# Patient 1

- The patient is a 2.5 year old girl who has come with abdominal distention.

- The symptoms began approximately 3 months ago, initially presenting as abdominal pain.

- The mother initially attributed the symptoms to weaning and did not pursue further evaluation.

- After some time, the mother noticed abdominal distension in the child and sought several medical visits.
- During this time, the child exhibited persistent abdominal pain and restlessness, particularly after meals.
- Initially, the physicians suggested a diagnosis of gastric bloating, recommended dietary modification, and prescribed probiotic medications.

- Ultimately, due to the persistent of symptoms and worsening abdominal swelling and pain, the patient presented to our emergency department and was admitted to the gastroenterology service.

- The abdominal pain was described as vague, diffuse across the abdomen, without localization to a specific area, and was unaffected by defecation.

- The child did not experience diarrhea, vomiting or fever during this period.

- the parents only reported constipation in the child.

- The child was born at 39 weeks of gestation and was admitted to the NICU for 2 days due to respiratory problems. Apart from this, there is no significant past medical history.

- The parents are non-consanguineous and have no underlying medical conditions.

- The patient is the second child, and the sibling is healthy.

- On general assessment, the child is alert and oriented, with good general condition and stable vital signs. The patient does not appear ill or toxic.

- Physical examination of the head, neck, chest, cardiovascular and respiratory systems, skin and extremities was unremarkable.

- On abdominal examination, significant swelling was observed, with uniform distension across the entire abdomen.

- Abdominal auscultation revealed normal bowel sounds.

- Palpitation revealed the liver approximately 5 cm below the costal margin, with a coarse, irregular texture.

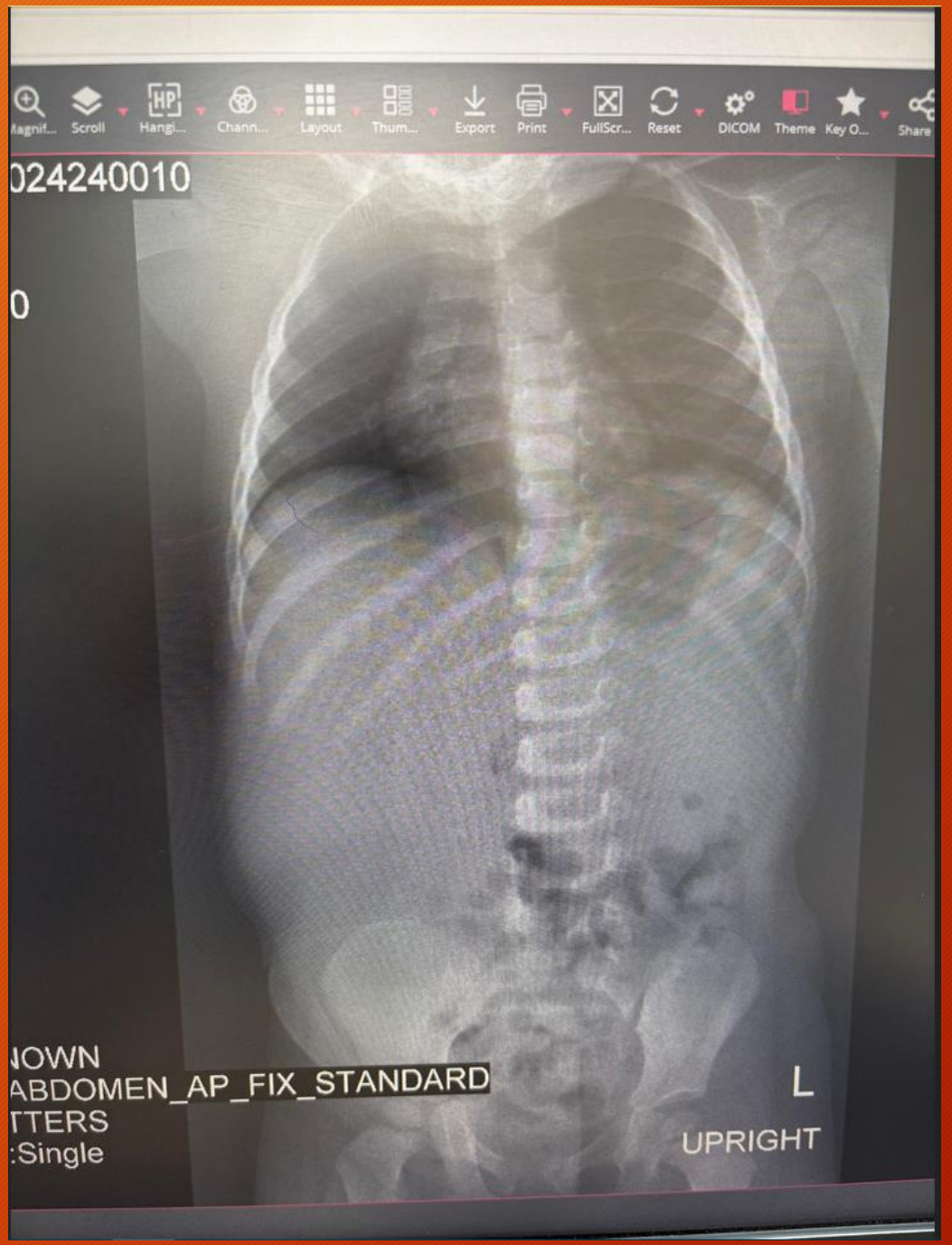
- The spleen was palpable about 4 cm below the costal margin.

# Lab Tests

CBC
- WBC = 7100 (N:62% L:32%)
- HGB = 10.9
- Plt = 175000

S/E
- Loose
- WBC: 2-3
- RBC: 2-3

| | | | |
|---|---|---|---|
| ESR: 16 | ALT: 22 | P: 4.2 | EBV IgM: 4.2 |
| CRP: 19.6 | LDH: 770 | Fibrinogen: 520 | EBV IgG: 13 |
| Uric Acid: 2.5 | Cr: 0.5 | Ferritin: 82.3 | Alb: 4.3 |
| AST: 45 | Ca: 9 | αFP: 3.75 | |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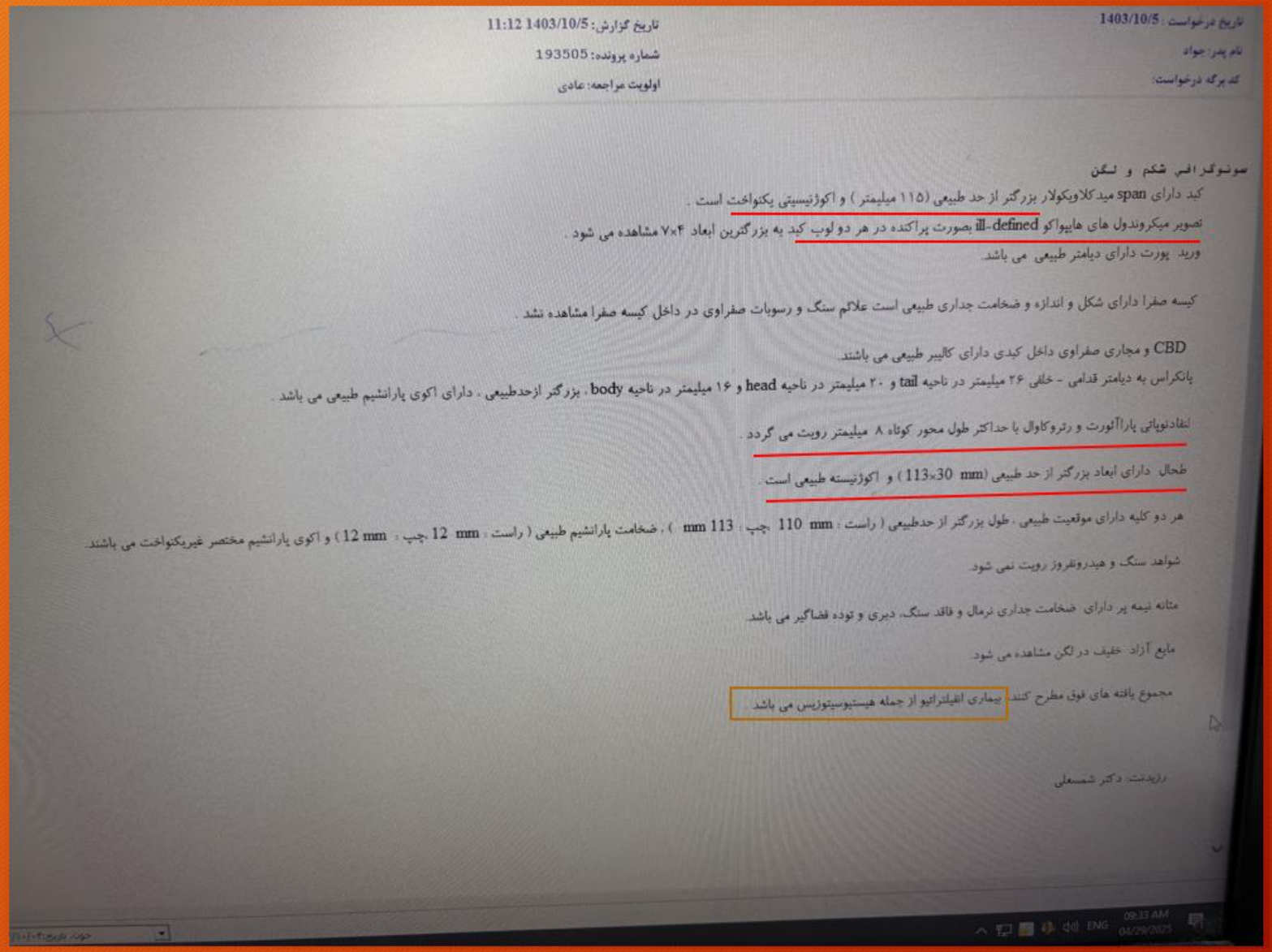


تاریخ درخواست: 1403/10/5
نام پدر: جواد
کد برگه درخواست:

تاریخ گزارش: 1403/10/5 11:12
شماره پرونده: 193505
اولویت مراجعه: عادی

سونوگرافی شکم و لگن

کبد دارای span مید کلاویکولار بزرگتر از حد طبیعی (۱۱۵ میلیمتر ) و اکوژنیسیتی یکنواخت است .

تصویر میکروندول های هایپواکو ill-defined بصورت پراکنده در هر دو لوب کبد به بزرگترین ابعاد ۷×۴ مشاهده می شود .

ورید پورت دارای دیامتر طبیعی می باشد.

کیسه صفرا دارای شکل و اندازه و ضخامت جداری طبیعی است علائم سنگ و رسوبات صفراوی در داخل کیسه صفرا مشاهده نشد .

CBD و مجاری صفراوی داخل کبدی دارای کالیبر طبیعی می باشند.

