Case presentation

Dept of Pediatric Nephrology , SMS Medical College, Jaipur

A Child With Joint Pains & Proteinuria

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Case presentation

- Chanda
- 12 year old
- female
- Hindu
- Resident of Bharatpur , Rajasthan
- We are presenting the case when child 1st presented to us in may 2024
- Admission Date - 23/5/2024

Presenting complaints

- C/o generalised swelling since 5-6 days
- C/o vomiting since 2-3 days
- C/o joint pain since 2-3 days

History of presenting illness

- Patient was apparently normal 6 days before admission, then presented with complaint of generalised swelling which started from face then progressive abdominal distension which was insidious in onset. It was followed by bilateral pedal pitting oedema .
- C/o vomiting since 2-3 days , non-bilious , non-projectile , 2-3 times/day , contains food and digested food particles . Not associated with blood in vomiting.
- C/o pain in bilateral wrist (Right>left) , bilateral ankle (Right>left) and bilateral knee joints since 2-3 days associated with swelling and restriction of movements.

Negative history

- No h/o fever
- No h/o pain abdomen
- No h/o loose stool or constipation
- No h/o jaundice
- No h/o hemetemesis / Malena / rectal bleeding
- No h/o muscle weakness
- No h/o skin rash
- No h/o oral ulcers/ alopecia
- No h/o weight loss
- No h/ breathing difficulty

- No h/o oral dryness
- No h/o dryness of eyes
- No h/o difficulty in vision
- No h/o Raynaud phenomenon
- No h/o skin thickening
- No h/o puffing fingers
- No h/o photosensitivity
- No h/o hematuria
- No h/o oliguria

Past history

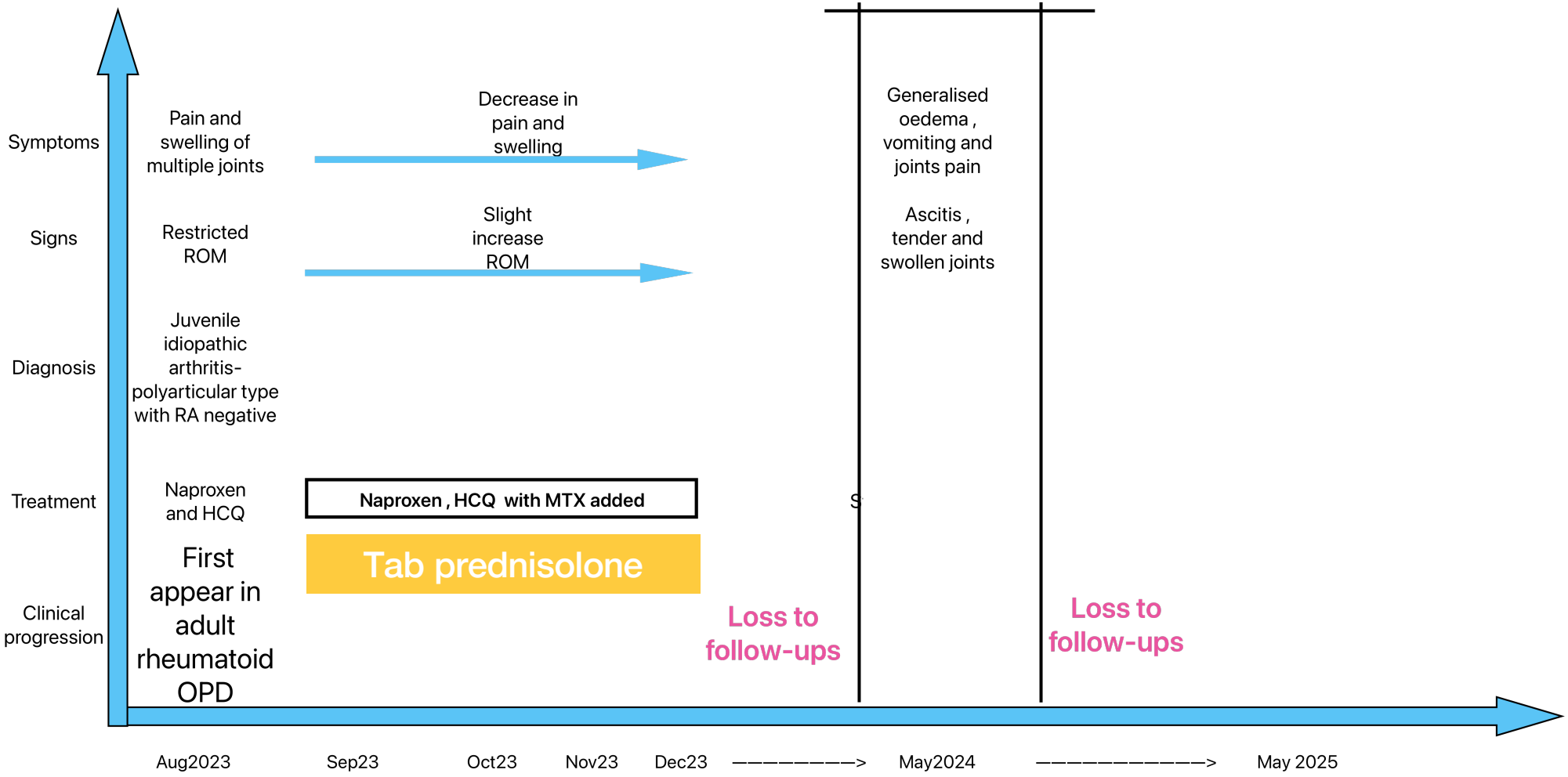
- H/o joint pain , swelling and limitation of joint movement since 3 years of age . OPD based medication taken
- Diagnosed as Juvenile idiopathic arthritis polyarticular (RF negative) with deformity in August 2023 . OPD based treatment taken for 4 months from adult rheumatology, SMS Hospital (investigation Table 1). Tab naproxen , tab hydroxychloroquine, tab methotrexate, tab IFA , tab folic acid & tab prednisolone 7.5mg was taken for 4 months then lost to follow up since dec 2023
- No history of previous hospitalisation.
- No h/o previous generalised odema

Aug 2023

Table 1

RBS	86mg/dl
S urea	74.5mg/dl
Creatinine	0.88mg/dl
Uric acid	6.52mg/dl
Calcium	8.10mg/dl
S total protein	7.35gm/dl
S albumin	2.11gm/dl
Na/K/Cl	131/4/97.7
SGOT/SGPT	21/6.2U/L
S ALP	156IU/L
VIT B12	873pg/ml
VIT D	12.85ng/ml
CRP	POSITIVE
Rheumatoid FACTOR	NEGATIVE
ESR	120
Urinary protein	+++

Course of illness



Family history

- History of arthralgia in grandmother since 20 years . Taking oral medication for pain relief on and off
- Grandfather expired due to renal failure in later age(no documents available) . ? Hepatorenal (ascites with renal failure)
- No history of generalised oedema or nephrotic syndrome in family
- No history of tuberculosis in family

Immunisation history

- Immunisation upto 5 years of age
- BCG scar marks present on left arm

Allergy history

- No known reaction from any drug
- No history of allergy from any medication / food / insect sting/ contact allergy/ transfusion reaction.

Summary

A 12 year old female who was previously diagnosed as juvenile idiopathic arthritis poly articular type with joint deformity now presented with complaints of generalised swelling, vomiting, Joint swelling and pain was suspected as a nephrotic syndrome and was further investigated for the same.

