IN THE NAME OF GOD

•CASE PRESENTATION

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• Iran university of medical sciences

• Aliasghar Hospital

Case 1

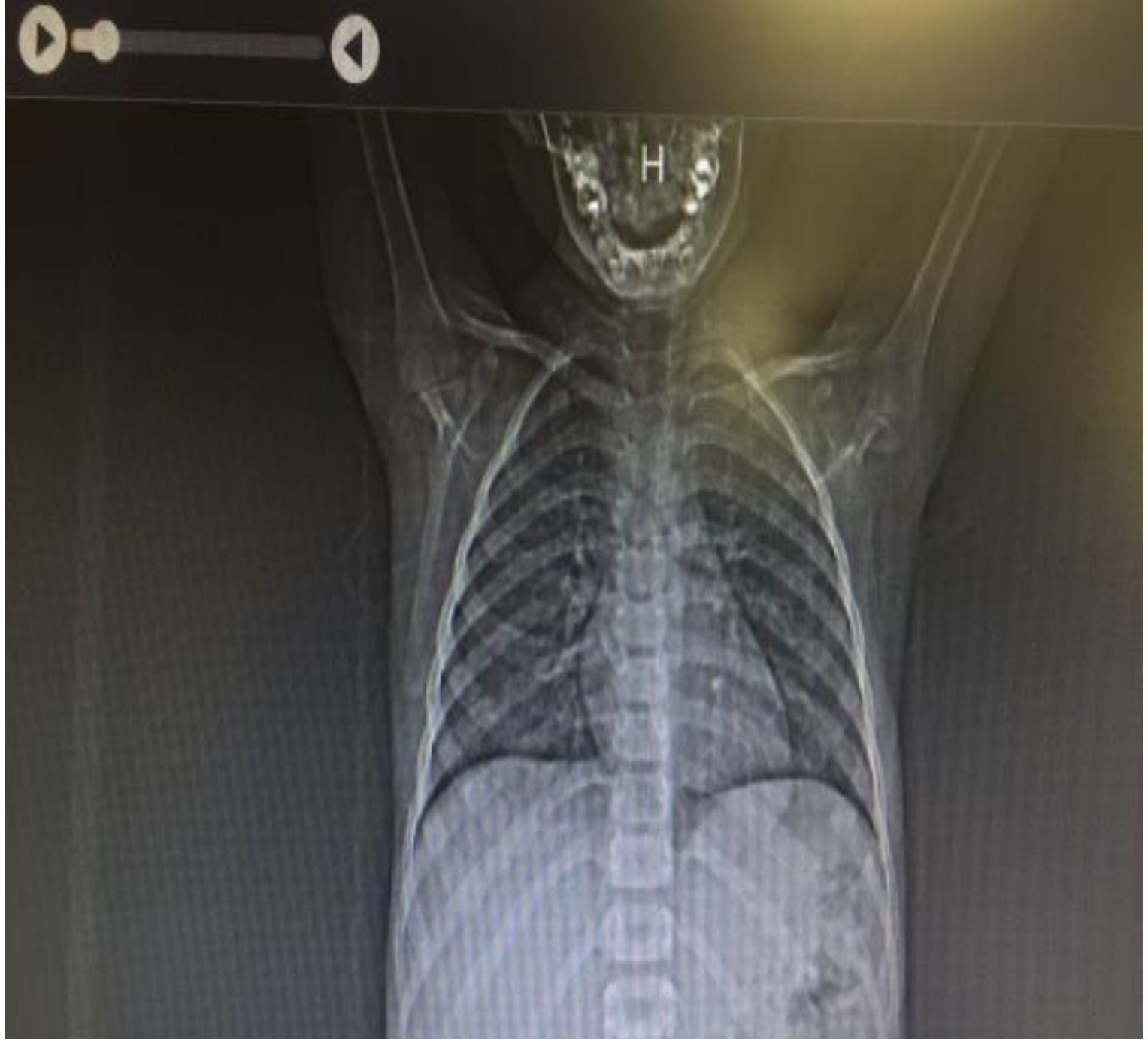
- A 7-year-old boy from unrelated parents complained of periodic fevers since three months ago, and leukopenia and anemia since one month ago.
- In the physical examination, the child did not have lymphadenopathy and organomegaly

Lab data

- WBC 1900 50% PMN 45% lym 5% mono
- RBC 3.03
- Hb 6.9 Retic 0.8%
- Hct 22 Coombs Direct Neg
- MCV 72.5
- MCH 22.6
- MCHC 31.2
- Plt 567
- ESR 72