پانکراس به دیامتر قدامی - خلفی ۲۶ میلیمتر در ناحیه tail و ۲۰ میلیمتر در ناحیه head و ۱۶ میلیمتر در ناحیه body ، بزرگتر ازحدطبیعی ، دارای اکوی پارانشیم طبیعی می باشد .

لنفادنوپاتی پاراآئورت و رتروکاوال با حداکثر طول محور کوتاه ۸ میلیمتر رویت می گردد .

طحال دارای ابعاد بزرگتر از حد طبیعی (113×30 mm ) و اکوژنیسته طبیعی است .

هر دو کلیه دارای موقعیت طبیعی ، طول بزرگتر از حدطبیعی ( راست : 110 mm ، چپ : 113 mm ) ، ضخامت پارانشیم طبیعی ( راست : 12 mm ، چپ : 12 mm ) و اکوی پارانشیم مختصر غیریکنواخت می باشند.

شواهد سنگ و هیدرونفروز رویت نمی شود.

مثانه نیمه پر دارای ضخامت جداری نرمال و فاقد سنگ، دبری و توده فضاگیر می باشد.

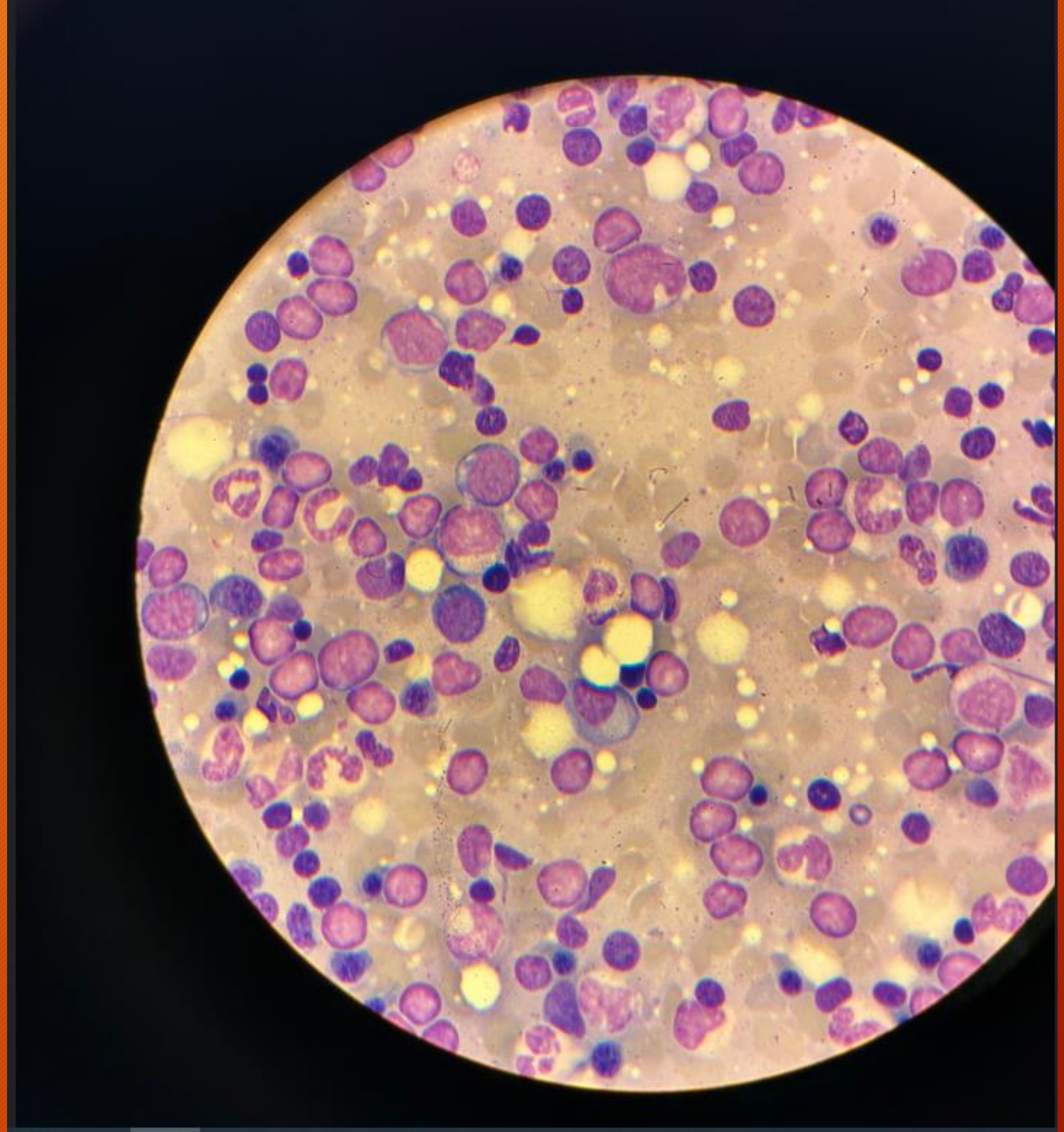
مایع آزاد خفیف در لگن مشاهده می شود.

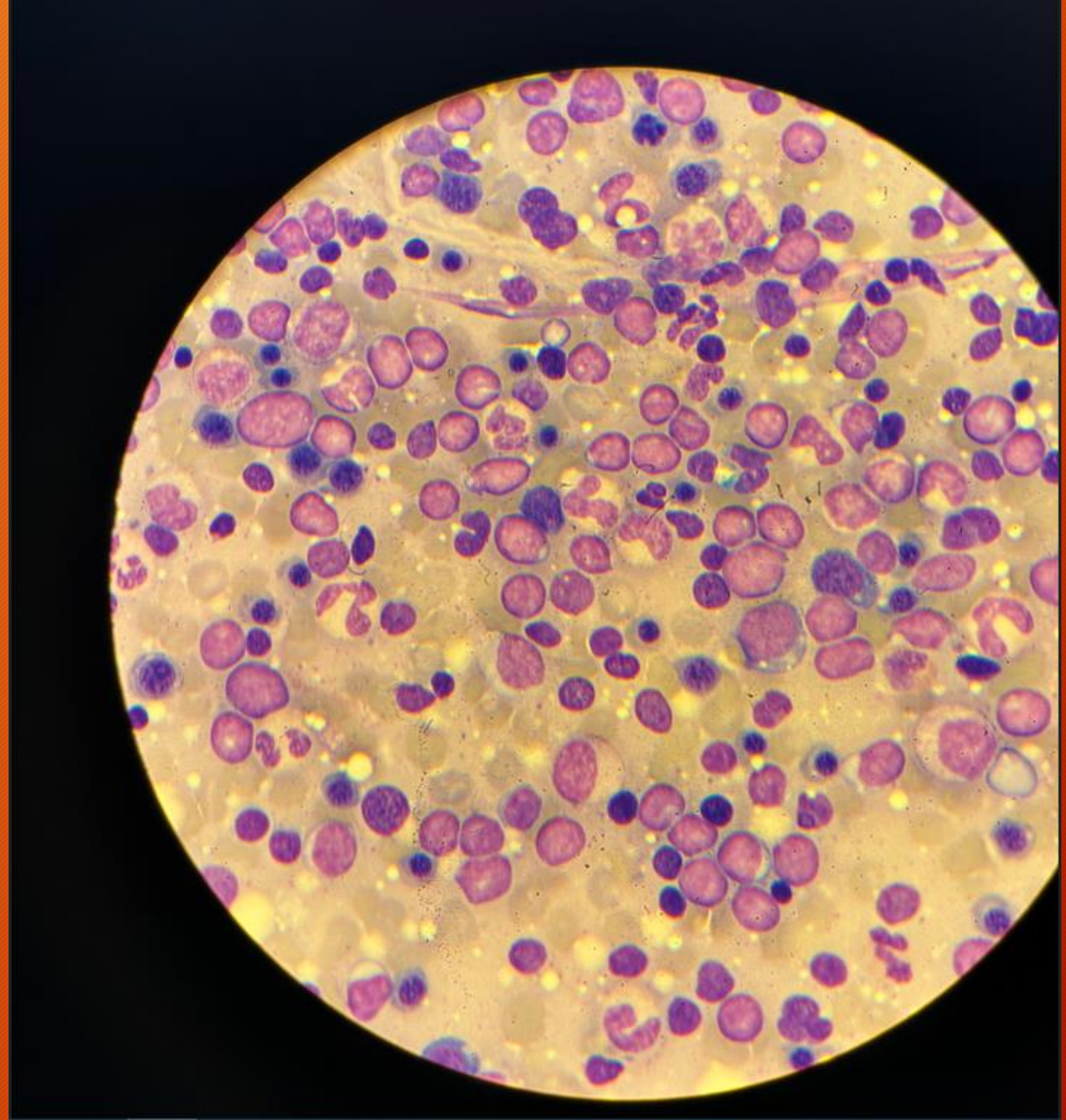
مجموع یافته های فوق مطرح کننده بیماری انفیلترانیو از جمله هیستیوسیتوزیس می باشد .

