–3%, and **juvenile myelomonocytic leukemia** (JMML) for 1–2%

ACUTE LYMPHOBLASTIC LEUKEMIA

Epidemiology

- It has a striking peak incidence at **2-3 years** of age and occurs more in **males** than in females at all ages.

- The disease is more common in children with certain **chromosomal abnormalities**, such as Down syndrome, Bloom syndrome, and ataxia-telangiectasia.

- Among **identical twins**, the risk to the second twin if one twin develops leukemia is greater than that in the general population

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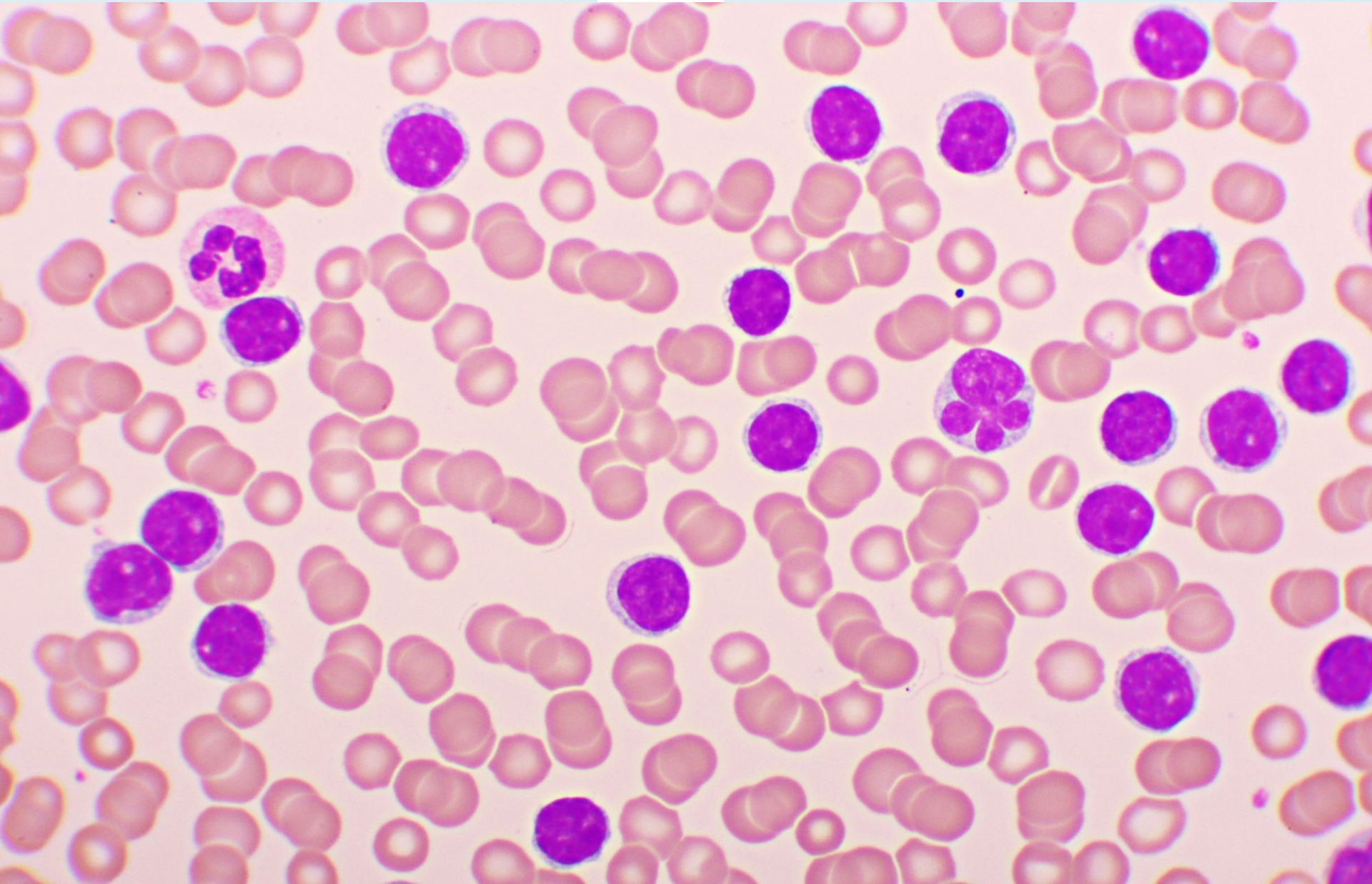

Cellular classification

- The classification of ALL depends on characterizing the malignant cells in the bone marrow to determine the **morphology**, **phenotype** as measured by cell membrane markers, and **cytogenetic** and **molecular genetic** features

- Phenotypically, surface markers show that approximately **85%** of cases of ALL are classified as **B**-lymphoblastic leukemia, approximately **15%** are **T**-lymphoblastic leukemia, and approximately **1%** are derived from **mature B** cells.