Lab data

- AST 86
- ALT 23
- ALK 214
- Ferritin 308
- Wright Neg coombs wright Neg 2ME Neg
- ANA Neg Anti DS DNA Neg
-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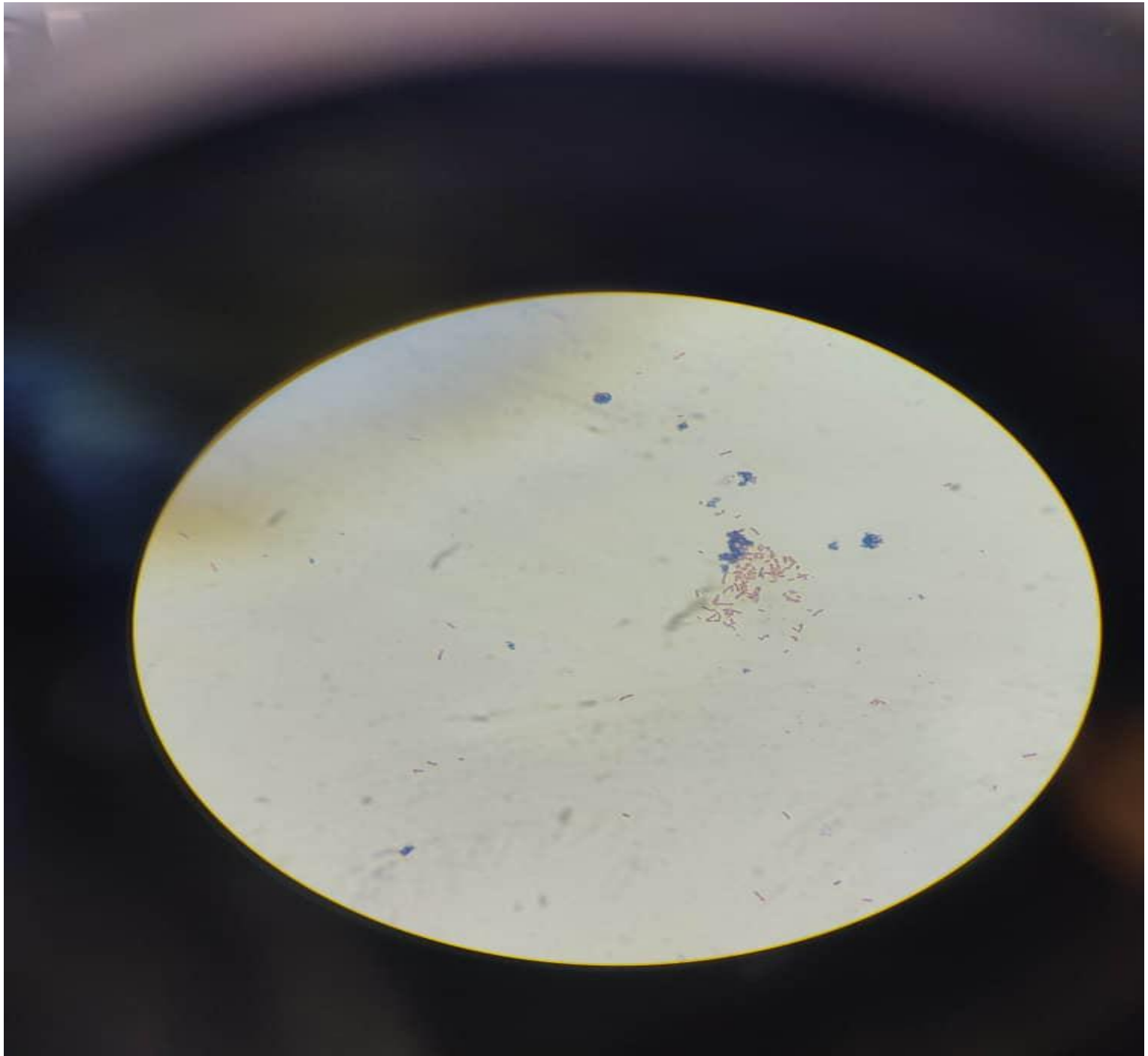
Abdominopelvic sonography

- Liver: normal size with increased echogenicity
- spleen is normal
- mesenteric and para aortic lymphadenopathy 27*16 mm

Bone marrow aspiration :

- Normocellular marrow with normal myeloid, erythroid and megakaryocyte series
- Hemophagocyte were not seen