General physical examination

- Patient was conscious
- Sick looking in appearance
- In lying down position
- Not comfortable in sitting position
- Puffiness on face was present
- Visible Oedema on abdomen present
- Bilateral pedal oedema present

No -

- Icterus
- Cyanosis
- Pallor
- Lymphadenopathy
- Rash
- Mucosal ulcer
- Alopecia
- No redness of eyes

Vitals

- Pulse rate - 84 per minute in right radial artery, regular good volume, no radio radial or radio femoral delay present
- Respiratory rate - 22 per minute, thoracic respiration
- Blood pressure - 108/ 70 measured in left arm in supine position by manual sphygmomanometer by appropriate size of cuff
- Temperature -98°F in left axilla by digital thermometer
- SPO2 - 99% in right index finger by pulse oximeter

Cont…

- Urinary protein - 3+
- Abdominal girth - 66 cm
- Weight - 37.5 kg

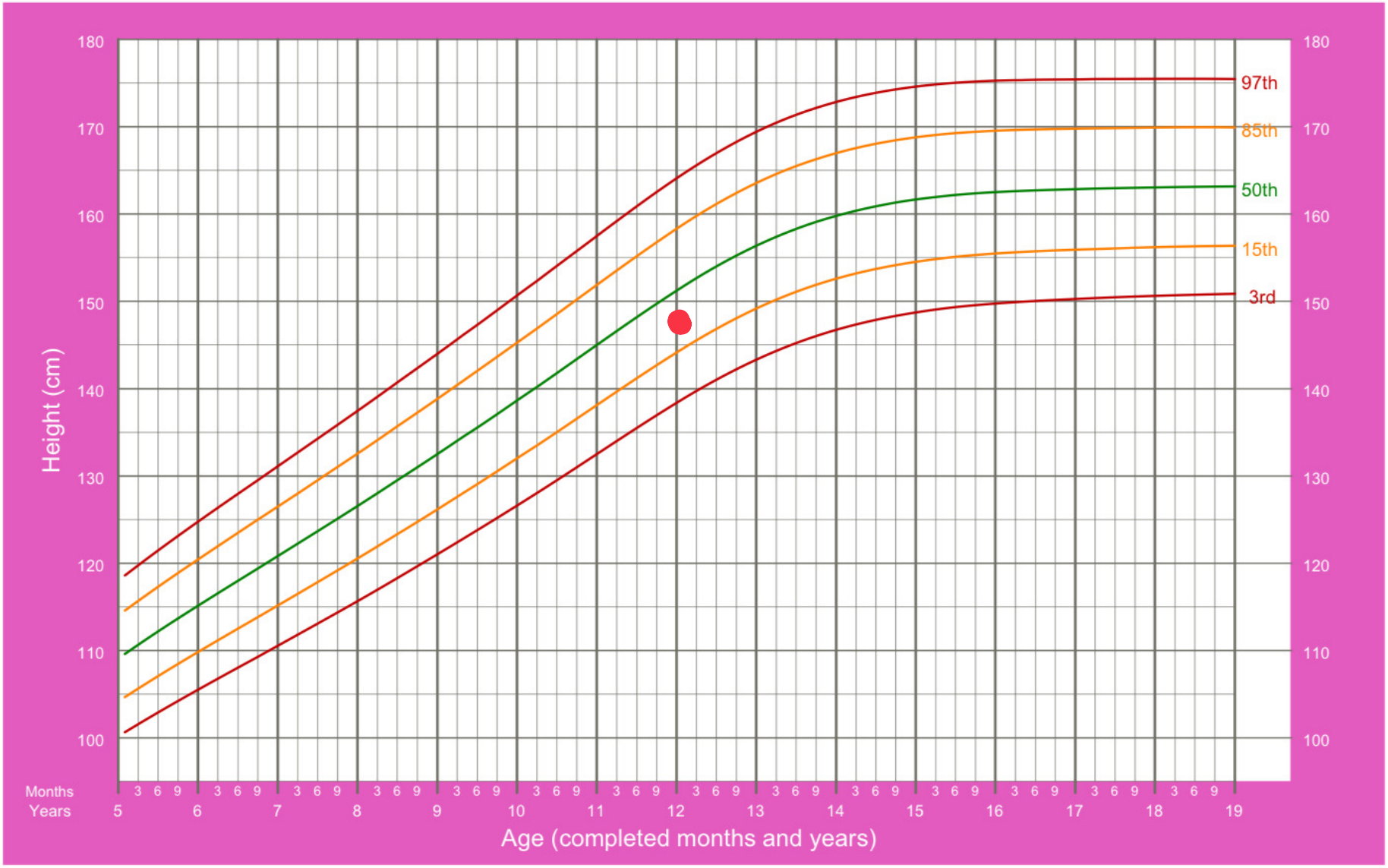
Anthropometry

- Weight - 37.5 kg (25th - 50th percentile)
- Height - 147.3 cm (15th - 50th percentile)
- BMI - 17.36 (50th - 75th percentile)
- SMR staging - Tanner stage IV

Height-for-age GIRLS

5 to 19 years (percentiles)

World Health Organization



2007 WHO Reference

Systemic examination

Gastrointestinal system examination

Inspection

- Abdomen is distended uniformly
- fullness of flank is present.
- Umbilicus is in normal position and transverse slit like in shape.
- All quadrant of the abdomen moves with respiration.
- Vein on the abdominal wall is not visible.
- There is no scar, sinuses or hernia present on the abdominal wall.

Palpation

- On superficial palpation- local temperature is normal ,abdomen was tense. There is no tenderness or guarding or rigidity.
- Deep palpation done by dipping method. liver is palpable 2cm below right sub-coastal margin. Spleen no palpable.
- Fluid thrill present

Percussion

- dull note on percussion of abdomen

Auscultation

- Bowel sound present

Genito-Urinary system examination

Inspection - abdomen distended, there is no mass , redness or scar on abdominal wall

Umbilicus is at position and transverse slit in shape

Tanner staging of genitalia - stage IV

No hernia visible on cough impulse

Palpation - fluid thrill present.

Bimanual kidney palpation cannot be possible due to a ascites.

fullness of renal angle, urinary bladder not palpable.

Percussion - dull note is present

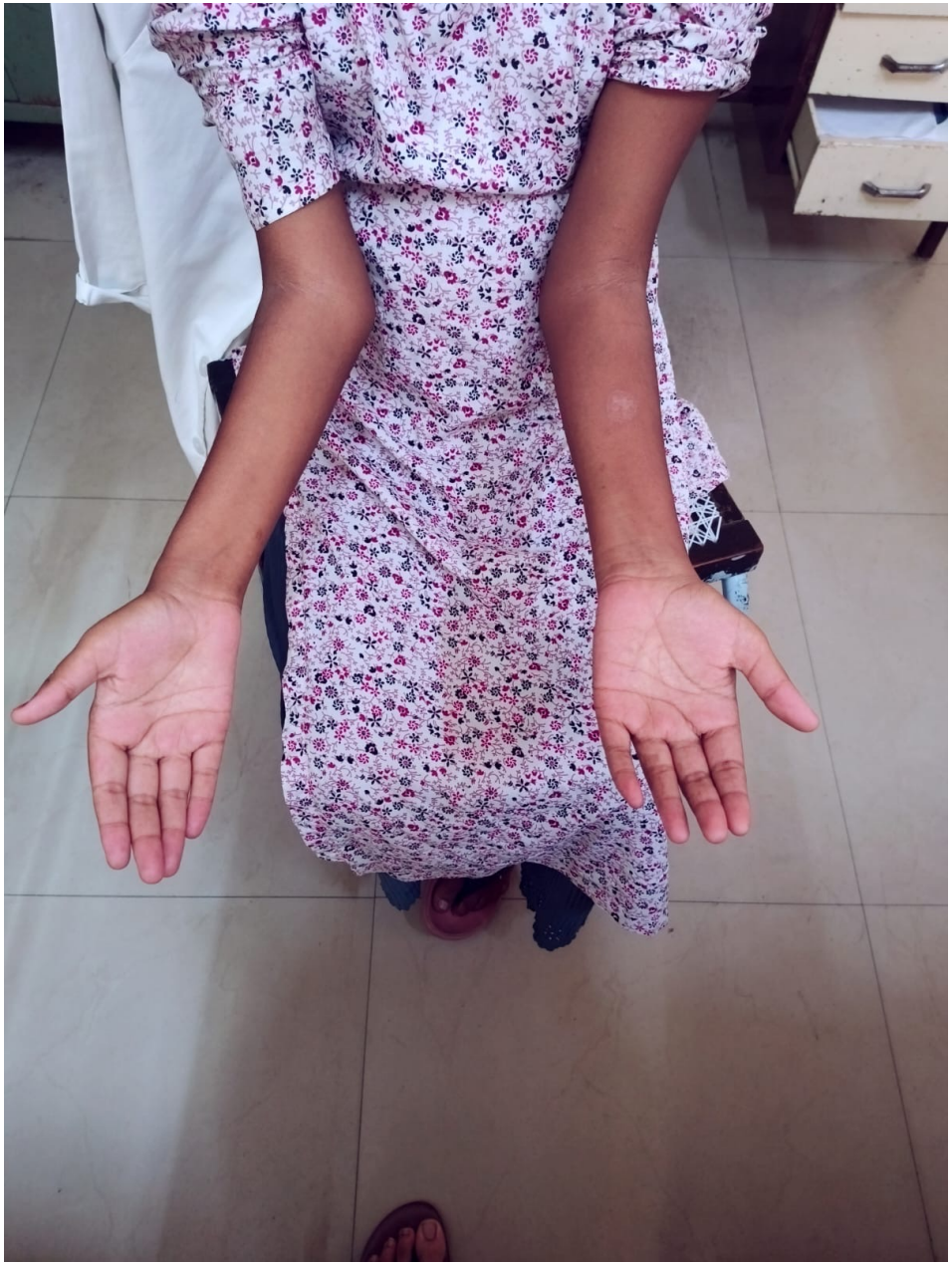
Auscultation- no Venus hum or renal artery bruit