- Chromosomal abnormalities are used to subclassify ALL into prognostic groups. Many genetic alterations, including **inactivation of tumor-suppressor genes** and **pathogenic gene variants** that activate the JAK-STAT or RAS pathways, have been discovered.

- The polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) techniques offer the ability to pinpoint molecular genetic abnormalities and can be used to detect small numbers of malignant cells at diagnosis as well as during follow-up (minimal residual disease [MRD]

Clinical manifestations

- The initial presentation of ALL usually is **nonspecific and relatively brief**. Anorexia, fatigue, malaise, irritability, and intermittent low-grade fever are often present.

- Signs and symptoms of bone marrow failure.

- Organ infiltration can cause lymphadenopathy, hepatosplenomegaly, testicular enlargement, or central nervous system (CNS) involvement (cranial neuropathies, headache, seizures)

Diagnosis

- The diagnosis of ALL is strongly suggested by peripheral blood findings that indicate bone marrow failure. Leukemic cells might not be reported in the peripheral blood in routine laboratory examinations.
- The bone marrow should be examined promptly to confirm the diagnosis. Bone marrow aspiration and biopsy, flow cytometry, cytogenetics, and molecular studies.
- ALL is diagnosed by a bone marrow evaluation that demonstrates >20% of the bone marrow cells as a homogeneous population of lymphoblasts.
- Initial evaluation also includes CSF examination. If lymphoblasts are found and the CSF leukocyte count is elevated, overt CNS or meningeal leukemia is present

Differential diagnosis

- When pancytopenia is present without peripheral blasts, aplastic anemia (congenital or acquired), marrow infiltration from metastatic disease, and hemophagocytic lymphohistiocytosis should be considered.
- Failure of a single cell line, as seen in transient erythroblastopenia of childhood, immune thrombocytopenia, and congenital or acquired neutropenia, is rarely the presenting feature of ALL.
- A high index of suspicion is required to differentiate ALL from infectious mononucleosis in patients with acute onset of fever and lymphadenopathy and from juvenile idiopathic arthritis in patients with fever, bone pain but often no tenderness. and joint swelling.

Table Prognostic Factors for Acute Lymphoblastic Leukemia

	FAVORABLE FACTOR	ADVERSE FACTOR
DEMOGRAPHIC AND CLINICAL FEATURES		
Age	1 year to <10 years	<1 year or ≥10 years
Sex	Female	Male
Ethnicity	White, Asian	Black, Hispanic
CLINICAL, BIOLOGIC, OR GENETIC FEATURES OF LEUKEMIA		
CNS involvement	No	Yes
Blood count at diagnosis	Low blood count; $<50 \times 10^9$ cells/L for B-cell acute lymphoblastic leukemia and $<100 \times 10^9$ cells/L for T-cell acute lymphoblastic leukemia	High blood count; $\geq 50 \times 10^9$/L for B-cell acute lymphoblastic leukemia and $\geq 100 \times 10^9$ cells/L for T-cell acute lymphoblastic leukemia
Immunophenotype	B-cell lineage	T-cell lineage
Cytogenetic features	Hyperdiploidy, *ETV6-RUNX*, *TCF3-PBX1*, and trisomy of chromosomes 4, 10, or 17	Hypodiploidy, *BCR-ABL1* Philadelphia chromosome-positive, *MLL* rearrangements, *TCF3-HLF*, and complex karyotype (≥5 chromosomal abnormalities)
Genomic features	*DUX4*-rearrangement (*ERG* deletion)	*IKZF1* deletions or pathogenic variants, Philadelphia chromosome-like, *MEF2D*-rearrangement
RESPONSE TO TREATMENT		
Minimal residual disease at specified time points	Low minimal residual disease $<10^{-3}$ nucleated cells or undetectable	Persistence of minimal residual disease $\geq 10^{-3}$ nucleated cells, the higher this value the worse the prognosis