بیمارستان فوق تخصصی حضرت علی اصغر (ع)

کد بیمار : [illegible]	محل درخواست: اورژانس تحت نظر	تاریخ ترخیص: [illegible]
نام بیمار: [illegible]	پزشک معالج : [illegible]	
سن : ۷ ساله	تاریخ مراجعه: 1401/4/18	
تاریخ درخواست: 1401/4/18	تاریخ گزارش: 1401/4/21 09:02	
نام پدر: اسماعیل	شماره پرونده: [illegible]	
کد برگه درخواست:	اولویت مراجعه: عادی	

سی تی اسکن

اسپیرال ریه و مدیاستن بدون تزریق

SPIRAL THORACIC CT SCAN – ©

The lungs demonstrate normal aeration.

There is no evidence of abnormal opacity or a nodular -mass lesion in the lung fields.

There is no evidence of an abnormal mediastinal mass on the unenhanced images.

There is no evidence of pleural effusion or thickening.

The thoracic wall is normal in appearance.
In limited cuts of upper abdomen, evidence of retrocroral lymphadenopathies is found.
Mild decreased liver parenchymal density in favor of fatty changes is also seen.

With The Best Regards

E.Zarei M.D

Radiologist

- **Mycobacterim – comlex PCR Negative**
- HBSAg neg
- HBSAb 15
- HCVAb neg

CD flowcytometry

- CD 4 3%
- CD8 39%
- CD 3 46%
- CD 5 40%
- CD 20 10%
- CD22 10%
- CD34 1%
- CD 16/56 6%
- CD45 88%

Final Diagnosis

- **HIV Ab pos**
- **HIV PCR POS**
- **NTM PCR POS**

Causes of pancytopenia
(organized by mechanism)

- **Acquired**
- Bone marrow infiltration/replacement
  - Malignant
    - Acute leukemias
    - Chronic leukemias/myeloproliferative neoplasms (MPN)
    - Myelodysplastic syndromes (MDS)
    - Metastatic cancer

Causes of pancytopenia (Acquired)

- Bone marrow infiltration/replacement
  - Non-malignant
    - Myelofibrosis
    - Infectious (eg, fungal, tuberculous)
    - Storage diseases
- Bone marrow failure
  - Immune destruction/suppression
- Aplastic anemia/paroxysmal nocturnal hemoglobinuria

Causes of pancytopenia(Acquired)

- Medications¶
  - Cytotoxic drugs
  - Idiosyncratic reactions to medications
- Autoimmune disorders
- (systemic lupus erythematosus [SLE], rheumatoid arthritis [RA], sarcoidosis)
- Hemophagocytic lymphohistiocytosis (HLH)

Causes of pancytopenia (Acquired)

- **Nutritional**
  - Megaloblastic (vitamin B12, folate)
  - copper deficiency,
  - zinc toxicity

Causes of pancytopenia(Acquired)

- **Marrow suppression**
  - Viral infection
  - (eg, HIV, hepatitis, Epstein-Barr virus [EBV])
- **Ineffective hematopoiesis**
- (MDS, nutritional)