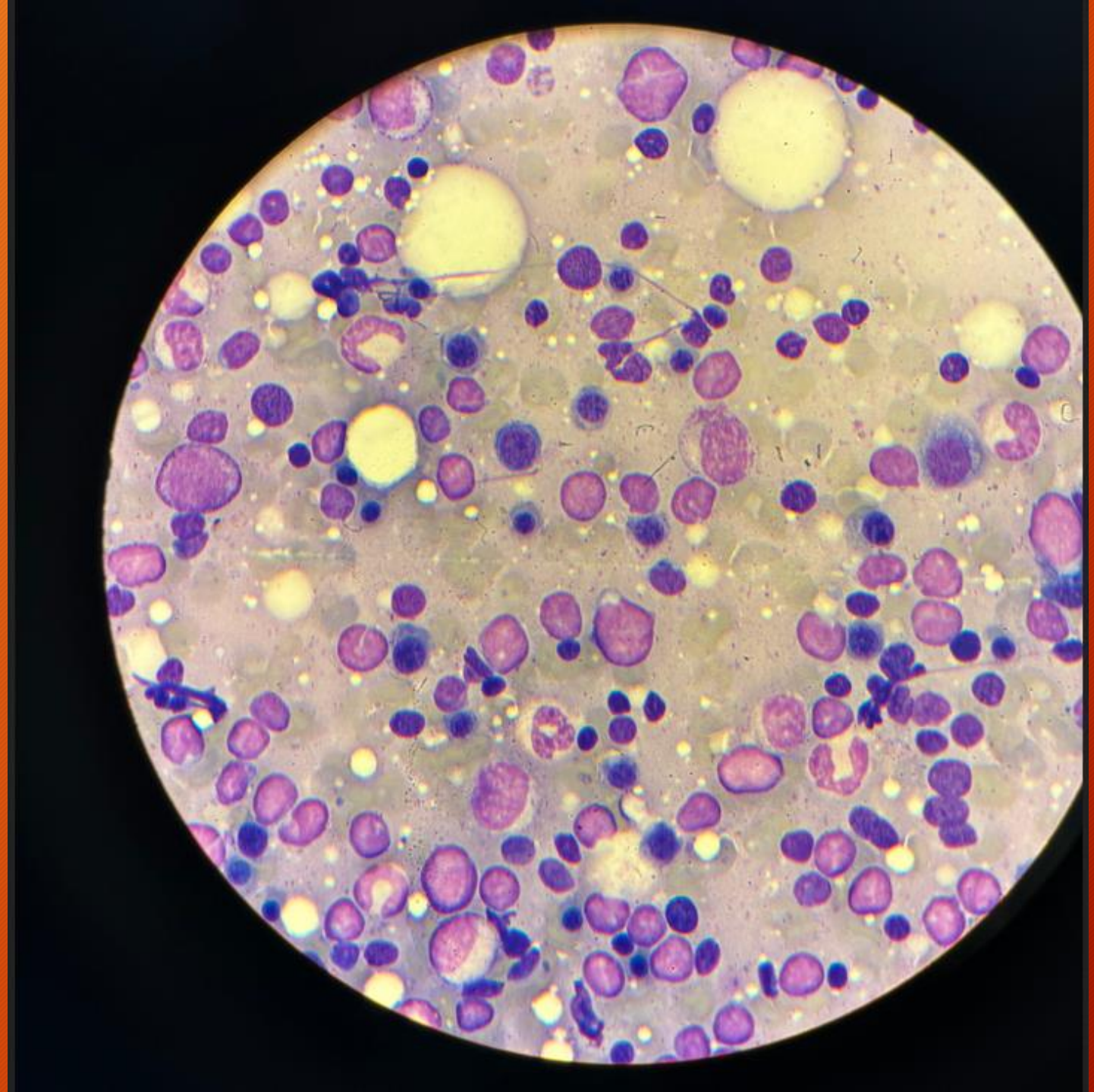
رزیدنت: دکتر شمسعلی

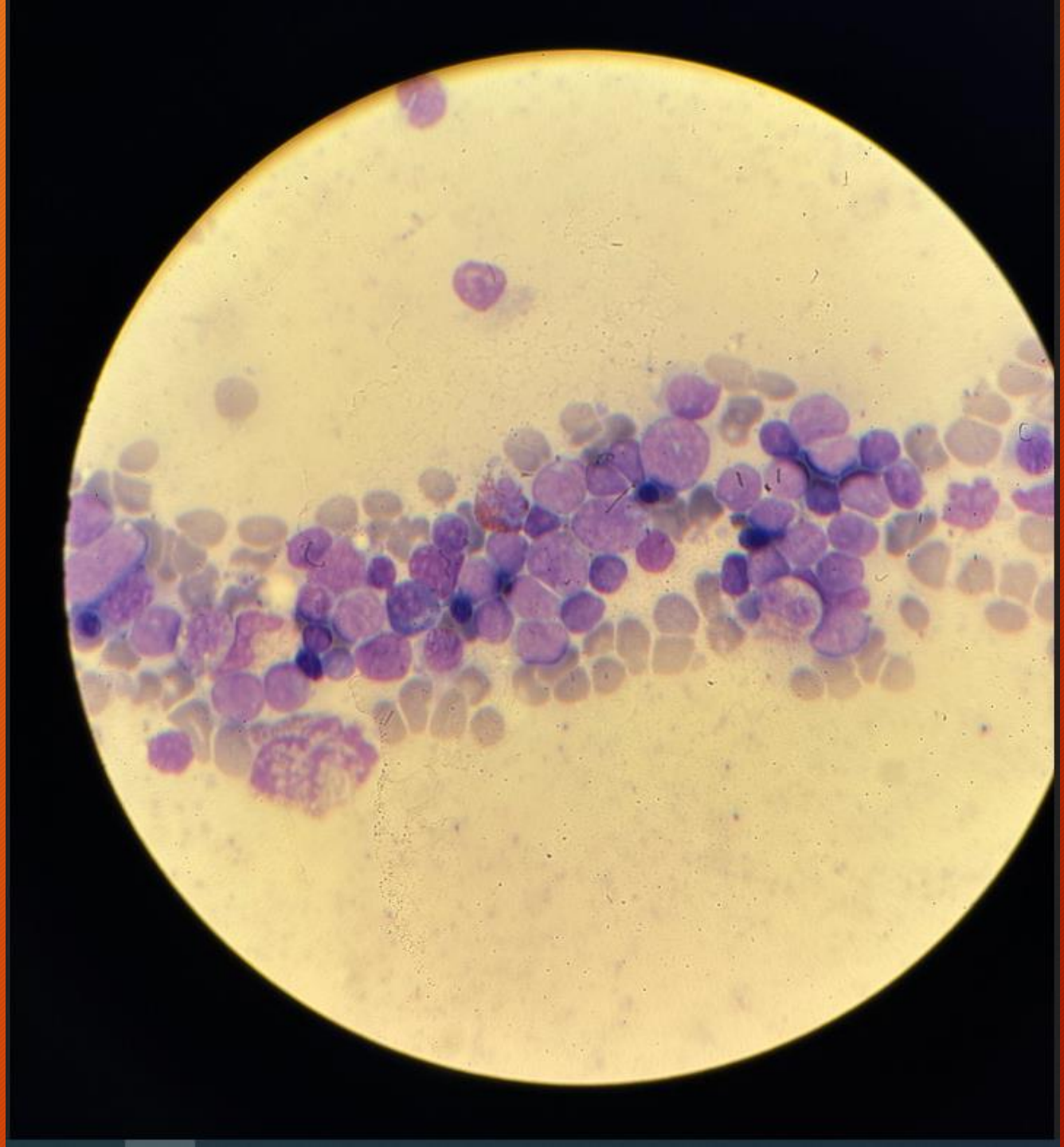
- Sonography of VOD was normal

- Due to sonographic findings, a hematology consultation was requested, leading to the decision to perform bone marrow aspiration and biopsy.









## Others

حق پذیرش

Pathology Report

Pathology No 03-819

Clinical Data

Specimen: Bone marrow biopsy

A 2 y/o girl with hepatosplenomegaly.

WBC: 7 RBC: 4.37 Hb: 11.7 MCV: 84 PLT: 155

MACROSCOPIC

The specimen received in formalin consists of multiple fragments of bony tissue TM: 2cm in length and 0.1cm in diameter.

SOS:M/2 EMB:100%

MICROSCOPIC

See the diagnosis.

DIAGNOSIS

Bone marrow, Biopsy:

-Acute Pre-B cell Lymphoblastic Leukemia (Involving about 60% of marrow space)

IHC study (Performed in Firozgar Hospital)

-CD79a: Positive stain in leukemic cells

-CD20: Negative stain in leukemic cells

-TDT: Positive stain in leukemic cells

ICDO C-42.1

M-9728/3

Pathologist: Dr.N. Mortazavi

Reprinted

*: Rechecked , H: High , L: Low, **:Urgent

Location: پاتولوژی

Lab Director: نفیسه مرتضوی

# Hepatomegaly

- Tender hepatomegaly
  - Infectious causes:
    - Acute hepatitis: HAV, HBV, HCV, EBV, CMV, HSV, Adenovirus
    - Bacterial infections: sepsis, typhoid fever, leptospirosis, brucellosis, TB
    - Liver Abscess
    - Parasitic infections: malaria, visceral leishmaniosis, schistosomiasis, echinococcosis

- Tender hepatomegaly
  - Congestive and vascular causes:
    - Right heart failure: congenital heart disease, myocarditis
    - Budd-Chiari syndrome (hepatic vein thrombosis)
    - Sickle cell disease: hepatic sequestration crisis
    - Veno-occlusive disease (sinusoidal obstruction syndrome): post chemotherapy, after HSCT

- Tender hepatomegaly
  - Metabolic and toxic causes:
    - Reye syndrome: Acute liver failure following viral illness and aspirin use
    - Drug/toxin induced liver injury: Acetaminophen, isoniazid, MTX

- Tender hepatomegaly
  - Infiltrative Disorders:
    - Histiocytic disorders: LCH, HLH
  - Autoimmune and inflammatory causes:
    - Autoimmune hepatitis
    - SLE
    - JIA

- Nontender hepatomegaly

  - Storage Disorders:

    - Glycogen storage diseases (GSD I, III, IV, VI, IX): excess glycogen deposition leads to a firm, smooth hepatomegaly

    - Lysosomal storage diseases:

      - ✓ Niemann-Pick disease: sphingomyelin accumulation

      - ✓ Gaucher disease: glucocerebroside accumulation

      - ✓ Mucopolysaccharidoses (Hurler, Hunter syndromes): coarse facies and skeletal abnormalities

- Nontender hepatomegaly
  - Hematologic and malignant causes:
    - Leukemia: Infiltration of the liver by leukemic cells can cause hepatomegaly
    - Lymphoma: Hepatomegaly can occur due to liver involvement
    - Neuroblastoma: Can metastasize to the liver, causing enlargement
    - Thalassemia Major: chronic extramedullary hematopoiesis

- Nontender hepatomegaly

  - Metabolic and Endocrine causes:

    - Congenital Hemochromatosis: Iron overload can lead to hepatomegaly
    - Wilson’s Disease: Copper accumulation can lead to hepatomegaly and liver damage
    - Non-alcoholic fatty liver disease (NAFLD) can cause hepatomegaly, especially in obese children
    - Congenital hypothyroidism

- Nontender hepatomegaly

  - Congenital and Genetic Disorders:

    - Alpha-1 Antitrypsin Deficiency: Can lead to liver enlargement and chronic liver disease

    - Cystic Fibrosis: Can cause hepatomegaly due to biliary obstruction and liver involvement

- Nontender hepatomegaly
  - Chronic infections and granulomatous diseases:
    - Congenital TORCH infections: Toxoplasmosis, Rubella, CMV, HSV, Syphilis
    - Chronic hepatitis B/C
    - TB, Brucellosis, Schistosomiasis

- Nontender hepatomegaly

  - Benign Liver Masses:

    - Hemangioma: The most common benign liver tumor in children, often seen in infants
    - Focal Nodular Hyperplasia (FNH): A benign proliferation of hepatocytes with a central scar
    - Hepatic Adenoma: A rare benign tumor of hepatocytes
    - Mesenchymal Hamartoma: A benign cystic lesion of the liver, most common in children <2 years

- Nontender hepatomegaly

  - Malignant Liver Masses:

    - Hepatoblastoma: The most common primary malignant liver tumor in children, typically occurring in children <3 years
    - Hepatocellular Carcinoma (HCC): A malignant tumor of hepatocytes, more common in older children and adolescents
    - Undifferentiated Embryonal Sarcoma: A rare, aggressive malignant liver tumor, typically seen in children aged 6–10 years
    - Metastatic Tumors: Liver metastases from other primary cancers (e.g., neuroblastoma, Wilms tumor, lymphoma).