ACUTE MYELOGENOUS LEUKEMIA

EPIDEMIOLOGY

The relative frequency of AML increases in adolescence, representing 36% of cases of leukemia in 15-19 year old. Acute promyelocytic leukemia (APL) is a subtype that is more common in certain regions of the world, but the incidence of the other types is generally uniform

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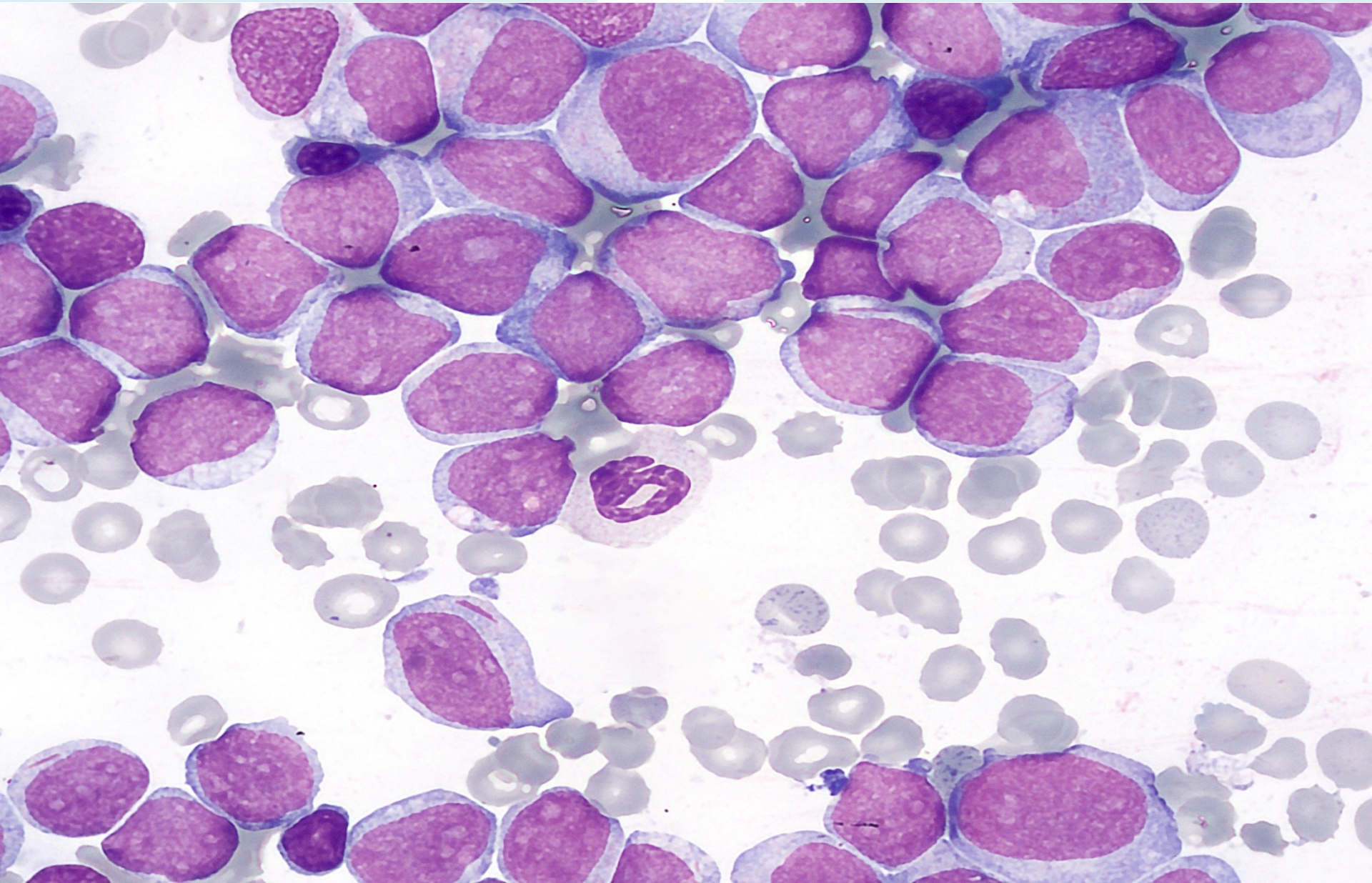