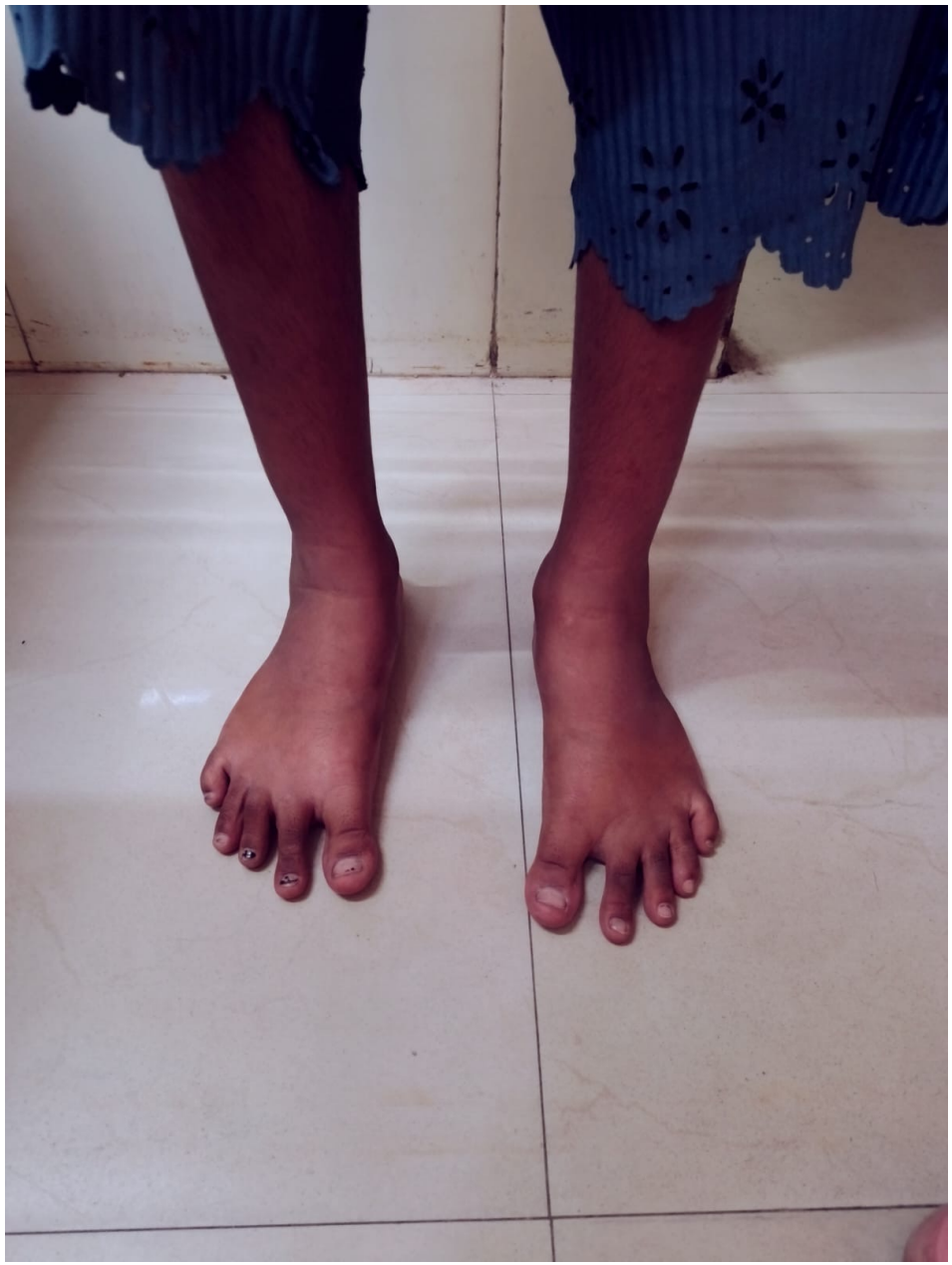
Musculoskeletal examination

- The articular examination did reveal swelling, tenderness or limited range of motion in following joints (Table 2) .
- Back examination was unremarkable.
- The patient had normal muscle strength in all proximal and distal muscle group.
- Muscle tenderness was not present
- Gait normal

Table 2

	Inspection	Palpation	Range of movement
Ankle joint	B/l Swelling , erythema, hallux varus	Ankle tenderness & swelling present	Restriction of dorsiflexion
Wrist joint	No Swelling	Tenderness present	Restriction
Elbow joint	B/L Cubitus valgus(right>left elbow)	Tenderness present	Flexion contracture Restriction in pronation of arm
Knee joint	No Swelling	Tenderness present	No movement restriction
Temporomandibular joint	No Swelling	Tenderness present	Movement restrictions Small mouth opening





Respiratory system Examination

Inspection

- chest wall symmetrical, breathing pattern is normal.

Palpation

- no abnormality or any crepitus

Percussion

- Resonant note in bilateral lung areas

Auscultation

- bilateral air entry equal.
- No other abnormal sound was present

Cardiovascular system Examination

Inspection- chest wall symmetrical, cyanosis absent, no scar mark

Palpation- temperature normal, heart rate 92 per minute regular, apical impulse Felt in left fourth intercostal space

Auscultation- heart sound heard in all five areas S1 S2 normal, no murmur heard

Nervous system examination

- Higher mental function- patient is conscious &oriented. Speech normal memory intact.
- Cranial nerve - all cranial nerve function intact
- Motor system - Tone normal. Power is 5/5in all four limbs. DTR 2+ in knee and ankle, plantar is flexor
- Stance and gait is normal
- Sensory system -all superficial sensation (touch, superficial pain, and temperature) and deep sensation (deep pain, pressure, position, vibration, and joint) are all intact
- Cerebellar sign- no cerebellar sign was present
- Normal spine and cranium
- No sign of meningeal irritability