- Nontender hepatomegaly
  - Other conditions:
    - Caroli disease: a congenital disorder characterized by multifocal, segmental dilatation of large intrahepatic bile ducts. The condition is usually associated with cystic kidney disease of varying severity
    - Polycystic liver disease: Polycystic liver disease predominantly occurs in patients with autosomal dominant polycystic kidney disease (ADPKD), with an increasing burden of liver cysts occurring with age and in patients with more advanced kidney disease

# INITIAL EVALUATION

- History
  - ❖ Presenting Symptoms
    - ➢ Constitutional Symptoms: Fever, weight loss, fatigue, or failure to thrive
    - ➢ Abdominal Symptoms: Pain, distension, or vomiting
    - ➢ Jaundice: Yellowing of the skin or eyes
    - ➢ Respiratory Symptoms: Dyspnea or cough (may suggest cardiac or systemic disease)
    - ➢ Neurological Symptoms: Developmental delay, seizures, or hypotonia (may suggest metabolic disorders)

- History
  - Past Medical History
    - Infections: History of viral hepatitis, tuberculosis, or parasitic infections
    - Chronic Diseases: Known liver disease, cardiac disease, or metabolic disorders
    - Surgeries: Previous abdominal surgeries or liver-related procedures

- History
  - Family History
    - Genetic Disorders: Family history of metabolic disorders (e.g., Wilson's disease, glycogen storage diseases) or liver diseases.
    - Infections: Family history of hepatitis B or C
  - Social History
    - Travel: Exposure to endemic areas for infections (e.g., malaria, schistosomiasis)
    - Dietary Habits: High fructose or galactose intake (may suggest metabolic disorders)
    - Toxin Exposure: Medications, herbal supplements, or environmental toxins

- Physical Examination

  - General Examination

    - Growth Parameters: Weight, height, and head circumference (failure to thrive may suggest chronic disease)

    - Vital Signs: Fever (infections), tachycardia (heart failure), or hypotension (shock)

- Physical Examination

  - Abdominal Examination

    - Liver Size and Consistency: Measure liver span by percussion and palpation (tender vs. nontender, smooth vs. nodular)
    - Splenomegaly: Often associated with portal hypertension or systemic diseases
    - Ascites: Fluid wave or shifting dullness (suggests liver dysfunction or portal hypertension)

- Physical Examination
  - Other Findings
    - Jaundice: Suggests liver dysfunction or hemolysis
    - Lymphadenopathy: May indicate infections or malignancies
    - Skin Findings: Bruising, petechiae (coagulopathy), or rashes (systemic diseases)
    - Neurological Signs: Developmental delay, hypotonia, or ataxia (metabolic disorders)

- Initial Laboratory Tests

  - Liver Function Tests

    - ALT/AST: Elevated in hepatocellular injury
    - Alkaline Phosphatase (ALP): Elevated in biliary obstruction or infiltrative diseases
    - Bilirubin: Elevated in liver dysfunction or hemolysis
    - Albumin and INR: Assess synthetic function of the liver

- Initial Laboratory Tests
  - Infectious Workup
    - Viral Serologies: Hepatitis B/C, EBV, CMV, HIV
    - Bacterial Cultures: Blood, urine, or stool cultures if infection is suspected
    - Parasitic Tests: Stool ova and parasites, serology for schistosomiasis or leishmaniasis

- Initial Laboratory Tests

  - Metabolic and Genetic Tests

    - Ammonia: Elevated in urea cycle disorders or liver failure
    - Lactate: Elevated in mitochondrial disorders
    - Alpha-1 Antitrypsin Level: For alpha-1 antitrypsin deficiency
    - Copper Studies: Ceruloplasmin and 24-hour urine copper for Wilson's disease
    - Ferritin and Iron Studies: For hemochromatosis

- # Initial Laboratory Tests

  - ## Hematologic Tests

    - Complete Blood Count (CBC): Anemia, thrombocytopenia, or leukocytosis
    - Peripheral Smear: For hemolysis or abnormal cells (e.g., blasts in leukemia)

- Initial Laboratory Tests
  - Tumor Markers
    - Alpha-Fetoprotein (AFP): Elevated in hepatoblastoma or hepatocellular carcinoma
    - Beta-HCG: Elevated in germ cell tumors

- Imaging Studies
  - Ultrasound
    - First-line imaging modality
    - Evaluates liver size, echotexture, and presence of masses, cysts, or biliary dilation

- Imaging Studies
  - CT or MRI
    - Provides detailed evaluation of liver parenchyma and vascular structures
    - Useful for characterizing masses (e.g., hemangioma, hepatoblastoma)

- Imaging Studies
  - Doppler Ultrasound
    - Assesses blood flow in the liver and portal vein (e.g., portal hypertension, Budd-Chiari syndrome)

- Specialized Tests

  - Liver Biopsy

    - Gold standard for diagnosing liver diseases (e.g., metabolic disorders, granulomatous diseases, malignancies).

    - Histopathology can reveal specific findings (e.g., glycogen accumulation, fibrosis, or tumor cells)

- Specialized Tests

  - Genetic Testing

    - For suspected metabolic or genetic disorders (e.g., Wilson’s disease, glycogen storage diseases)

  - Endoscopy

    - To evaluate for varices or portal hypertensive gastropathy in cases of portal hypertension

# Multiple ill-defined micronodules in the liver

- Infectious Causes
  - ❖ Granulomatous Infections
    - ➢ Tuberculosis (TB): Hepatic TB can cause granulomas and micronodules, often as part of disseminated disease
    - ➢ Fungal Infections: Histoplasmosis, coccidioidomycosis, or cryptococcosis can cause granulomatous hepatitis
    - ➢ Brucellosis
    - ➢ Schistosomiasis: Chronic infection can cause granulomas and fibrosis

- Infectious Causes
  - ❖ Viral Infections
    - ➢ Chronic Hepatitis B or C: Can cause nodular regeneration and fibrosis
    - ➢ Cytomegalovirus (CMV): Can lead to hepatitis and micronodules, especially in immunocompromised children.
    - ➢ Epstein-Barr Virus (EBV): Can cause hepatitis and granulomatous inflammation

- Infectious Causes
  - ❖ Parasitic Infections
    - ➢ Visceral Leishmaniasis (Kala-azar): Can cause hepatosplenomegaly and micronodules due to macrophage infiltration.
    - ➢ Toxoplasmosis

- Metabolic and Genetic Disorders

  - Glycogen Storage Diseases (GSD)

    - Type I (von Gierke Disease): Glycogen accumulation in the liver causes hepatomegaly and nodular changes.

    - Type III (Cori Disease): Similar to Type I but with additional muscle involvement

  - Wilson's Disease: Copper accumulation in the liver leads to inflammation, fibrosis, and nodular regeneration

  - Alpha-1 Antitrypsin Deficiency: Abnormal protein accumulation in hepatocytes causes liver damage and nodular changes

  - Hemochromatosis: Iron overload can lead to liver damage and nodular regeneration

- Malignancies
  - Primary Liver Tumors
    - Hepatoblastoma
    - Hepatocellular Carcinoma (HCC)
  - Metastatic Disease
    - Neuroblastoma
    - Wilms Tumor
    - Lymphoma/Leukemia: Infiltration of the liver by malignant cells

- Malignancies
  - ❖ Hematologic Malignancies
    - ➢ Langerhans Cell Histiocytosis (LCH): Can cause liver infiltration and micronodules

- Systemic Diseases
  - Sarcoidosis: A multisystem granulomatous disorder that can involve the liver, causing granulomas and micronodules
  - Autoimmune Hepatitis
  - Primary Sclerosing Cholangitis (PSC)

# Patient 2

- The patient is a 14 year-old male who presented with a history of recurrent bleeding episodes.

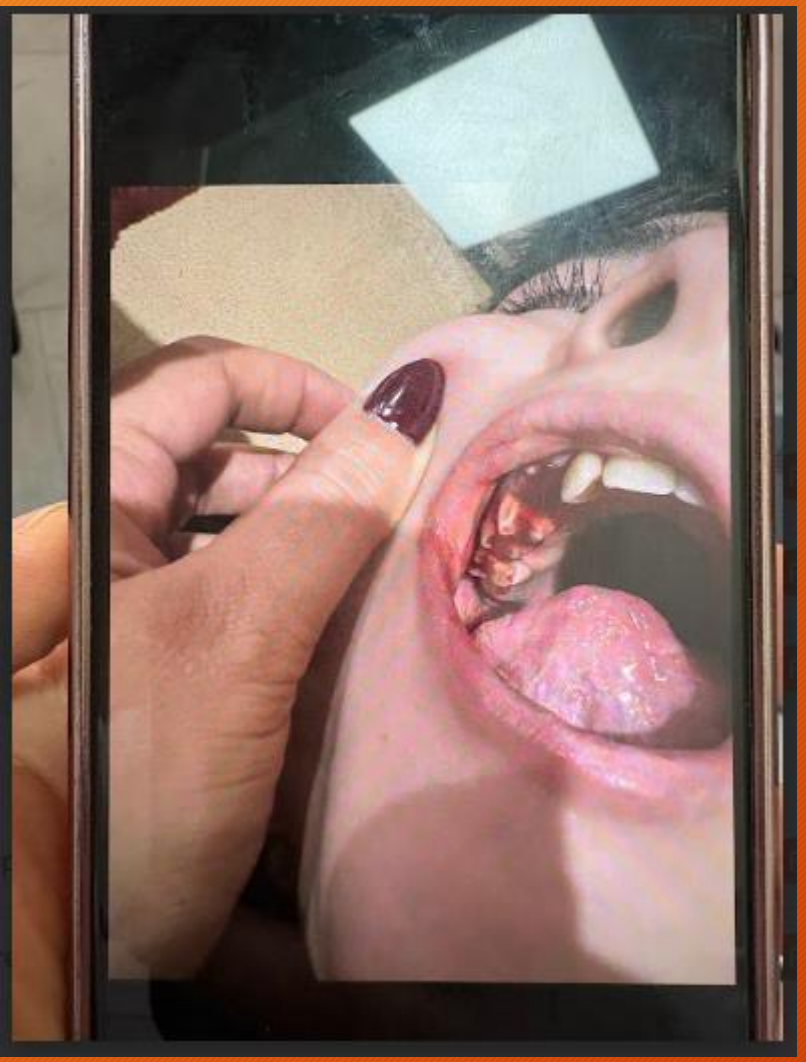
- The patient’s problems began around the age of 5, when he experienced upper and lower gastrointestinal bleeding after returning from a swimming pool.