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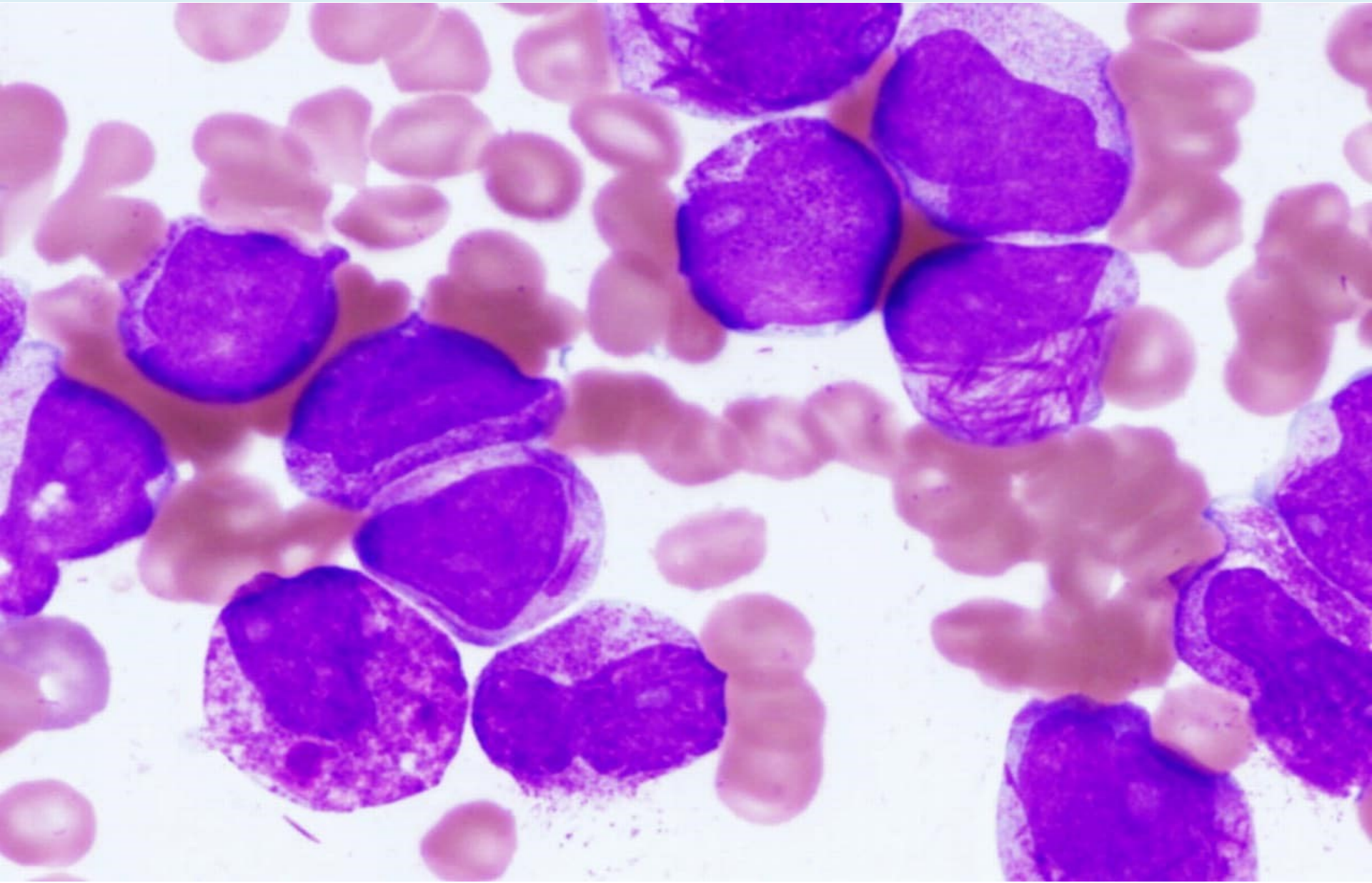

Clinical manifestations

- Patients with AML can present with any or all of the findings associated with marrow failure in ALL.