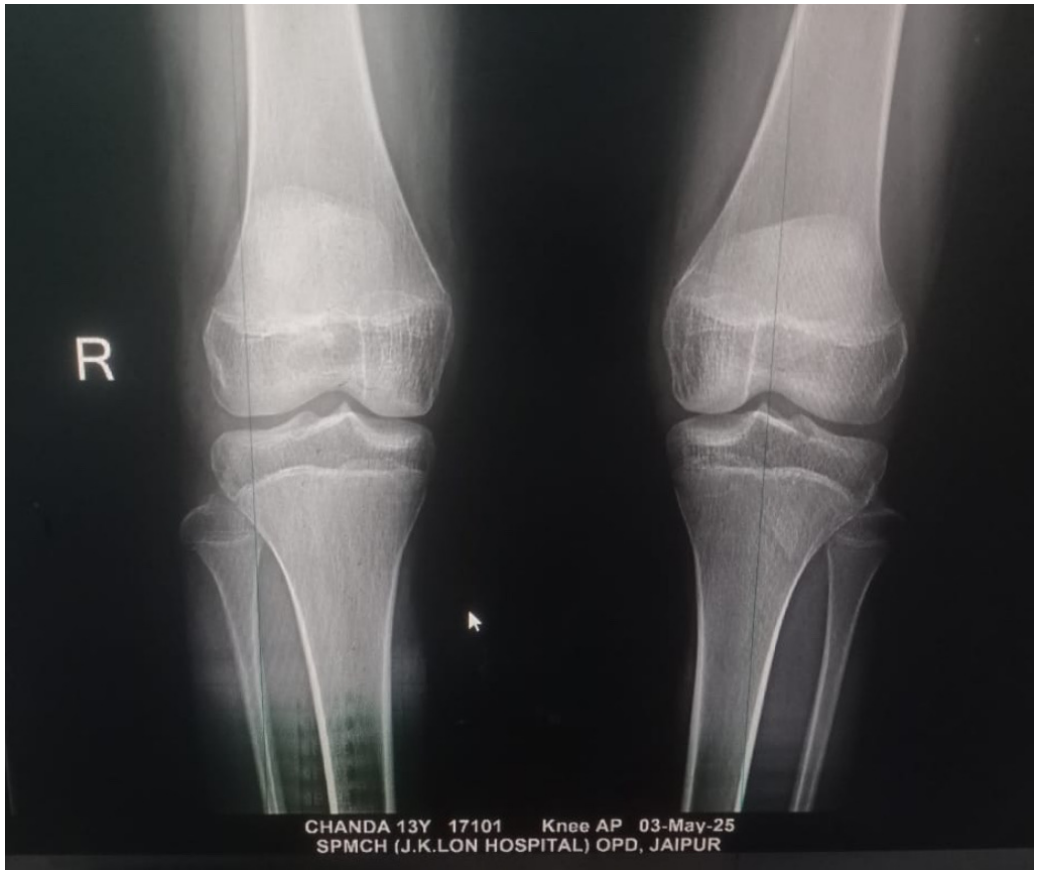
Investigations

Hb	10.3gm/dl	**Up/Uc ratio**	**10**
WBC	6.9k	**S lipase**	25.1U/L
Platelet count	1.56 lakh	**S Amylase**	21.89U/L
S creatinine	0.54mg/dl	**Rhumetoid factor**	Negative
S urea	20.47mg/dl	**Anti CCP**	<0.40(negative)
Na/k/Cl	131/4.0/111	**ESR**	**105mm/hr**
S total protein	**4.5gm/dl**	**CRP**	Negative
Albumin	**1.16gm/dl**	**Antinuclear antibody**	0.1 (negative)
S total bilirubin	0.6mg/dl	**Anti ds-DNA**	Negative
Direct bilirubin	0.24mg/dl	**C3 levels**	180
SGPT	7.77	S ferritin	165.9ng/ml
SGOT	32.78	**HbsAg**	Negative
PT-INR	1.15	**HIV**	non-reactive
S LDH	**543 IU/L**	**Anti HCV**	Negative
S alkaline phosphate	154 IU/L	**Ext viral markers**	Negative
S Cholesterol	**440.29mg/dl**	S calcium	7.7 mg/dl
CPK-NAC	56IU/L	DCT	Negative

ANA QUALITATIVE PROFILE 18 ANTIGENS , IgG (IMMUNOBLOT)

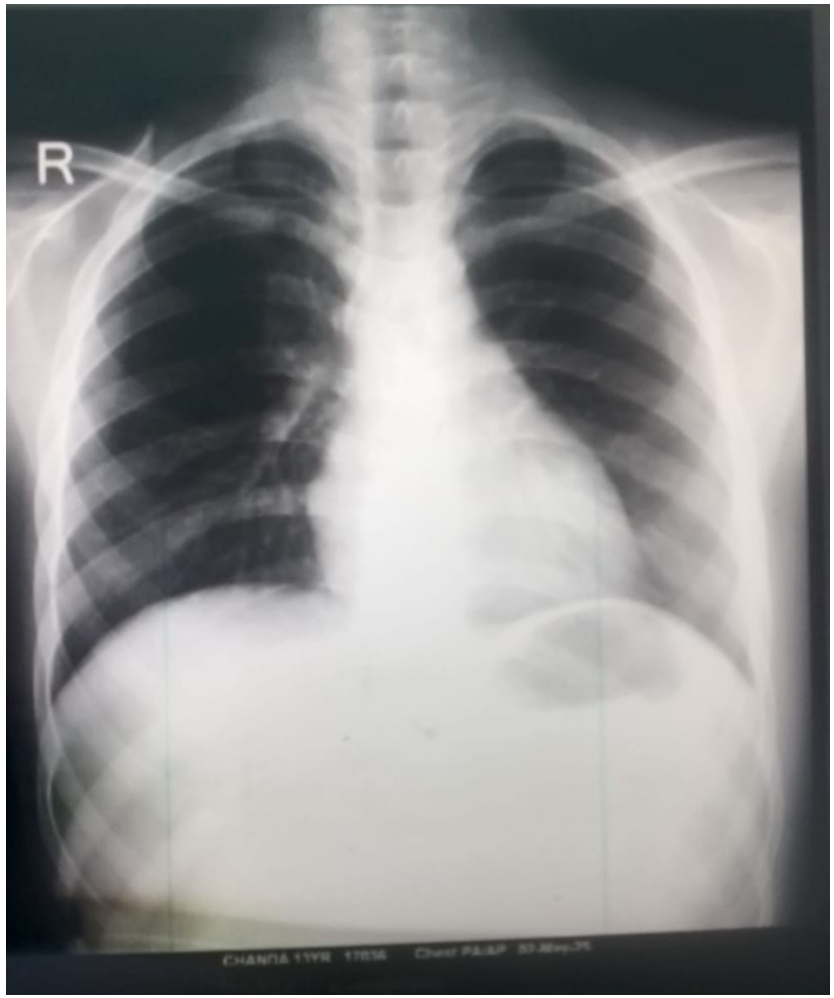
Mi-2	Negative
Ku	Negative
nRNP/Sm	Negative
SM	Negative
SS-A	Negative
Ro-52	Negative
SS-B	Negative
Scl-70	Negative
PM-Scl 100	Negative
Jo-1	Negative
CENP-B	Negative
PCNA	Negative
ds-DNA	Negative
Nucleosomes	Negative
Histones	Negative
Rib-P Protein	Negative
AMA-M2	Negative
DFS70	Negative

X-Ray



X-ray bilateral knee showing decreased bone mineral density with mild decrease in joint space & thinning of cortex

X-Ray



Chest X-Ray shows normal lung field , no hilar lymphadenopathy

USG abdomen

- No hepatosplenomegaly
- Right kidney 101x36mm size & left kidney 111x43mm size
- Gross Ascites present

Renal Doppler

- segmental artery intermediate resistance

USG chest

- bilateral mild pleural effusion

Sputum CBNAAT negative

Ophthalmology examination -

Vision normal ,Fundus - NAD, Slit lamp - normal examination

Urine routine microscopy

Foamy urine , protein 4+

HRCT chest

- bilateral plural effusion(right is more than left)
- multiple calcified lymph node in subcarinal and left hilar region

Renal biopsy

Single core of renal biopsy showing cortical tissue having 16 glomeruli , all of which are normocellular with mild stiffening of the GBM. Mild mesangial hyper-cellularity is noted in four of these. No sclerosis or crescents noted.

Tubules - shows mild degenerative changes with presence of RBC cast in the lumen. No atrophy seen.

Immunofluorescence findings -13 non-sclerosed glomeruli studied

IgG- 2+ to 3+ pseudo-linear
IgM- 1+ fine capillary wall granular
IgA- 2+ capillary wall granular
C3 - negative to trace
C1q - negative
Kappa- 2+ capillary wall granular
Lambda- 1+ capillary wall granular

Impression-Overall light microscopy and IF findings are in favour of **Membranous nephropathy.**

Provisional diagnosis

A 13 year old female child having chronic poly-arthritis with joint deformity now presented with generalised swelling and nephrotic range Proteinuria , Renal biopsy s/o Membranous nephropathy .