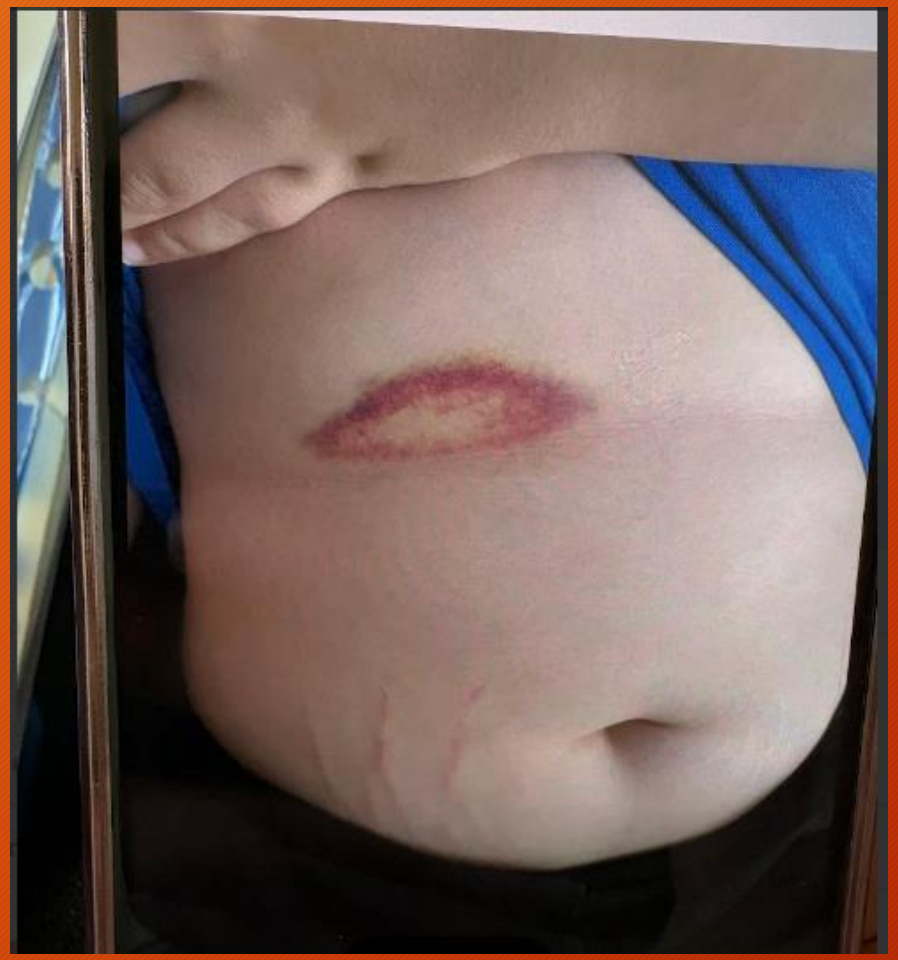
- Due to the GI bleeding, he was hospitalized for one week, but no specific diagnosis was established.

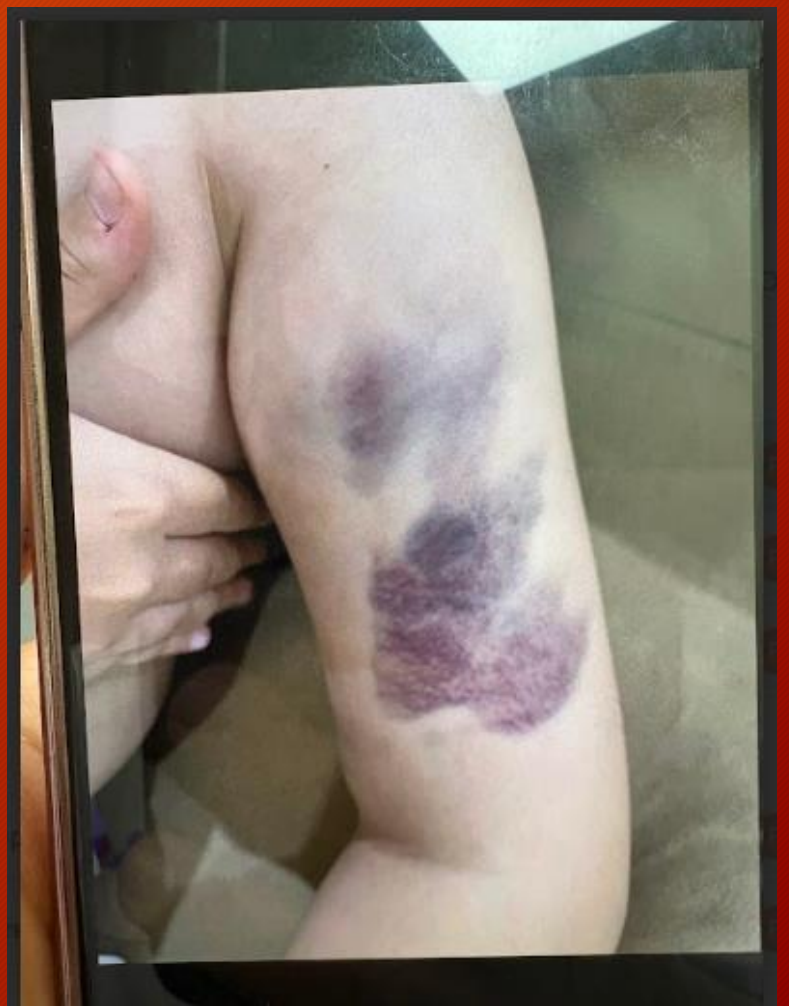
- At the age of 8, he experienced severe bleeding for four days following the loss of a primary tooth.

- Approximately one year later, the patient developed severe pain and swelling in the left ankle after falling from a height, which was diagnosed as a fracture and treated with casting.

- From this point onward, the patient experienced episodes of severe pain and swelling in one of his joints, particularly the ankles, elbows, and knees, with frequency of approximately every one to two months.



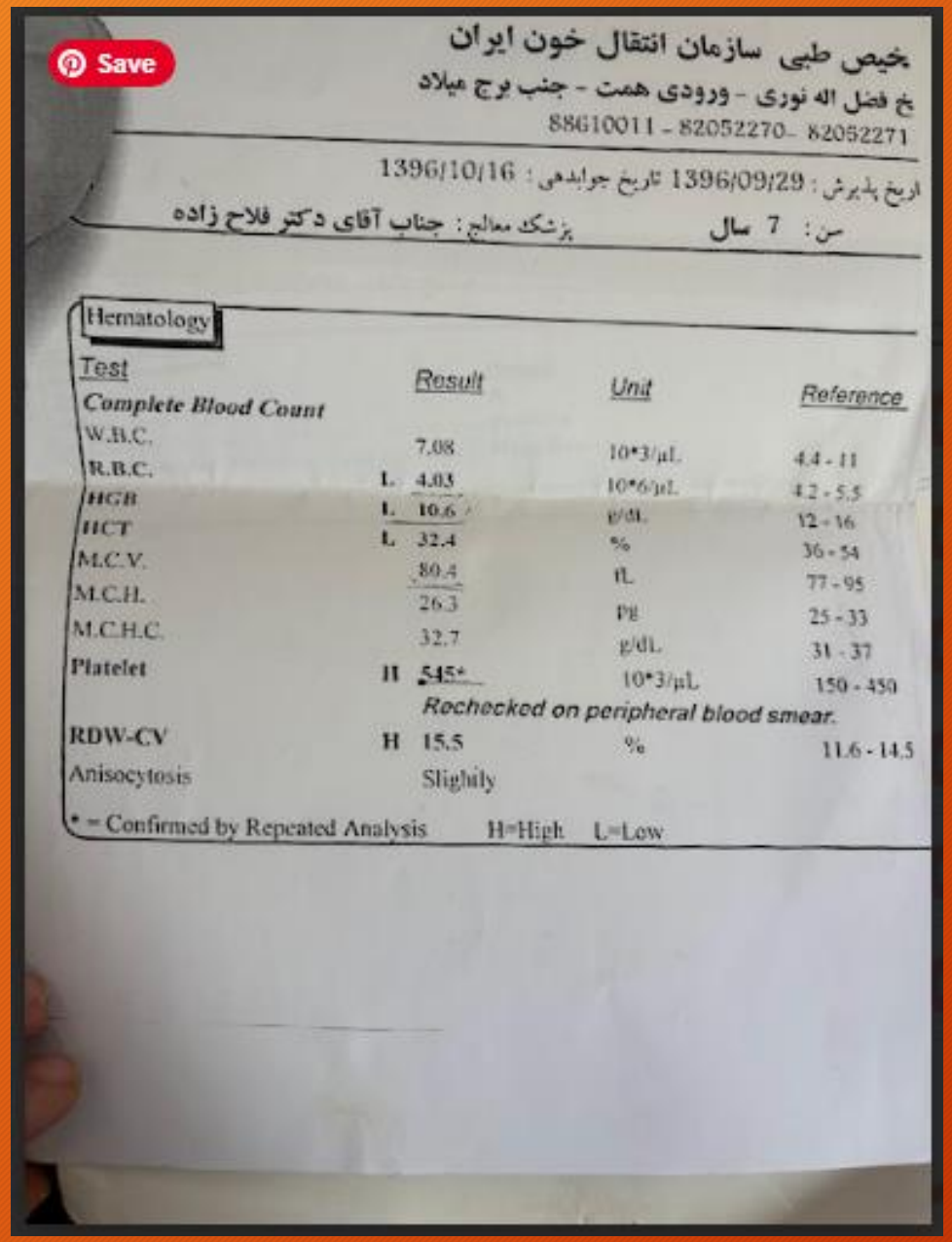




- Initially, the patient presented to orthopedics and underwent cast immobilization of the affected joints; however, no sustained improvement was observed.

- Subsequently, the patient was referred to rheumatologists and underwent various diagnostic workups, during which a diagnosis of rheumatologic disorders was considered.

- However, the patient ultimately did not respond to rheumatologic treatments either.