- In addition, patients with AML may present with signs and symptoms that are uncommon in ALL, including **subcutaneous nodules** or "**blueberry muffin**" lesions (especially in infants), **infiltration of the gingiva** (especially in monocytic subtypes), signs and laboratory findings of **disseminated intravascular coagulation** (especially indicative of APL

CHRONIC MYELOGENOUS LEUKEMIA

- Clonal disorder of the hematopoietic tissue that accounts for 2–3% of all cases of childhood leukemia.

- Approximately 99% of the cases are characterized by a specific translocation, t(9;22)(q34;q11), known as the Philadelphia chromosome, resulting in a BCR-ABL fusion protein

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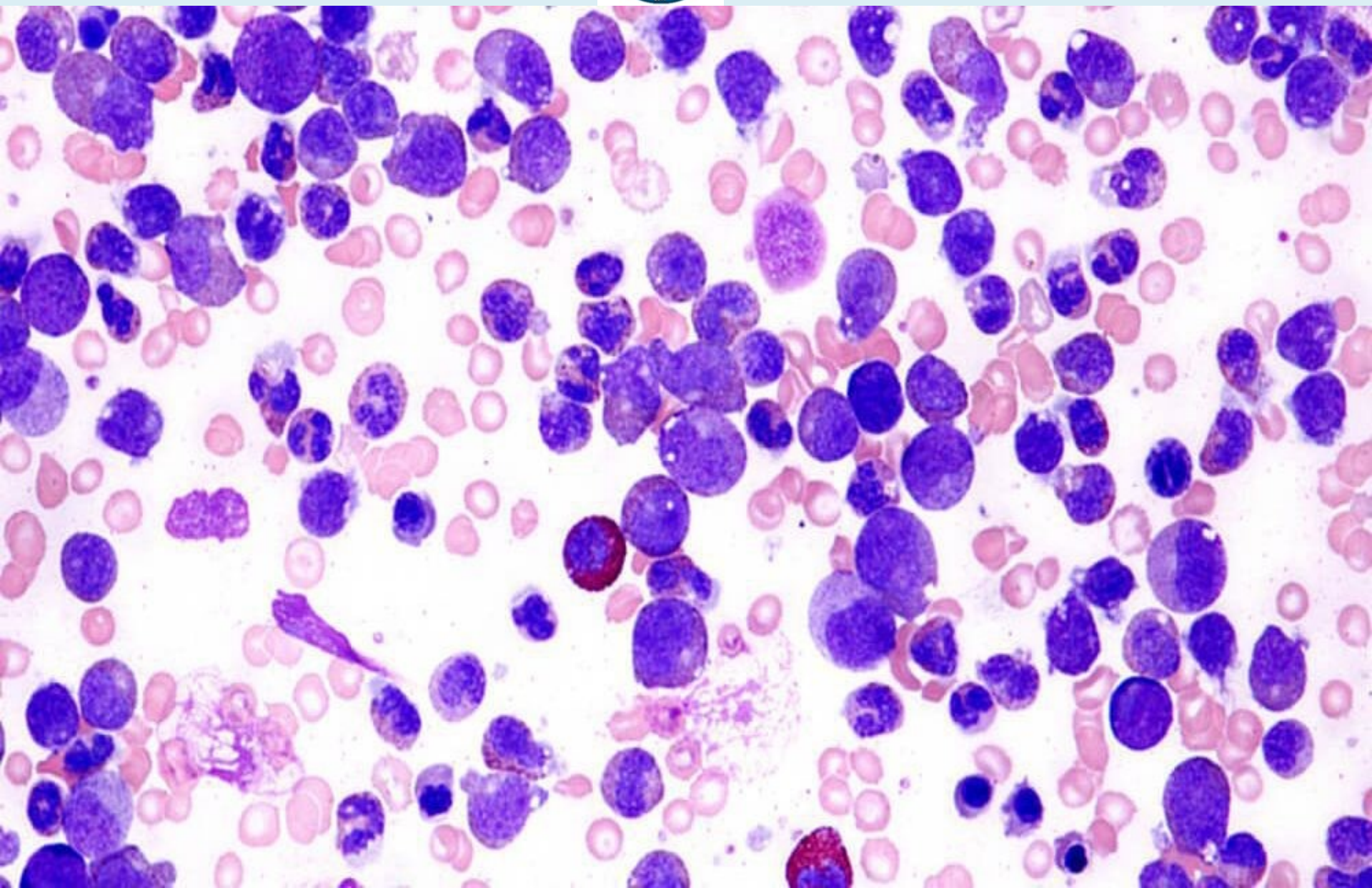


JUVENILE MYELOMONOCYTIC LEUKEMIA

Formerly termed juvenile chronic myelogenous leukemia, is a clonal proliferation of hematopoietic stem cells that typically affects children <2 years old. JMML is rare, constituting **<1%** of all cases of childhood leukemia. Patients with this disease **do not have** the Philadelphia chromosome characteristic of CML

CENTRAL NERVOUS SYSTEM TUMORS IN CHILDHOOD

- Primary central nervous system (CNS) tumors are a heterogeneous group of diseases that are, collectively, the most common malignancy in childhood and adolescence.