Provisional diagnosis is ***Juvenile idiopathic arthritis polyarticular type RF negative with membranous nephropathy.***

Differential diagnosis

1. Poly articular (RF negative) JIA
2. Systemic lupus erythematosus
3. Paediatric onset “Adult-type” Sarcoidosis
4. Juvenile systemic sclerosis
5. Sjogren syndrome

Diagnosis	Points in favour	Against
POLYARTICULAR (RF-) JIA	• Chronic polyarthritis • Erosive arthritis with deformity • No systemic features • (Fever, rash, oral ulcers, fatigue etc) • No LAP , HSM , Serositis • Acute phase reactants : increased ESR • Absence of autoantibodies(ANA by IFA - negative, IMMUNOBLOT-negative) • Renal involvement association with membranous nephropathy* (Uncommon but reported)	None

* Global Journal of Pediatrics = Glob J Pediatr, Vol. 1 (Iss 2). p. 1008.

Diagnosis	Points in favour	Against
SLE	• Chronic polyarthritis • Membranous nephropathy	• Erosive arthritis with deformity • No systemic features (fever, fatigue , oral ulcers , malar rash etc) • No LAP, HSM , Serositis • Absence of autoantibodies (ANA-IFA negative, immunoblot negative)

Diagnosis	Points in favour	Against
PAEDIATRIC ONSET "ADULT-TYPE" SARCOIDOSIS	• Chronic polyarthritis • Hilar lymphadenopathy (HRCT chest) • Absence of autoantibodies(ANA by IFA - negative, IMMUNOBLOT- negative) • membranous nephropathy	No systemic features (fever, malaise, weight loss) No cutaneous manifestations No eye involvement No peripheral lymphadenopathy Normal calcium levels

Diagnosis	Points in favour	Against
JUVENILE SYSTEMIC SCLEROSIS	• Chronic polyarthritis • Membranous nephropathy	• No skin thickening • No Raynaud's phenomenon • Absence of autoantibodies (ANA-IFA negative, anti-topomerase SCL-70 negative) • No lung or cardiac involvement (ILD , PAH)

Diagnosis	Points in favour	Against
SJOGREN SYNDROME	• Chronic polyarthritis • Membranous nephropathy	• No dryness of oral mucosa • No parotid enlargement • No ocular involvement • No Raynaud phenomenon • Absence of autoantibodies (ANA-IFA negative, anti Ro/SSA & anti La/SSB negative)

Learning points

Definition of JIA-ILAR

ILAR defines juvenile idiopathic arthritis as:

Arthritis of one or more than one joint with

- Age of onset <16 years,
- duration of illness, more than Or equal to 6 weeks
- Exclusion of other form of juvenile arthritis

ciations for Rheumatology (ILAR) classification criteria for

1	Systemic arthritis
2	Oligoarthrtitis Persistent Extended
3	Polyarthritis RF-negative
4	Polyarthritis RF-positive
5	Psoriatic arthritis
6	Enthesitis-related arthritis
7	Undifferentiated arthritis Fits no category Fits more than one category

SLE

Learning points

SLICC† Classification Criteria for Systemic Lupus Erythematosus

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus*
2. Chronic Cutaneous Lupus*
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm^3)

Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs' test (do not count in the presence of hemolytic anemia)

SLICC criteria - Score 3 with no laboratory criteria

Membranous lupus nephritis

- The class V or membranous , form of lupus nephritis may be indistinguishable from idiopathic MN clinically and even serologically.
- The lesion accounts for 20% of patient with lupus nephritis and often present as nephrotic syndrome in young women who do not have other clinical or serological manifestation of systemic lupus, although they usually developed these later.
- In patient with lupus MN anti-DNA antibody levels and ANA titers are often low and the antibody is of very low avidity compared with that in the patients with class IV lesions

Biopsy

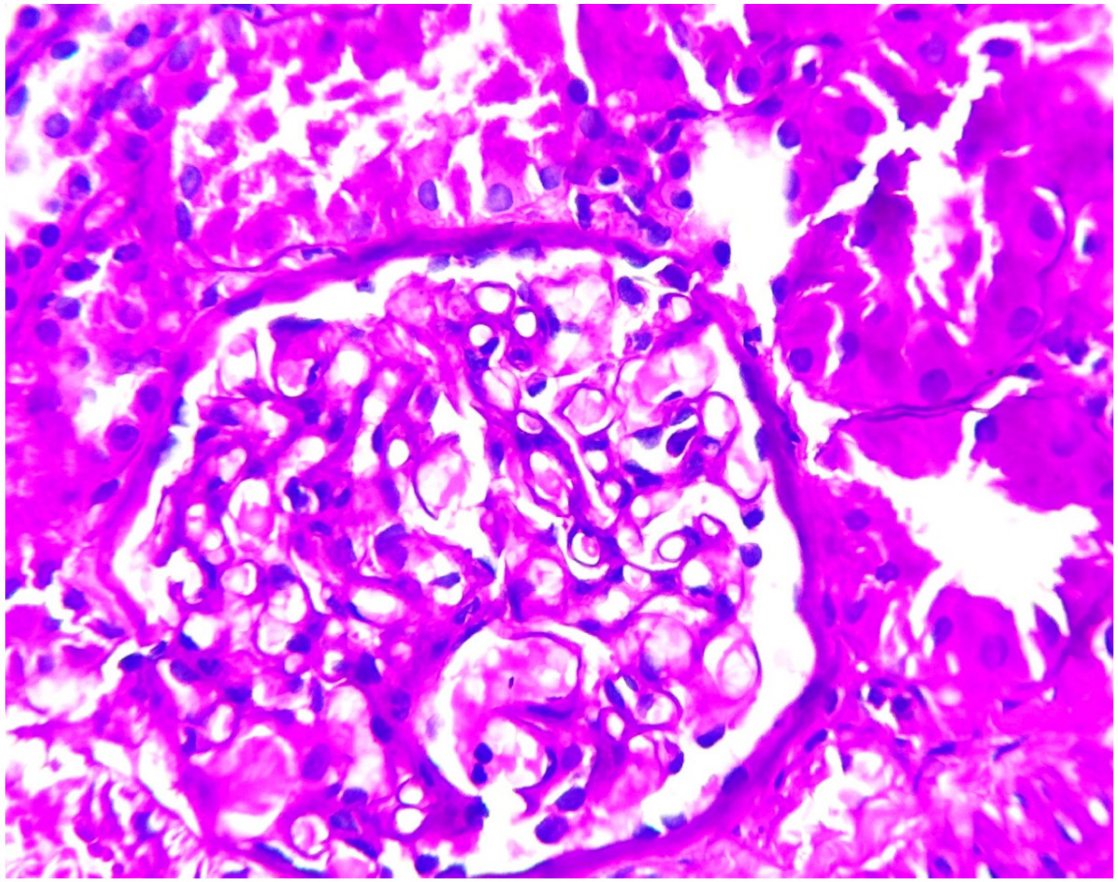
- **LIGHT MICROSCOPY:**

- Mild stiffening of basement membrane.
- Focal mesangial hypercellularity in 4 glomeruli.