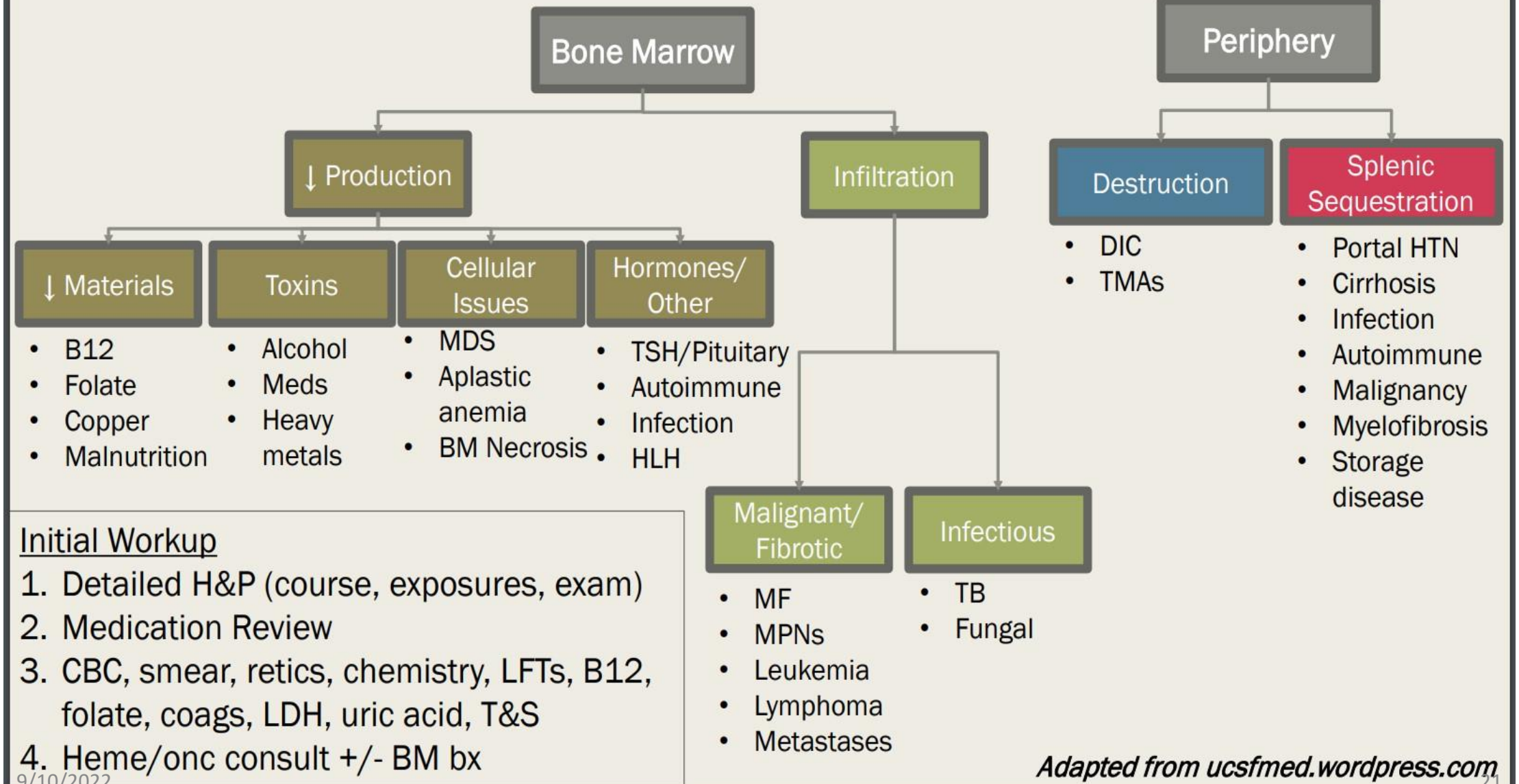
Causes of pancytopenia (Acquired)

- **Destruction/sequestration**
- Consumption
    - Disseminated intravascular coagulation
  - Splenomegaly
    - Portal hypertension/cirrhosis
    - Infections (EBV)
    - Autoimmune disorders (SLE, RA/Felty syndrome)
    - Malignancies (eg, lymphomas, MPN)
    - Myelofibrosis with myeloid metaplasia
- Storage diseases (Gaucher)

Causes of pancytopenia(congenital)

- **Congenital**
- Chédiak–Higashi syndrome
- Wiskott Aldrich syndrome
- Fanconi anemia
- Dyskeratosis congenital
- Shwachman-Diamond syndrome
- Hemophagocytic lymphohistiocytosis (HLH)

PANCYTOPENIA FRAMEWORK



Initial Workup

1. Detailed H&P (course, exposures, exam)
2. Medication Review
3. CBC, smear, retics, chemistry, LFTs, B12, folate, coags, LDH, uric acid, T&S
4. Heme/onc consult +/- BM bx

Adapted from ucsfmed.wordpress.com

Pancytopenia with HSM

- Infections
- Malignancy
- Autoimmune
- HLH
- LCH
- Bone Marrow Infiltration

Pancytopenia Without HSM

- Bone Marrow Failure
- Aplastic Anemia
- PNH
- Megaloblastic anemia
- Drugs
- MDS

Disseminated nontuberculous mycobacterial (NTM) infections and NTM bacteremia in children

- In children, NTM cause four main clinical syndromes:
- -lymphadenopathy,
- -skin and soft tissue infection (SSTI),
- - pulmonary disease (predominantly in children with underlying pulmonary conditions),
- -disseminated disease (predominantly in children with immune compromise). ●

NTM

- M. avium complex (MAC) is the most common cause of disseminated NTM infection in children without central vascular access .
- In children with indwelling vascular catheters, Mycobacterium mucogenicum and other species that are ubiquitous in water supplies have been reported

NTM

- Disseminated NTM is rare in immune-competent children.
- Most case series of disseminated NTM describe disseminated M. avium complex (MAC) in children with acquired immunodeficiency virus .
- However, with the advent of potent antiretroviral therapy, the incidence of disseminated MAC in HIV-positive children has declined .