- The clinical presentation of the patient with a brain tumor depends on the tumor **location**, the tumor **type**, and the **age** of the child. Signs and symptoms are related to obstruction of cerebrospinal fluid (CSF) drainage paths by the tumor, leading to increased intracranial pressure (ICP) or causing focal brain dysfunction.

CENTRAL NERVOUS SYSTEM TUMORS IN CHILDHOOD

- The classic triad of **headache**, **nausea**, and **vomiting** as well as **papilledema** is associated with midline or infratentorial tumors. Disorders of equilibrium, gait, and coordination occur with infratentorial tumors. Torticollis may occur in cases of cerebellar tonsil herniation. Blurred vision, diplopia, and nystagmus also are associated with infratentorial tumors.
- Supratentorial tumors are more commonly associated with focal motor weakness, focal sensory changes, language disorders, focal seizures, and reflex asymmetry.

NEUROBLASTOMA

- Neuroblastomas are embryonal cancers of the **peripheral sympathetic nervous system** with heterogeneous clinical presentation and course, ranging from tumors that undergo spontaneous regression to very aggressive tumors unresponsive to very intensive multimodal therapy

- Neuroblastoma is the most common extracranial solid tumor in children and is the most commonly diagnosed malignancy in the first year of life.

Clinical manifestations

- Approximately half of neuroblastoma tumors arise in the **adrenal glands**, and most of the remainder originate in the **paraspinal sympathetic ganglia**.

- Metastatic spread, which is more common in children older than 1 year of age at diagnosis, occurs via local invasion or distant hematogenous or lymphatic routes.

Diagnosis

- Neuroblastoma is usually discovered as a mass or multiple masses on plain radiography, CT, or MRI.
- Tumor markers, including catecholamine metabolites homovanillic acid and vanillylmandelic acid, are elevated in the urine of approximately 95% of cases and help to confirm the diagnosis.

Treatment

The patient's age and tumor stage are combined with cytogenetic and molecular features of the tumor to determine the treatment risk group and estimated prognosis for each patient.

WILMS TUMOR (NEPHROBLASTOMA)

- The most common primary malignant renal tumor of childhood. It is the second most common malignant abdominal tumor in childhood after neuroblastoma.

- The most common sites of metastases are the lungs, regional lymph nodes, and liver. Histologically, the classic Wilms tumor is made up of varying proportions of blastemal, stromal, and epithelial cells.

- Wilms tumor has been associated with genetic abnormalities. The first identified Wilms tumor gene, WT1, located at 11p13.