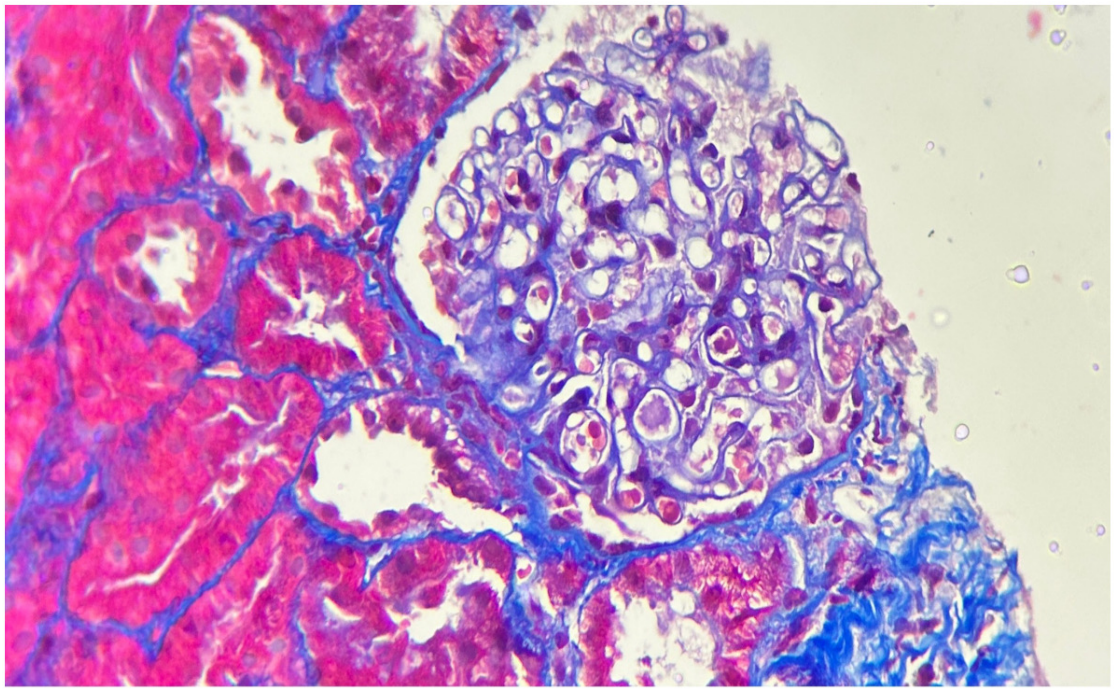
- Tubules, interstitium and blood vessels were unremarkable with an occasional caste.

PAS stain (40x)

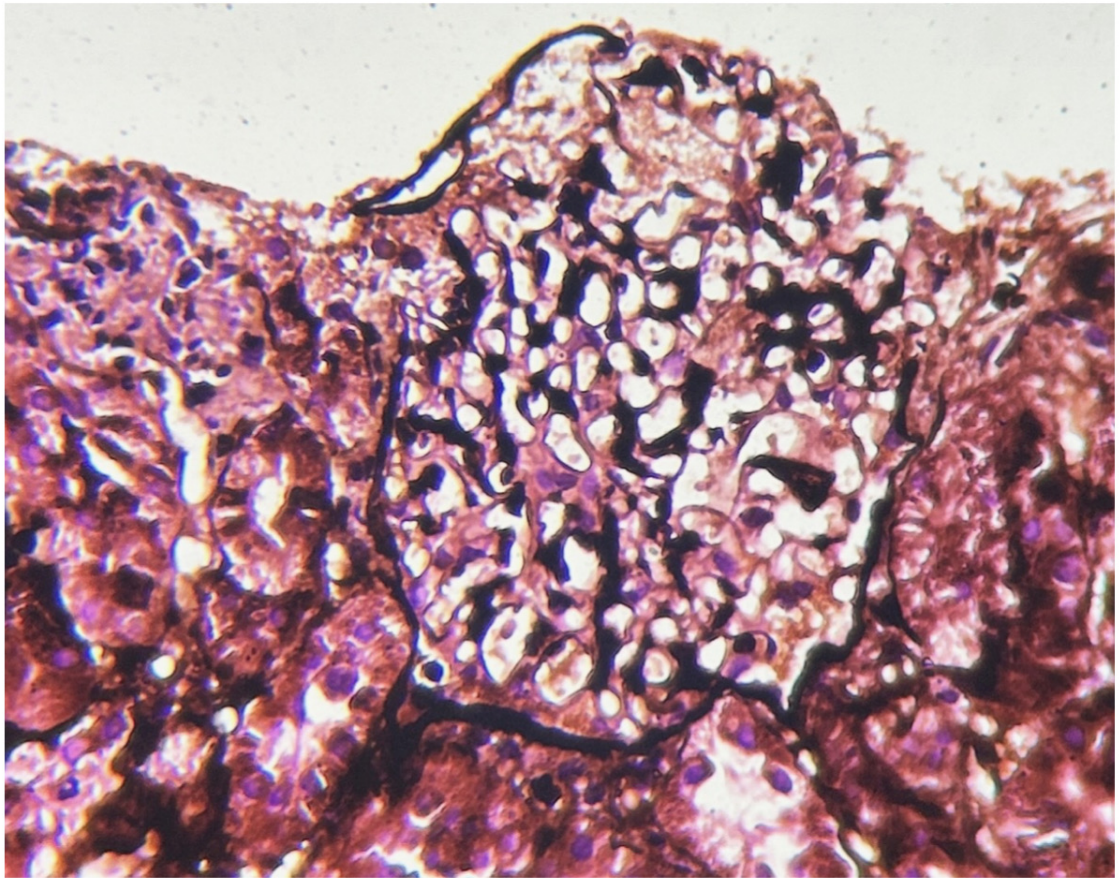
Rounding of capillary walls



Masson Trichome Stain (MT) 40 x



Methanamine Silver Stain (40x)



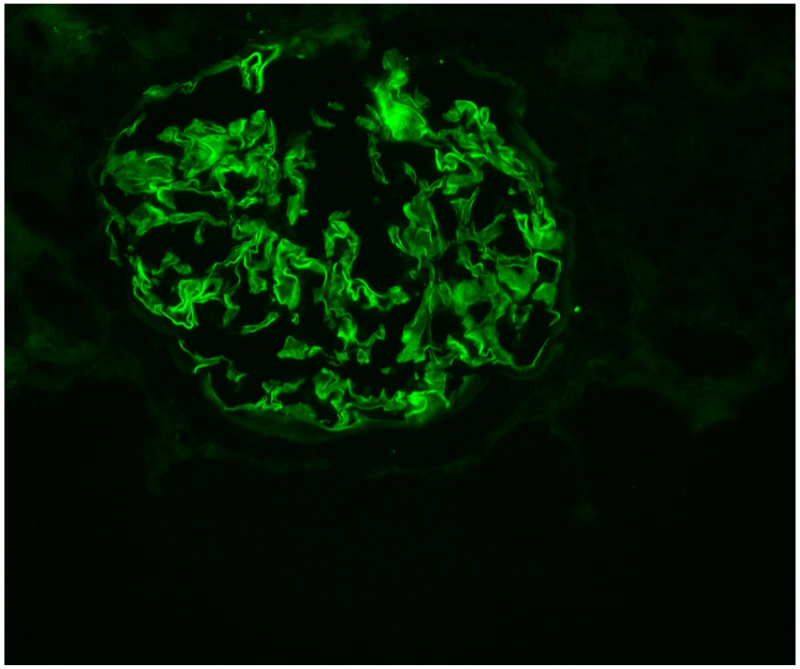
DIF STUDY

13 glomeruli studied

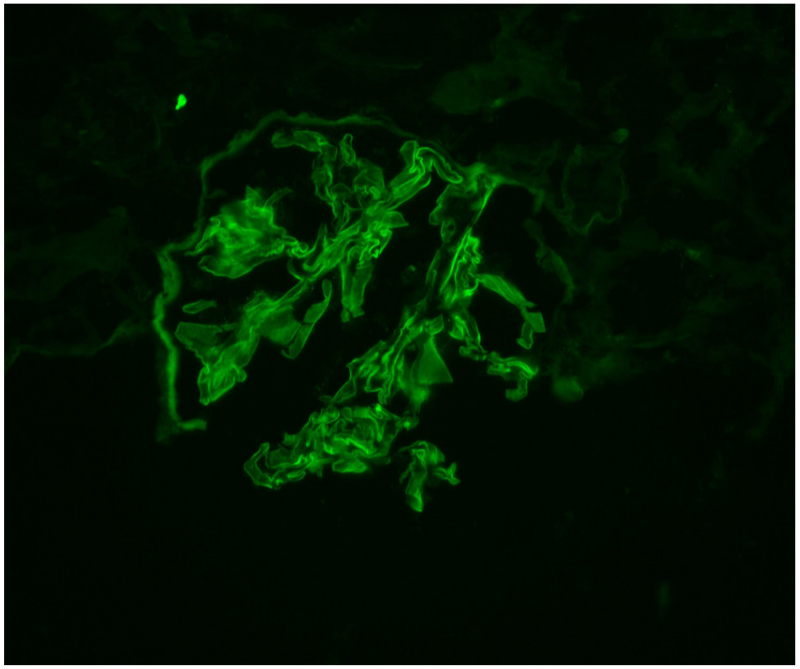
- IgG- 2+ to 3+ Fine capillary wall granular
- IgM- 1+ CWG
- IgA- 1+ to 2+ Fine capillary wall granular
- C3- Negative to trace
- C1q- Negative
- Kappa- 2+ CWG
- Lambda- 1+ CWG