بخیص طبی سازمان انتقال خون ایران

خ فضل اله نوری - ورودی همت - جنب برج میلاد

88610011 - 82052270- 82052271

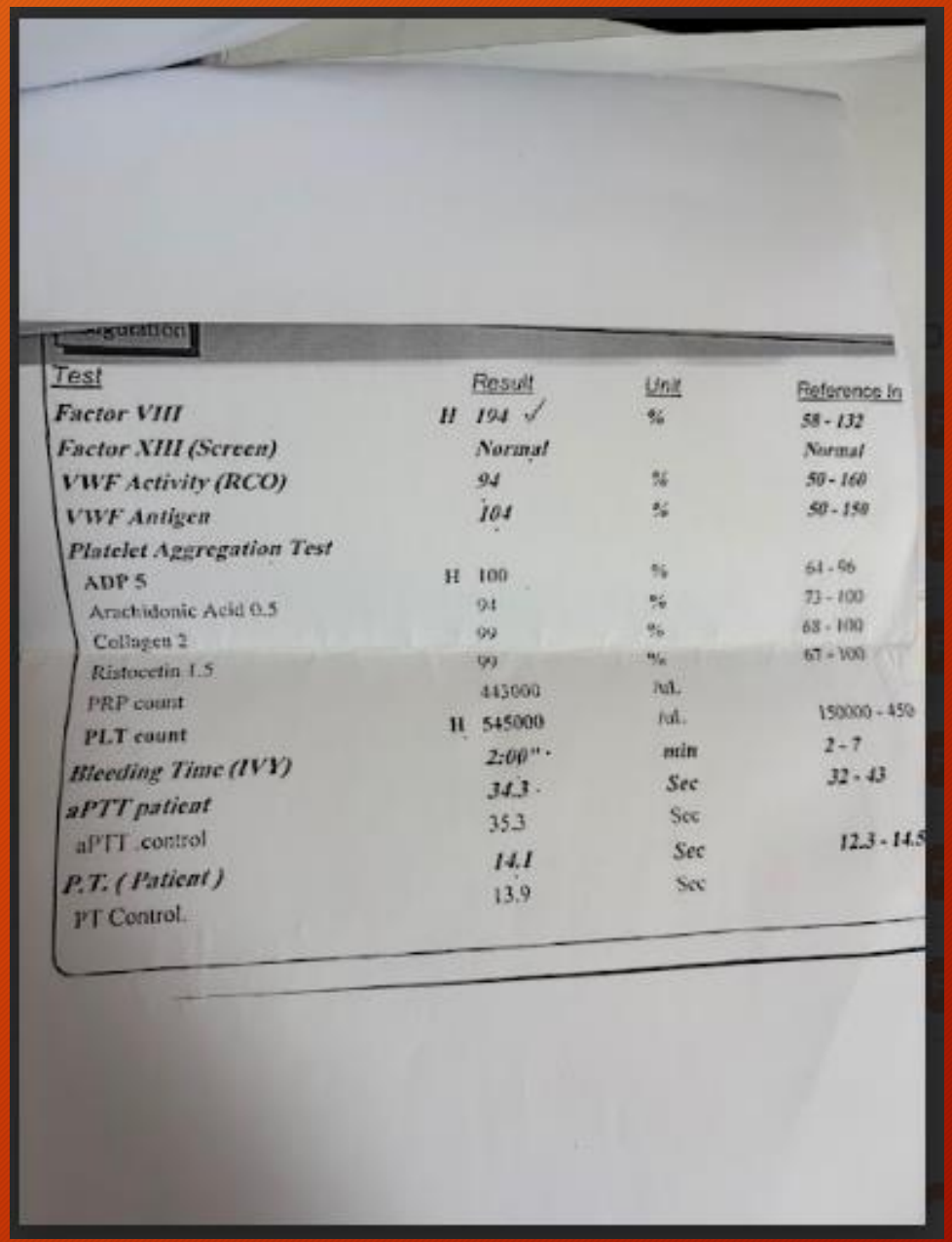
تاریخ پذیرش : 1396/09/29 تاریخ جوابدهی : 1396/10/16

سن : 7 سال پزشک معالج : جناب آقای دکتر فلاح زاده

Hematology

| Test | | Result | Unit | Reference |
|---|---|---|---|---|
| **Complete Blood Count** | | | | |
| W.B.C. | | 7.08 | 10*3/µL | 4.4 - 11 |
| R.B.C. | L | 4.03 | 10*6/µL | 4.2 - 5.5 |
| HGB | L | 10.6 | g/dL | 12 - 16 |
| HCT | L | 32.4 | % | 36 - 54 |
| M.C.V. | | 80.4 | fL | 77 - 95 |
| M.C.H. | | 26.3 | Pg | 25 - 33 |
| M.C.H.C. | | 32.7 | g/dL | 31 - 37 |
| Platelet | H | 545* | 10*3/µL | 150 - 450 |
| | | *Rechecked on peripheral blood smear.* | | |
| RDW-CV | H | 15.5 | % | 11.6 - 14.5 |
| Anisocytosis | | Slighily | | |

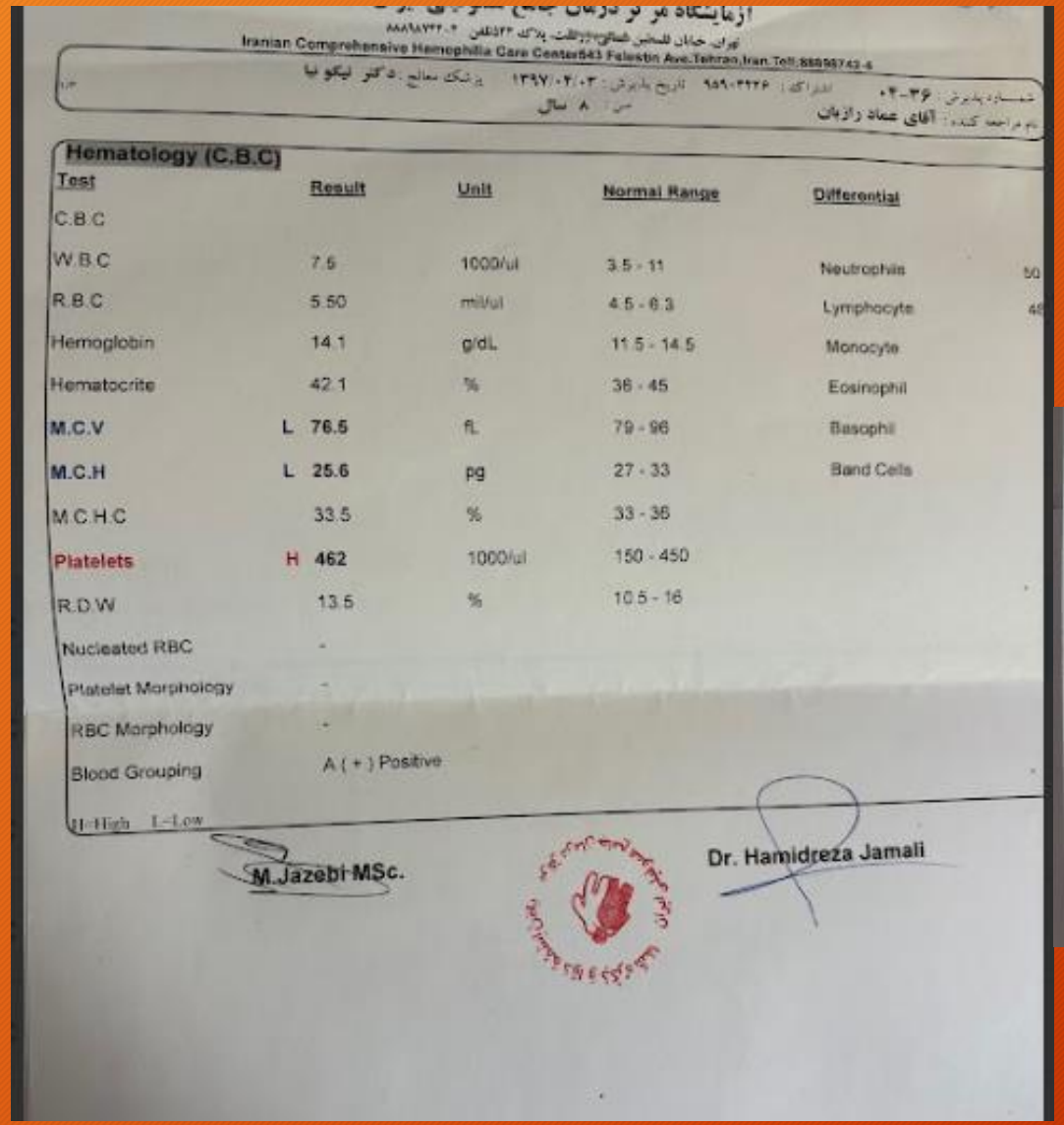
* = Confirmed by Repeated Analysis H=High L=Low



Coagulation

| Test | | Result | Unit | Reference In |
|---|---|---|---|---|
| **Factor VIII** | H | 194 ✓ | % | 58 - 132 |
| **Factor XIII (Screen)** | | Normal | | Normal |
| **VWF Activity (RCO)** | | 94 | % | 50 - 160 |
| **VWF Antigen** | | 104 | % | 50 - 150 |
| **Platelet Aggregation Test** | | | | |
| ADP 5 | H | 100 | % | 64 - 96 |
| Arachidonic Acid 0.5 | | 94 | % | 73 - 100 |
| Collagen 2 | | 99 | % | 68 - 100 |
| Ristocetin 1.5 | | 99 | % | 67 - 100 |
| PRP count | | 443000 | /uL | |
| **PLT count** | H | 545000 | /uL | 150000 - 450 |
| **Bleeding Time (IVY)** | | 2:00" - | min | 2 - 7 |
| **aPTT patient** | | 34.3 | Sec | 32 - 43 |
| aPTT control | | 35.3 | Sec | |
| **P.T. ( Patient )** | | 14.1 | Sec | 12.3 - 14.5 |
| PT Control | | 13.9 | Sec | |

- Meanwhile, the patient was referred to pediatric hematologists and underwent various diagnostic evaluations, all of them returned normal results, and no definitive diagnosis was established.