Clinical presentation

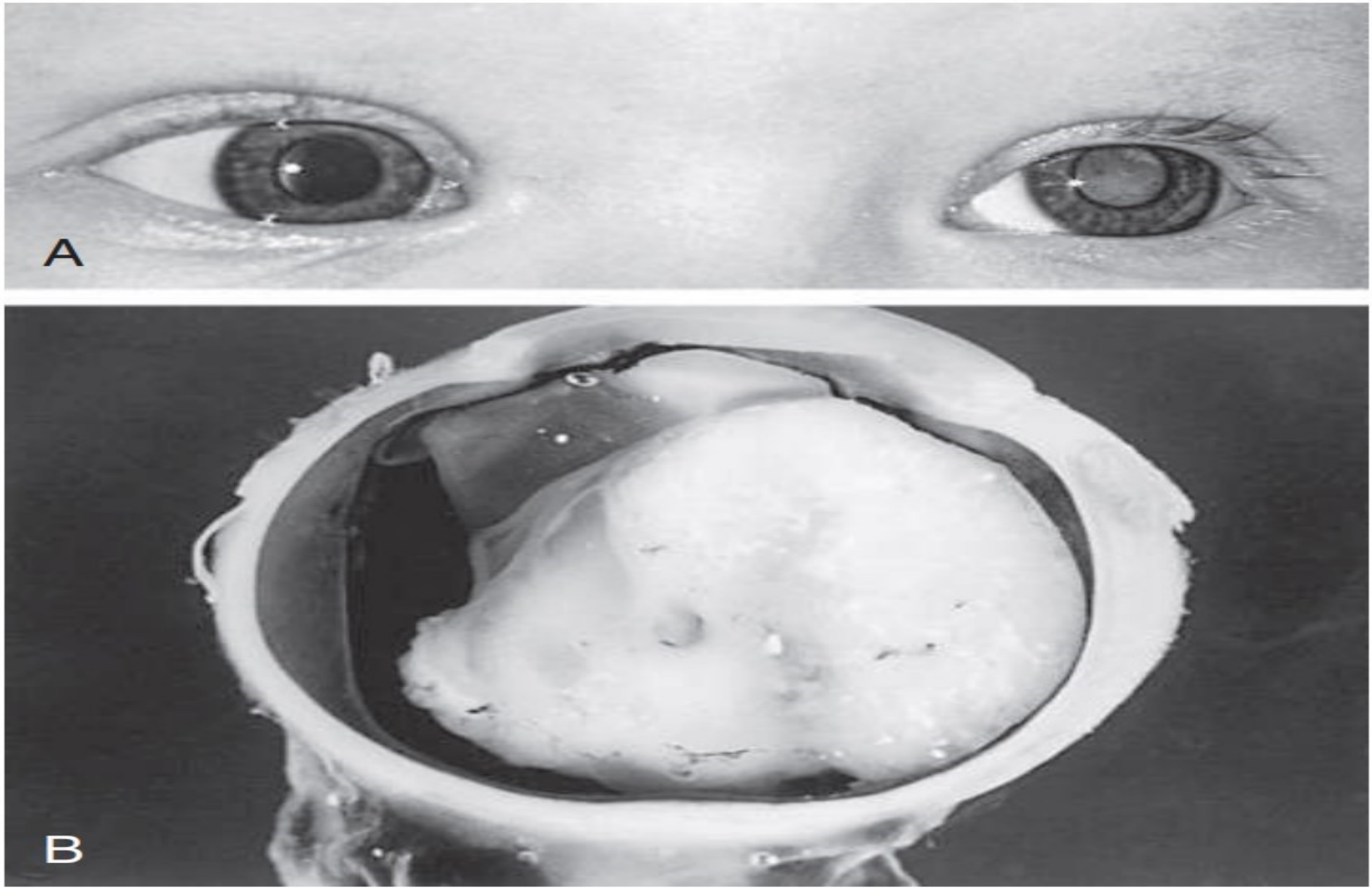
- The most common initial clinical presentation for Wilms tumor is the incidental discovery of an **asymptomatic abdominal mass** by parents while bathing or clothing an affected child or by a physician during a routine physical examination.
- **Hypertension** is present in about 25% of patients at presentation and has been attributed to increased renin activity.
- **Abdominal pain** (40%), **gross painless hematuria** (18%), and constitutional symptoms such as fever, anorexia, and weight loss are other findings at diagnosis.

RETINOBLASTOMA

- An embryonal malignancy of the retina and the most common intraocular tumor in children.
- Retinoblastoma progresses to metastatic disease and death in >40% of children in low income countries
- The median age at diagnosis is approximately 2 years, and >90% of cases are diagnosed in children <5 years old.
- Overall, 66–75% of children with retinoblastoma have unilateral tumors, with the remainder having bilateral retinoblastoma

Diagnosis

- Characteristic ophthalmologic findings of a chalky, white-gray retinal mass with a soft, friable consistency.
- Imaging studies are not diagnostic, and biopsies are contraindicated.
- Indirect ophthalmoscopy with slit-lamp evaluation can detect retinoblastoma tumors, but a complete evaluation requires an examination under general anesthesia by an experienced ophthalmologist to obtain complete visualization of both eyes.
- Orbital ultrasonography, CT, or MRI is used to evaluate the extent of intraocular disease and extraocular spread


A
B

Treatment

The primary goal of treatment is always cure; the secondary goals include preserving vision and the eye itself and decreasing the risk of late side effects, mainly secondary malignancies.

THANK YOU