RISK FACTORS

- — Cases of nontuberculous mycobacteria (NTM) bacteremia or disseminated NTM disease in children have been reported among children with:
- Congenital defects in interferon-gamma and interleukin (IL)-12 synthesis and response pathways,
- ● Chemotherapy for malignancy Solid organ (particularly organs other than the lungs) or hematopoietic cell transplantation
- ● Intravenous catheter (particularly in immune-compromised patients)

CLINICAL FEATURES

- — Disseminated NTM disease occurs almost exclusively in immune-compromised children.
- Clinical features are nonspecific and may include fever, weight loss, sweating, diarrhea, generalized lymphadenopathy, generalized cutaneous lesions abdominal tenderness, and hepatosplenomegaly .
- Symptoms and signs reflect the major sites of involvement (eg, bone marrow, lymphoreticular system, gastrointestinal tract, lungs).
- Skin lesions may be the first manifestation of disseminated infection .

Case 2

- A 3-year-old girl complained of abdominal pain since two months ago, which improved with symptomatic treatment,
- she was hospitalized a week ago due to jaundice.
- She was hospitalized for two days and discharged with a possible diagnosis of hepatitis A.
- She returned again a week later with vomiting and jaundice.

1400/12/06

WBC	13.3	PMN 67%	Band 3%	lym 21%	mono 9%
RBC	5.77				
Hb	14.2				
MCV	74				
MCH	24				
MCHC	33				
Plt	251000				
ESR	3				

1400/12/06

- AST 302
- ALT 450
- ALK 586
- BILI T 3.9 D 2.2

Abdominopelvic sonography 1400/12/06

- Liver span is normal with increased echogenesity
- Other finding is normal

1400/12/14

- WBC 2450 PMN 3% lym 75% mono 10% Eos 6% Retic count 10.5 %
- RBC 3.55 DAT ++
- Hb 9 cold agglutinine neg
- MCV 85 G6PD NL
- MCH 27 IgE 12
- MCHC 32 IgG 2202
- Plt 307000 IgM 252 IgA 235

1400/12/14

- AST 2024
- ALT 1574
- ALK 797
- BILI T 17 D 9.5
- Ammonia 110
- Lactate 26
- LDH 775
- Lipase 11
- Albumine 4