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پزشک معالج : دکتر لیکو نیا

شماره پذیرش : ۰۴-۳۶ تاریخ پذیرش : ۱۳۹۷/۰۲/۰۳ شماره اتاق : ۹۵۹۰۴۲۲۶

نام مراجعه کننده : آقای عماد رازیان سن : ۸ سال

**Hematology (C.B.C)**

| Test | | Result | Unit | Normal Range | Differential | |
|---|---|---|---|---|---|---|
| C.B.C | | | | | | |
| W.B.C | | 7.9 | 1000/ul | 3.5 - 11 | Neutrophils | 50 |
| R.B.C | | 5.50 | mil/ul | 4.5 - 6.3 | Lymphocyte | 45 |
| Hemoglobin | | 14.1 | g/dL | 11.5 - 14.5 | Monocyte | |
| Hematocrite | | 42.1 | % | 36 - 45 | Eosinophil | |
| M.C.V | L | 76.5 | fL | 79 - 96 | Basophil | |
| M.C.H | L | 25.6 | pg | 27 - 33 | Band Cells | |
| M.C.H.C | | 33.5 | % | 33 - 36 | | |
| Platelets | H | 462 | 1000/ul | 150 - 450 | | |
| R.D.W | | 13.5 | % | 10.5 - 16 | | |
| Nucleated RBC | | - | | | | |
| Platelet Morphology | | - | | | | |
| RBC Morphology | | - | | | | |
| Blood Grouping | | A ( + ) Positive | | | | |

H=High L=Low

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**Coagolation Laboratory(Factor Assay )**

| Test | Result | Unit | Normal Range |
|---|---|---|---|
| F VIII Activity ( 1- Stage method ) | 99 | % | 50 - 150 |
| vWF Activity ( RiCof method ) | 78 | % | 50 - 150 |
| vWF Antigen ( Turbidimetric method ) | 86 | % | 50 - 150 |

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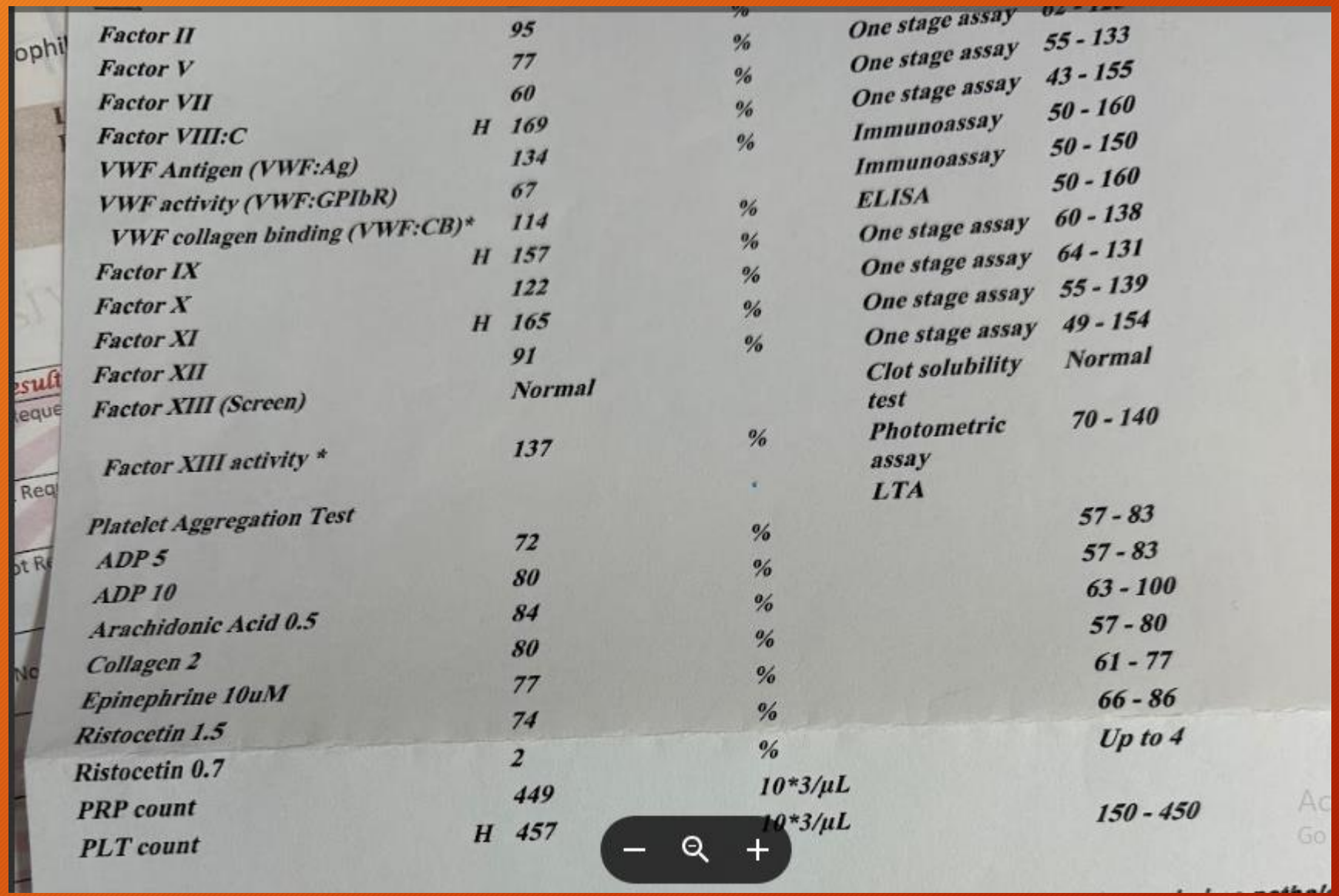

| | | | | | |
|---|---|---|---|---|---|
| Factor II | | 95 | % | One stage assay | 55 - 133 |
| Factor V | | 77 | % | One stage assay | 43 - 155 |
| Factor VII | | 60 | % | One stage assay | 50 - 160 |
| Factor VIII:C | H | 169 | % | Immunoassay | 50 - 150 |
| VWF Antigen (VWF:Ag) | | 134 | | Immunoassay | 50 - 160 |
| VWF activity (VWF:GPIbR) | | 67 | % | ELISA | 60 - 138 |
| VWF collagen binding (VWF:CB)* | | 114 | % | One stage assay | 64 - 131 |
| Factor IX | H | 157 | % | One stage assay | 55 - 139 |
| Factor X | | 122 | % | One stage assay | 49 - 154 |
| Factor XI | H | 165 | % | One stage assay | Normal |
| Factor XII | | 91 | | Clot solubility test | |
| Factor XIII (Screen) | | Normal | | Photometric assay | 70 - 140 |
| Factor XIII activity * | | 137 | % | | |
| Platelet Aggregation Test | | | | LTA | |
| ADP 5 | | 72 | % | | 57 - 83 |
| ADP 10 | | 80 | % | | 57 - 83 |
| Arachidonic Acid 0.5 | | 84 | % | | 63 - 100 |
| Collagen 2 | | 80 | % | | 57 - 80 |
| Epinephrine 10uM | | 77 | % | | 61 - 77 |
| Ristocetin 1.5 | | 74 | % | | 66 - 86 |
| Ristocetin 0.7 | | 2 | % | | Up to 4 |
| PRP count | | 449 | 10*3/µL | | |
| PLT count | H | 457 | 10*3/µL | | 150 - 450 |

- It is noteworthy that the patient's parents are first degree relatives.

- The patient's sister developed a severe headache at the age of 6 after returning from school; upon hospital evaluation, intracranial hemorrhage was diagnosed, and unfortunately, she passed away.

- The patient's mother also reports spontaneous bruisings on her skin.

- Ultimately, the patient underwent whole exome sequencing due to suspicion of a rare hereditary bleeding disorder, and the Scott syndrome was established.

and treatment efficacy in two pediatric cases of ANKRD26-related thrombocytopenia.

## 3. Carrier Status Finding:

| Gene | Variant | Chr. Location | Genome Refrence | Disease | Classification | Zygosity/ Inheritance |
|---|---|---|---|---|---|---|
| ANO6 (NM_001025356.3) | c.70+11922_70+11926del<br><br>ENST00000320560.13: c.70+11922_70+11926del | chr12-45228291 CTTTTT>C | Hg 38 | Scott syndrome | VUS | Het/AR |

- ✓ The classification of the examined variant is based on the current findings from the ACMG (2024) database and it is possible to change these classifications in the future.
- ✓ Please note, all WES variants confirmation by Sanger sequencing must be performed
- ✓ Genetic counseling is recommended.

## RESULTS:

### Possibly High Impact Findings:

| Gene | Variant | Chr. Location | Genome Refrence | Disease | Classification | Zygosity/ Inheritance |
|---|---|---|---|---|---|---|
| ANKRD26 (NM_014915.3) | c.2375+577del ENST00000376087.5:c.2375+577del | chr10-27039387 GA>G | Hg 38 | Thrombocytopenia 2 | VUS* | Het/AD |

*VUS: A variation in a genetic sequence for which the association with disease risk is unclear.

### Variants Interpretation:

### ANKRD26: c.2375+577del

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Haemophilia WILEY

REVIEW ARTICLE

# Bleeding of unknown cause and unclassified bleeding disorders; diagnosis, pathophysiology and management

Will Thomas[1] | Kate Downes[2,3] | Michael J. R. Desborough[4]

- Bleeding of unknown cause (BUC)
- Unclassified bleeding disorders (UBD)
- bleeding assessment tool (BAT) score

- BUC/UBD has been defined as an elevated bleeding assessment tool (BAT) score with normal diagnostic work-up.

AND

- A significant bleeding history with no reproducible abnormality with the standard tests of hemostasis.

- Many adults report bleeding symptoms, such as epistaxis (25%) and bruising (18%), necessitating differentiation from healthy patients.

- Diagnosis of BUC/UBD is of importance because the bleeding symptoms may cause distress and concern, but also because there is the need to try and ensure safe haemostasis for invasive procedures/childbirth.

- Conventional tests of hemostasis have limitations as they may miss monogenic disorders.

- There has to be a balance between the cost-benefits of extensive investigation with low yields of diagnoses, weighed against the value of diagnosing these disorders.

- There are a number of other conditions causing bleeding symptoms which may not be related to a platelet or coagulation factor disorder.

- A case-control study showed that the prevalence of symptomatic joint hypermobility was 24% in a bleeding disorders clinic (containing patients with hemophilia, platelet disorders, hemophilia and BUC/UBD) compared to 2% in the general population.

# Minimum investigations prior to a diagnosis of BUC/UBD

**TABLE 1** Suggested history, examination and investigations for a patient with a suspected bleeding tendency

History and examination

1. Structured bleeding questionnaire is recommended
2. Medical history, drug history including alcohol and over the counter medicines
3. Family history of bleeding disorders; check for history of consanguinity
4. Check for symptoms of collagen vascular disorders such as joint dislocations/subluxations, joint hypermobility, skin laxity and delayed wound healing
5. Examine for signs associated with other bleeding disorders (see Table 2)

Investigations

1. Full blood count ± blood film
2. Liver and renal function
3. Prothrombin time, activated partial thromboplastin time and Clauss fibrinogen
4. von Willebrand factor antigen, activity (RiCof or GP1bR) and collagen binding activity
5. Factors VIII, IX, XI and XIII
6. Platelet light transmission aggregometry and platelet nucleotides (or equivalent tests)

TABLE 2 Disorders of coagulation which may present with normal tests of coagulation or which cannot be diagnosed from standard laboratory tests

| Disorder | Pathology | Conventional laboratory tests | References |
|---|---|---|---|
| Factor V Short disorders; East Texan Bleeding Disorder and Factor V Amsterdam | Mutation in exon 13 of the factor 5 gene, causing aberrant splicing, with subsequent increased levels of factor V short; this binds TFPI and prolongs its half-life and function | Prolonged PT ± APTT but normal coagulation factors including factor V | [49,62] |
| Thrombomodulin coagulopathy | Markedly increased thrombomodulin plasma concentrations due to a mutation that causes shedding into the plasma | Normal | [24] |
| Heterozygous tissue factor deficiency | Modifier of initiation of coagulation and deficiency causes bleeding | Normal | [63] |
| PAI-1 deficiency | Decreased antigen/activity levels; usually inhibits tPA | Normal | [64] |
| Alpha-2 antiplasmin deficiency | Decreased antigen/activity levels; usually inhibits plasmin | Normal | [64] |
| Scott syndrome | Impairment of externalization of platelet phospholipid phosphatidylserine | Normal | [65] |
| Quebec bleeding disorder | Profibrinolytic platelets with increased alpha granule urokinase plasminogen activator (uPA) | 50% may have mild thrombocytopenia, absent secondary aggregation with epinephrine is expected, with or without impaired aggregation responses to other agonists | [43,64] |
| $\alpha_1$-antitrypsin Pittsburgh | A mutation in α1-antitrypsin that allows it to function as a potent thrombin inhibitor | Prolonged APTT, PT & TT | [66] |

Abbreviations: APTT, activated partial thromboplastin time; PAI-1, Plasminogen activator inhibitor-1; PT, prothrombin time; TFPI, tissue factor pathway inhibitor; tPA, tissue plasminogen activator; TT, thrombin time; uPA, urokinase-type plasminogen activator .