DIF STUDY

IgG

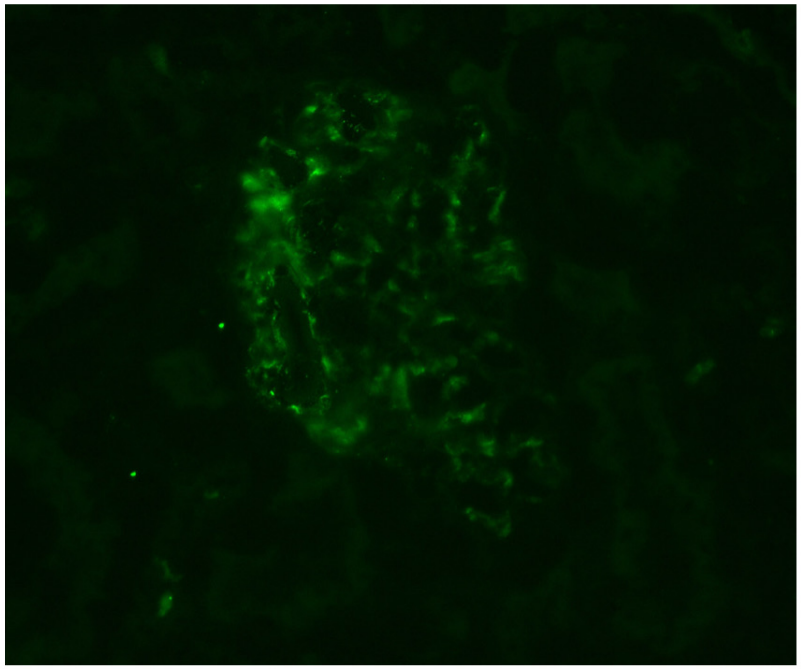


IgA



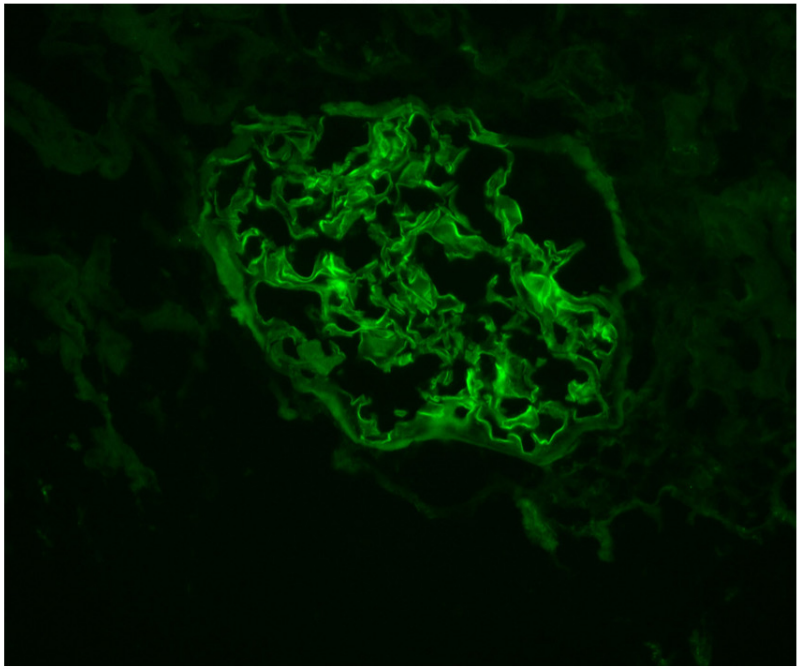
DIF STUDY

IgM



DIF STUDY

KAPPA



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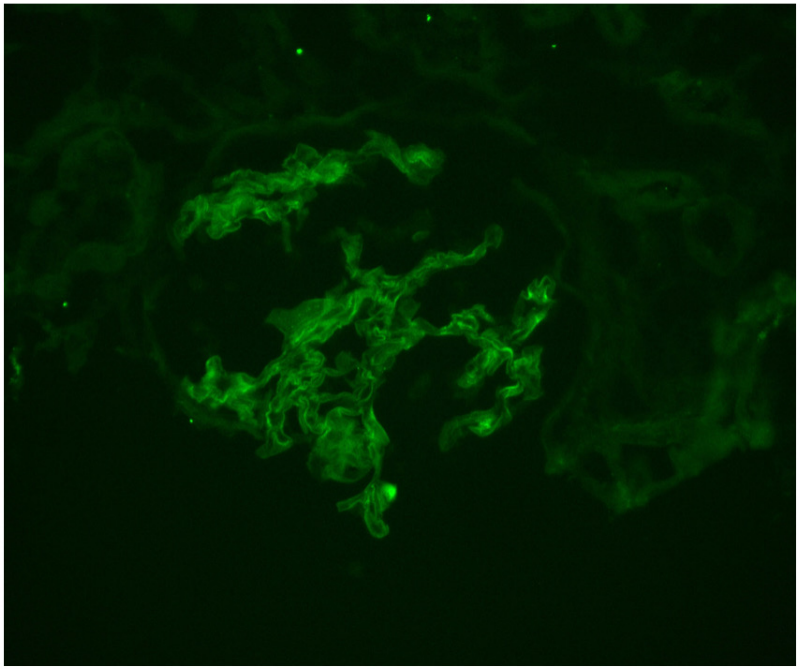
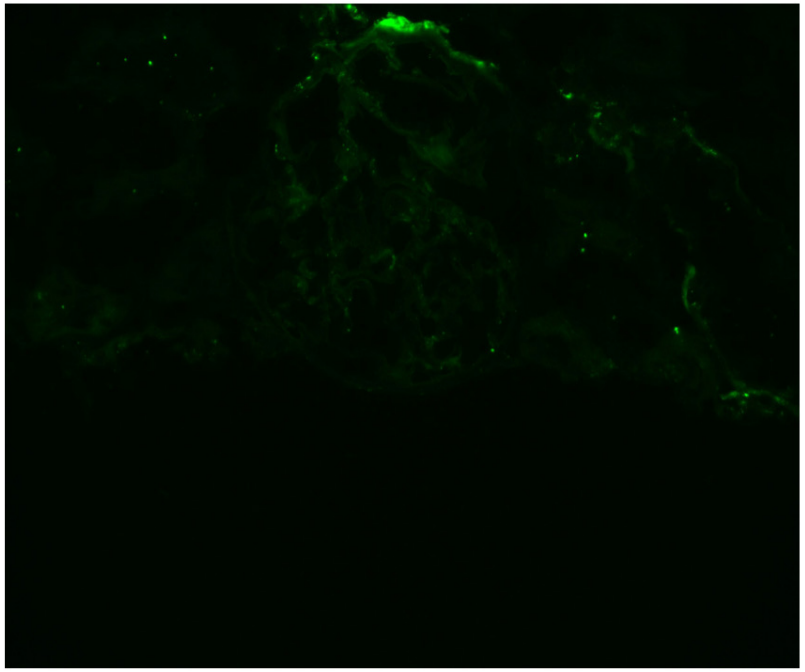
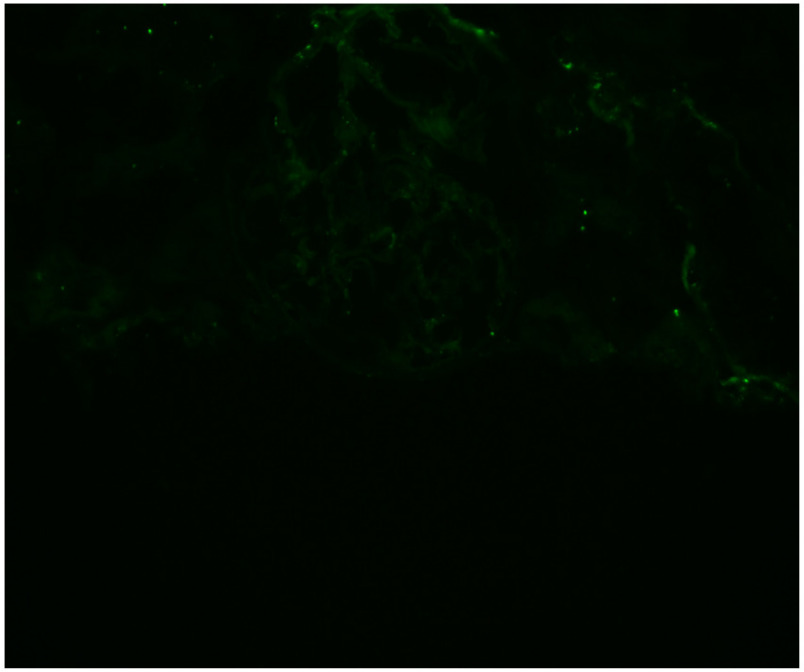