GGT 41

HBSAg neg

HCV Ab neg

HAV Ab neg

HIV Ab neg

PT 14.4 INR 1.2

PTT 37

Ferritin 336

EBV Ab Igm neg

LKM Ab neg

Anti SMA neg

ANA neg

Anti DS DNA neg

Covid -19 PCR neg

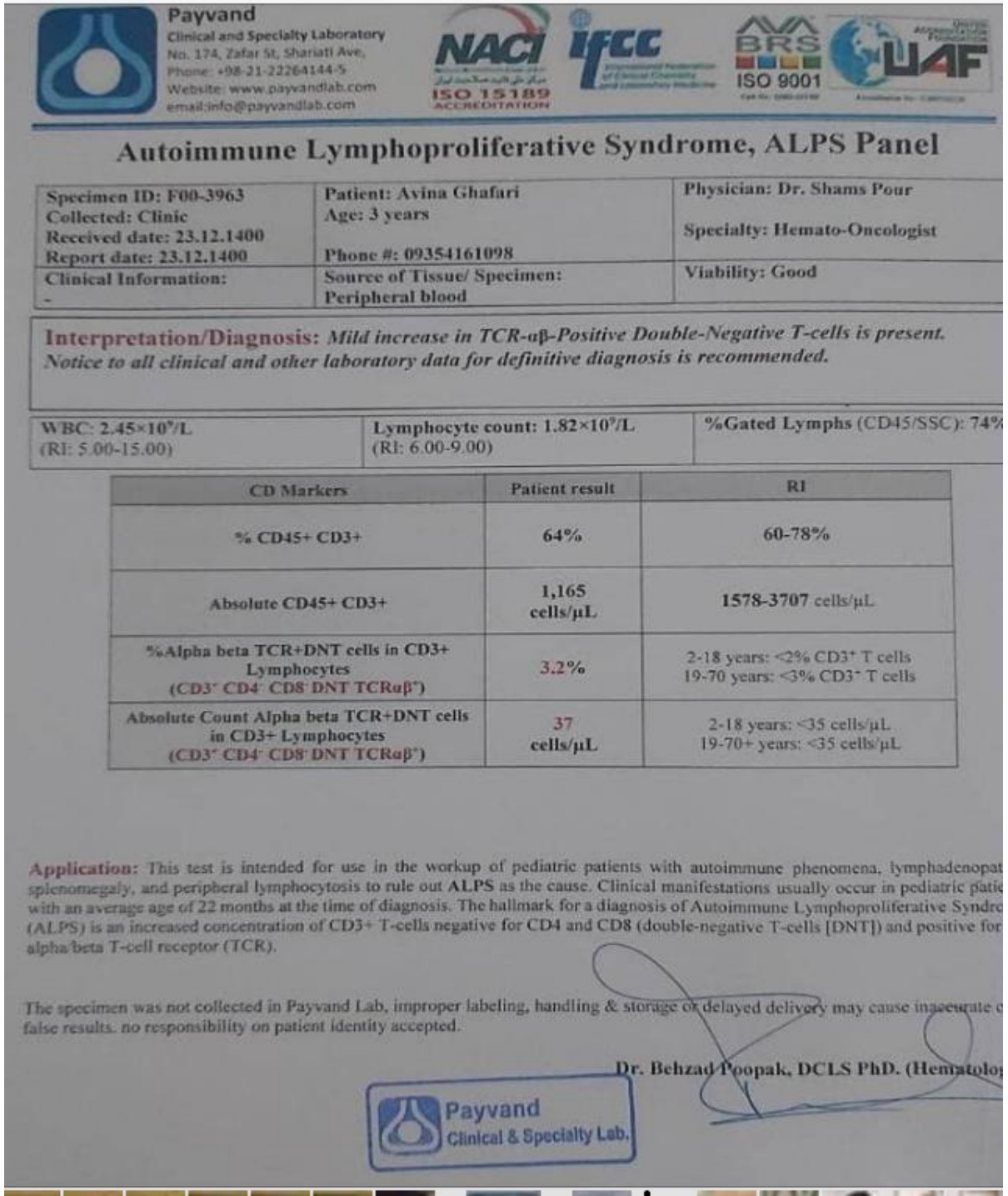
Fibrinogen 258

TG 178

CMV Ab Igm neg

1400/12/14

- Abdominopelvic Sonography ;
- Hepatosplenomegaly
- Liver 105mm
- Spleen 108*32 mm



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ISO 15189 ACCREDITATION

ISO 9001

Autoimmune Lymphoproliferative Syndrome, ALPS Panel

Specimen ID: F00-3963 Collected: Clinic Received date: 23.12.1400 Report date: 23.12.1400	Patient: Avina Ghafari Age: 3 years Phone #: 09354161098	Physician: Dr. Shams Pour Specialty: Hemato-Oncologist
Clinical Information: -	Source of Tissue/ Specimen: Peripheral blood	Viability: Good

Interpretation/Diagnosis: ***Mild increase in TCR-αβ-Positive Double-Negative T-cells is present.***
Notice to all clinical and other laboratory data for definitive diagnosis is recommended.

WBC: 2.45×10³/L (RI: 5.00-15.00)	Lymphocyte count: 1.82×10³/L (RI: 6.00-9.00)	%Gated Lymphs (CD45/SSC): 74%

CD Markers	Patient result	RI
% CD45+ CD3+	64%	60-78%
Absolute CD45+ CD3+	1,165 cells/µL	1578-3707 cells/µL
%Alpha beta TCR+DNT cells in CD3+ Lymphocytes (CD3⁺ CD4⁻ CD8⁻ DNT TCRαβ⁺)	3.2%	2-18 years: <2% CD3⁺ T cells 19-70 years: <3% CD3⁺ T cells
Absolute Count Alpha beta TCR+DNT cells in CD3+ Lymphocytes (CD3⁺ CD4⁻ CD8⁻ DNT TCRαβ⁺)	37 cells/µL	2-18 years: <35 cells/µL 19-70+ years: <35 cells/µL

Application: This test is intended for use in the workup of pediatric patients with autoimmune phenomena, lymphadenopat splenomegaly, and peripheral lymphocytosis to rule out **ALPS** as the cause. Clinical manifestations usually occur in pediatric patie with an average age of 22 months at the time of diagnosis. The hallmark for a diagnosis of Autoimmune Lymphoproliferative Syndro (ALPS) is an increased concentration of CD3+ T-cells negative for CD4 and CD8 (double-negative T-cells [DNT]) and positive for alpha/beta T-cell receptor (TCR).