TABLE 3 Disorders associated with bleeding which may present with normal haematological investigations (other acquired disorders which present with bleeding have been omitted as haematological parameters will be abnormal, such as immune thrombocytopenia or hyperfibrinolysis from cancer)

| Disorder | Clinical manifestations | Pathology | References |
|---|---|---|---|
| Achenbachs syndrome | Paroxysmal bruising of the fingers | Unknown though vasospasm and vascular fragility have been proposed | [67] |
| Amyloidosis | Cerebral, cutaneous (including 'racoon eyes', intra-cranial and gastrointestinal bleeding. | Acquired coagulation factor deficiency, platelet dysfunction, abnormal fibrin polymerization/ fibrinolysis, impaired vasoconstriction and increased blood vessel fragility. | [68] |
| Autoerythrocyte syndrome (also known as psychogenic purpura and Gardner Diamond Syndrome) | Recurrent, spontaneous, painful ecchymosis, frequently preceded by a prodrome of pain or itching of the skin | Pathology unclear but lesions reproduced when autologous red cells injected intra-dermally | [69,70] |
| Exercise induced purpura | Purpuric patches on the lower limbs after exercise | Leukocytoclastic vasculitis | [71] |
| Hereditary haemorrhagic telangiectasia | Recurrent epistaxis, GI bleeds, haemorrhage from visceral AVM (eg cerebral and pulmonary). Telangiectasia on skin and mucosal surfaces. | Autosomal dominant condition characterized by multiple AVMs with causative genetic variants described in *ACVRL1*, *ENG*, *GDF2* or *SMAD4* | [72] |
| Lysinuric protein intolerance | Symptoms begin after weaning and include osteoporosis and short stature but also cardiac, renal and pulmonary disease. Potentially life threatening bleeding events. | Autosomal recessive disorder, which is a transport disorder of cationic amino acid | [73] |

| | | | |
|---|---|---|---|
| Medications | Bruising and bleeding from skin or GI tract | Medication dependant such as anti-depressants or anticoagulants (eg warfarin) | |
| Osteogenesis imperfecta | Variety of bleeding symptoms including bruising, bleeding after procedures and epistaxis | Causative genetic variants in collagen genes (*COL1A1* and *COL1A2)* | [74] |
| Scurvy | Malaise, lethargy, purpura, intra-cerebral haemorrhage, sub-periosteal haemorrhage, perifollicular haemorrhage, corkscrew hairs, poor wound healing and scorbutic gums | Vitamin C deficiency. Vitamin C is needed for hydroxylation of collagen | [75] |
| Senile purpura | Scattered purpuric patches and white pseudo-scars with skin atrophy | Loss of skin's ability to withstand mechanical force in older age but exact mechanism is unclear | [76] |
| Skin fragility and connective tissue disorders (eg Ehlers-Danlos syndrome) | Excessive bruising but systemic manifestations of the specific condition | Capillary and perivascular tissue fragility | [77] |
| Uraemia | Bruising and haemorrhage | Acquired platelet dysfunction | |
| Vasculitis (eg Henoch-Schönlein purpura) | Purpuric rash and pulmonary haemorrhage | Part of the systemic manifestation of the specific vasculitis; blood vessel inflammation | |

Abbreviations: AVM, arteriovenous malformation; GI, gastrointestinal.

- In 2019, the United Kingdom Hemophilia Centre Doctors Organization reported 741 patients with unclassified bleeding disorders (UBD), making up 2.4% of the total 30,445 registered patients, with 87% being female.

- Later studies show that 40%–70% of patients with mild bleeding symptoms have normal lab results, and some studies may include patients who do not actually have a bleeding disorder.

- The number of UBD/BUC patients reporting a family history of bleeding is 30%–40%.

- These disorders may be polygenic, autosomal recessive, acquired or multi-factorial due to a number of inborn hemostatic risks.

- Patients are predominantly female (usually > 60% cases of BUC/UBD).

- Symptoms of heavy menstrual bleeding (HMB) and post-partum hemorrhage may lead to more diagnoses in women than in men.

- Other plausible explanations would be the biological effects of gender on bleeding or increased reporting of symptoms in comparison to males.

- The prevalence of bleeding disorders in women with heavy menstrual bleeding is significant and for von Willebrand disease (vWD) has been described as being from 5% to 24%.

- Thirdly, the age of presentation is usually in the 30s, possibly due to the accumulation of symptoms prompting referral.

- A study of 90 patients with bleeding of unknown cause (BUC) or unclassified bleeding disorders (UBD), mostly women (98%) with an average age of 46, found that higher bleeding scores were linked to a greater likelihood of future bleeding events.

- Since 1995, there has been much research into quantitative BAT which previously have been reviewed.

- Commonly used BAT tools:
  - ISTH BAT (female score 6+, male score 4 + considered significant)
  - Vicenza BAT (female score 5+, male score 3 + considered significant)
  - MCMDM-1 VWD BAT (score of 4 + considered significant for the condensed version

- These tools are validated for diagnosing von Willebrand disease (vWD) and platelet function disorders.

- However, alternative causes of bleeding, such as uterine atony during childbirth, can elevate BAT scores, complicating their interpretation.

- A recent study showed similar haemostatic abnormalities in patients with and without bleeding symptoms highlighting the challenges of using BAT.

- BAT provides a structured approach to bleeding symptom assessment but has limited diagnostic accuracy.

- There are no validated diagnostic criteria for BUC/UBD, and there is no agreement on which patients truly have a bleeding disorder.

- This poses a problem for clinicians and patients, with risks of over- or under-diagnosis, lack of standardized care, and heterogeneity in clinical studies

# 5 | INVESTIGATION OF BLEEDING IN PATIENTS WITH BUC/UBD BEYOND CONVENTIONAL HAEMOSTASIS ASSAYS

## 5.1 | Thrombin generation

- Thrombin generation is measured by triggering blood clotting with tissue factor (TF), calcium, and phospholipids, then tracking thrombin production.

- The TF concentration matters:

  - High TF → Only measures the extrinsic clotting pathway

  - Low TF (≤1 pM) → Gives a broader assessment but is more prone to errors from contact activation. Adding corn trypsin inhibitor can help reduce these errors

- Thrombomodulin coagulopathy: Thrombin generation is low, but standard tests are normal.
- Genetic testing or thrombomodulin levels may be more useful here.
- BUC/UBD patients: Studies show inconsistent thrombin generation results, with no clear diagnostic pattern.
    - One small study found high TFPI (Tissue Factor Pathway Inhibitor) activity in 63% of BUC/UBD patients with abnormal thrombin generation

## 5.2 | Viscoelastic testing

- Tests like thromboelastography (TEG) and rotational thromboelastometry (ROTEM) measure blood clotting.

- They use activators to track clot formation, assessing:
  - Fibrinogen
  - Platelets
  - Clotting factors
  - Fibrinolysis

- Different ROTEM cartridges test specific pathways:
  - INTEM: Intrinsic pathway
  - EXTEM: Extrinsic pathway
  - FIBTEM: Fibrinogen levels
  - NATEM: Overall coagulation (calcium-activated)

- A study of 73 BUC/UBD patients (NATEM) found only 9% had minor clotting abnormalities, similar to chance.
- Another study (121 patients, EXTEM/INTEM/FIBTEM) showed normal clotting in BUC patients.
- A larger study (217 patients, mostly without BUC/UBD) found no significant clotting issues, even in the few BUC/UBD cases.

- In summary, ROTEM/TEG results in BUC/UBD patients are typically normal, with few exceptions.

# vWF and blood group O

- People with blood group O are more likely to experience certain bleeding issues, such as nosebleeds, bleeding ulcers, post-tonsillectomy bleeding, and trauma-related bleeding.

- This is because blood group O is often linked to lower levels of von Willebrand factor (vWF), similar to mild vWD.

- In a study of BUC/UBD patients, 46.2% had blood group O — higher than in the general population.

- Since low vWF (0.3-0.5 IU/mL) in group O can cause mild bleeding, it’s likely that some BUC/UBD cases are linked to this.

# Platelet function assessment

- Standard platelet function tests (like light transmission aggregometry or PFA assays) are rarely used in BUC/UBD due to inconsistent results.

- Electron microscopy (1,800 patients) showed:

  - 53.7% had a normal number of dense granules, but they were smaller than in healthy people.

  - Their platelet storage volume was reduced, similar to patients with δ-granule deficiency

# Investigation of fibrinolysis

- Inherited problems with two proteins that control blood clotting alpha-2-antiplasmin (A2AP) and plasminogen activator inhibitor 1 (PAI-1) can cause mild to moderate bleeding.

- Another condition, Quebec platelet disorder, leads to overactive clot-dissolving platelets due to excess urokinase-type plasminogen activator (uPA).

- These issues don’t show up on standard blood tests.

- While testing for A2AP and PAI-1 can be done in unexplained bleeding cases, these conditions are very rare, making such tests often unnecessary.

- Tests like clot lysis time and euglobulin clot lysis time measure how quickly clots break down.

- Some studies found that clots form slower and dissolve faster in BUC, However, other research showed the opposite —clots took longer to dissolve.

- Because results are inconsistent, these tests aren’t reliable enough for regular use in diagnosing BUC.

# Summary

- The lab tests mentioned are only useful for research at this stage—they haven’t proven what actually causes the bleeding in BUC/UBD patients.

# USE OF GENETIC TESTING

- Genetic testing has long been used in hematology clinics to diagnose bleeding disorders by analyzing genes like Factor 8, Factor 9, and vWF.

- Recent advances, such as high-throughput sequencing (HTS), have allowed broader genetic testing in patients with unexplained bleeding (BUC/UBD).

- Extensive gene panels can detect rare mutations (e.g., in SERPINF2 or THBD) not covered by standard tests.

- Yet, due to their rarity, routine HTS for BUC/UBD isn’t cost-effective.