The specimen was not collected in Payvand Lab, improper labeling, handling & storage or delayed delivery may cause inaccurate false results. no responsibility on patient identity accepted.

Dr. Behzad Poopak, DCLS PhD. (Hematolo

Payvand
Clinical & Specialty Lab.

Autoimmune lymphoproliferative syndrome (ALPS):

- — Autoimmune lymphoproliferative syndrome (ALPS) is characterized by dysregulation of the immune system due to an inability to regulate lymphocyte homeostasis through the process of lymphocyte apoptosis (a form of programmed cell death).
- The consequences include lymphoproliferative disease, manifested by lymphadenopathy, hepatomegaly, splenomegaly, and an increased risk of lymphoma, as well as autoimmune disease, typically involving blood cells.

ALPS

- — ALPS due to germline pathogenic variants in the Fas cell surface death receptor (FAS) gene that encodes an apoptosis-associated antigen (ALPS-FAS) is the most common and best-characterized type of ALPS, although it is nonetheless a rare condition.

ALPS

- — ALPS typically manifests in the first years of life.
- The most common presenting clinical manifestations are noninfectious, nonmalignant lymphoid expansion with lymphadenopathy, splenomegaly, and/or hepatomegaly and autoimmune cytopenias, including thrombocytopenia and hemolytic anemia.
- Lymphoma is a late complication.
- All disease manifestations appear to be more common in males than females .

ALPS

- The lymphoproliferation typically manifests in the first years of life in individuals with ALPS-FAS.
- In some persons, *splenomegaly is the predominant or only manifestation of lymphoproliferation*
- Lymphadenopathy tends to decrease in the second decade of life, whereas splenomegaly often does not.
- A frequent cause of death in patients treated with splenectomy is sepsis; therefore, splenectomy should be avoided.

ALPS

- Autoimmunity
- — Autoimmunity is a common feature of ALPS .
- It is typically limited to the hematopoietic system, but other organs (eg, liver, kidneys) are sometimes involved.
- Autoimmunity can be the first ALPS manifestation, although it is not always present at the time of diagnosis or at the time of the most extensive lymphoproliferation.

ALPS

- Combinations of cytopenias (also known as Evans syndrome) that occur concomitantly and/or sequentially are typical, with Coombs-positive autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) the most common combination, followed by ITP and autoimmune neutropenia (AIN).

DIAGNOSIS

- Whom to test
- — The diagnosis of ALPS should be suspected in patients with lymphoid expansion with:
- lymphadenopathy,
- splenomegaly, and/or hepatomegaly;
- autoimmune disease with blood cytopenias including thrombocytopenia and hemolytic anemia;
- and/or lymphoma.

Diagnostic criteria

- — A revised set of diagnostic criteria was published in 2010 .
- A defnitive diagnosis of ALPS is based upon the presence of both required criteria and one primary accessory criterion.
- A probable diagnosis is based upon the presence of both required criteria plus one secondary accessory criterion.

Required criteria

- — Evidence of lymphoproliferation is required for the diagnosis of ALPS.
- Chronic (more than six months) nonmalignant, noninfectious lymphadenopathy, splenomegaly, or both.
- If only lymphadenopathy is present, it must affect two or more nodal chains.
- Hepatomegaly also may be present but is not required for diagnosis.

Required criteria

- Elevated (>2 percent or >68 cells/microL) percent and/or number of peripheral blood CD3 positive T cells that express the alpha beta T cell receptor (TCR) but lack both CD4 and CD8 coreceptor (alpha beta double-negative T [DNT] cells) on flow cytometry in the context of normal or elevated total lymphocyte counts.

Primary accessory criteria

- Defective lymphocyte apoptosis.
- If the assay is abnormal (≤50 percent of the cell death seen in a control sample assayed simultaneously), it is helpful, but not always practical, to repeat at least once for confirmation.
- Germline pathogenic variant in FAS, FASLG, or CASP10 or somatic pathogenic variant in FAS.

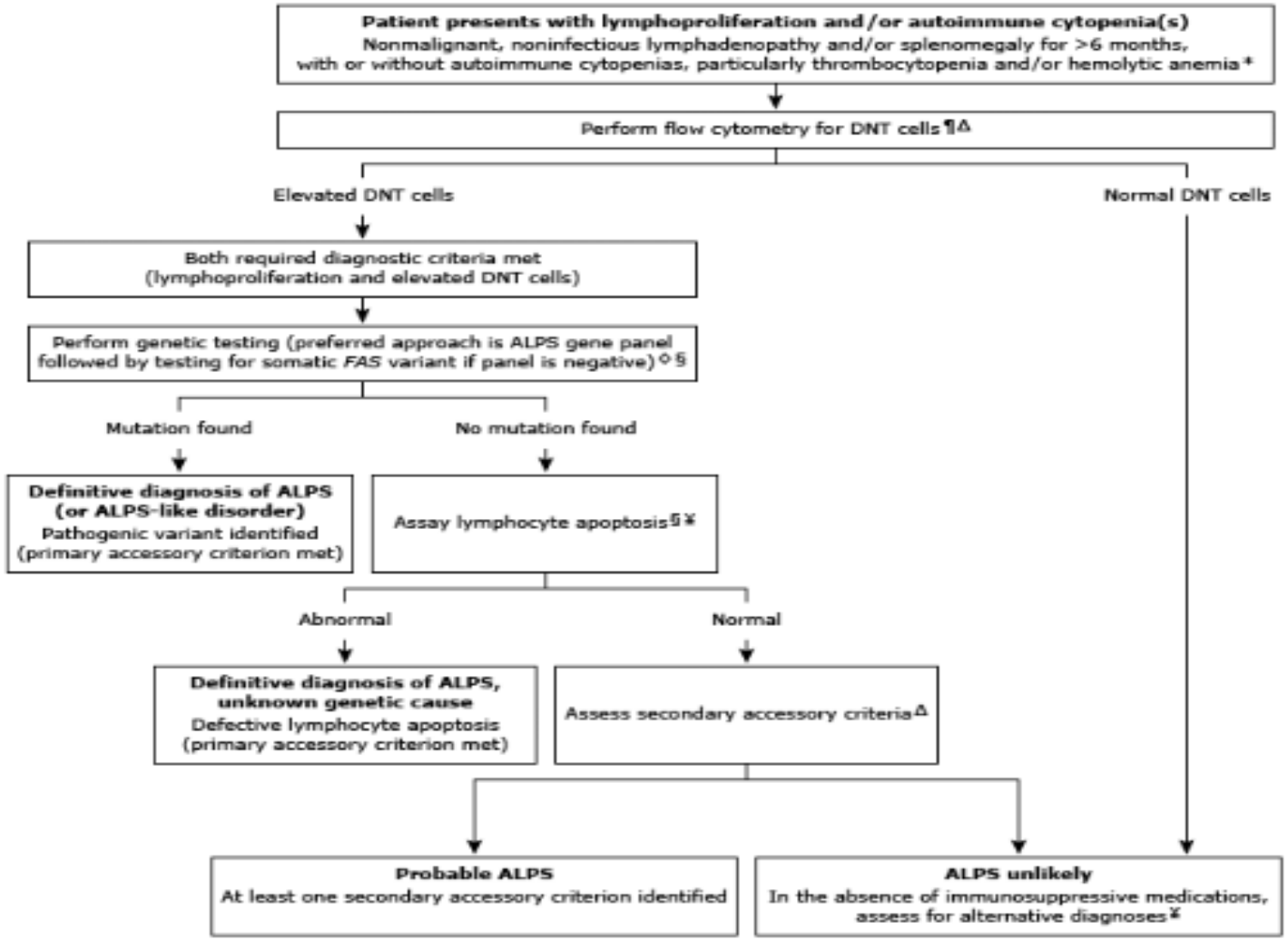
Secondary accessory criteria

- Elevated levels of any of the following ALPS biomarkers:
- plasma (or serum) levels of soluble Fas ligand (FasL; >200 pg/mL),
- interleukin (IL) 10 (>20 pg/mL),
- IL-18 (>500 pg/mL),
- and vitamin B12 (>1500 ng/L).
- Autoimmune blood cytopenias with hypergammaglobulinemia (elevated polyclonal IgG levels).
- Positive family history of confirmed ALPS or nonmalignant, noninfectious lymphoproliferation with or without autoimmunity.

Secondary accessory criteria

- Typical immunohistologic findings, including lymph node pathology (usually obtained for evaluation of possible lymphoma) and T cell studies (flow cytometry, immunohistochemicalanalysis, and polymerase chain reaction [PCR] assessing for TCR gene rearrangement), as determined by an experienced hematopathologist.

Autoimmune lymphoproliferative syndrome (ALPS) diagnostic algorithm



Definitive diagnosis: Both required criteria plus one primary accessory criterion.

Probable diagnosis: Both required criteria plus one secondary accessory criterion.

THANK YOU