DIF STUDY

C3

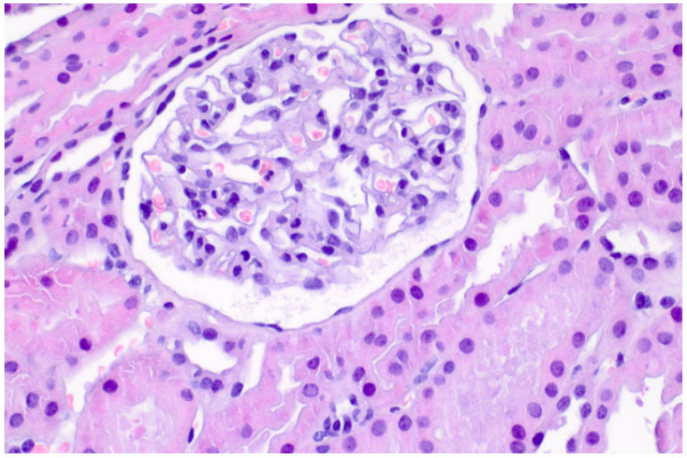


C1q

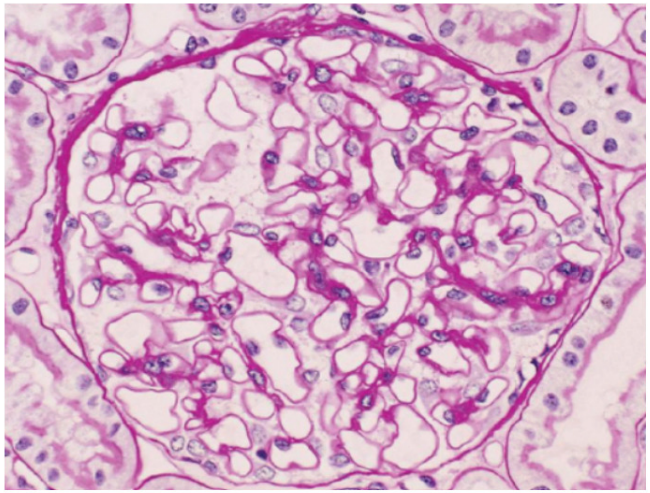


IMPRESSION

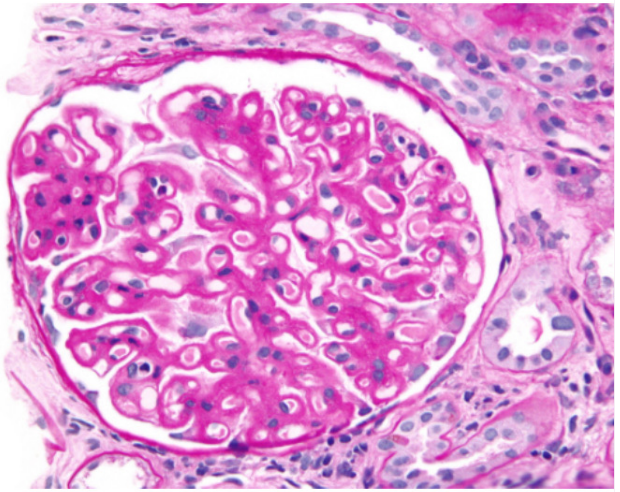
- Overall findings are in favour of **Membranou.s Nephropathy**



Normal glomerulus



Early Membranous



Membranous

PRIMARY MEMBRANOUS

LIGHT MICROSCOPY

- Diffuse and global thickening of glomerular capillary walls.
- No proliferation
- Usually no interstitial inflammation.

DIF STUDY

Intense **GRANULAR/PSEUDOLINEAR IgG** deposits along capillary walls.

C3 deposits may also be seen frequently.

ELECTRON MICROSCOPY

Subepithelial electron dense deposits are seen.

SECONDARY MEMBRANOUS

LIGHT MICROSCOPY

- Diffuse and global thickening of glomerular capillary walls
- Endocapillary hypercellularity
- Mesangial hypercellularity.
- Rarely crescents
- Interstitial inflammation seen.

DIF STUDY

FULL HOUSE PATTERN is seen. All Igs are deposited along with **C1q**.

Location of deposits is Capillary wall along with mesangium. Extraglomerular deposits also seen.

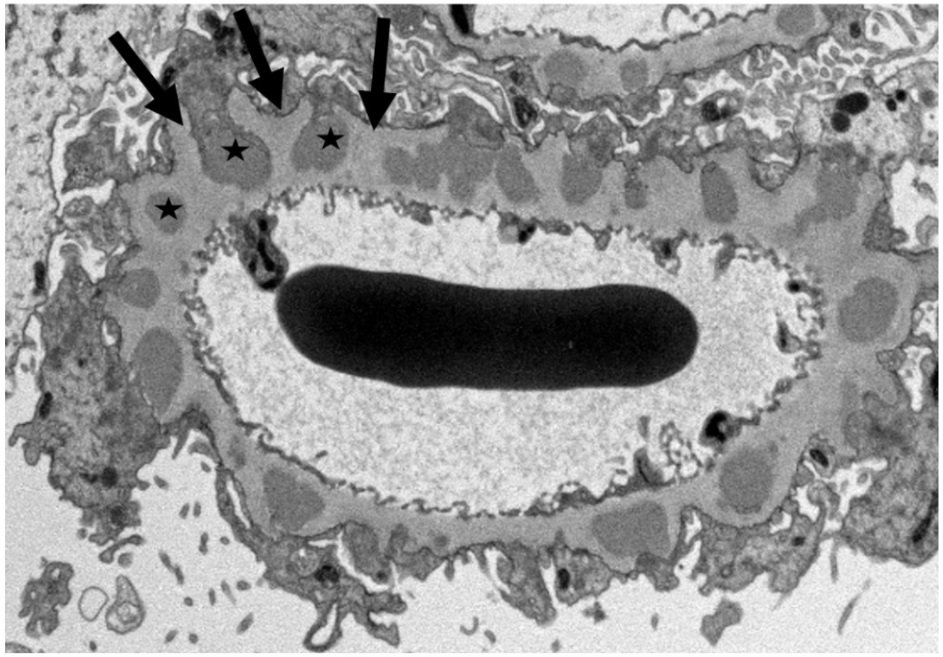
ELECTRON MICROSCOPY

Electron dense deposits are seen in subepithelial along with mesangial and subendothelial location.

ELECTRON MICROSCOPY

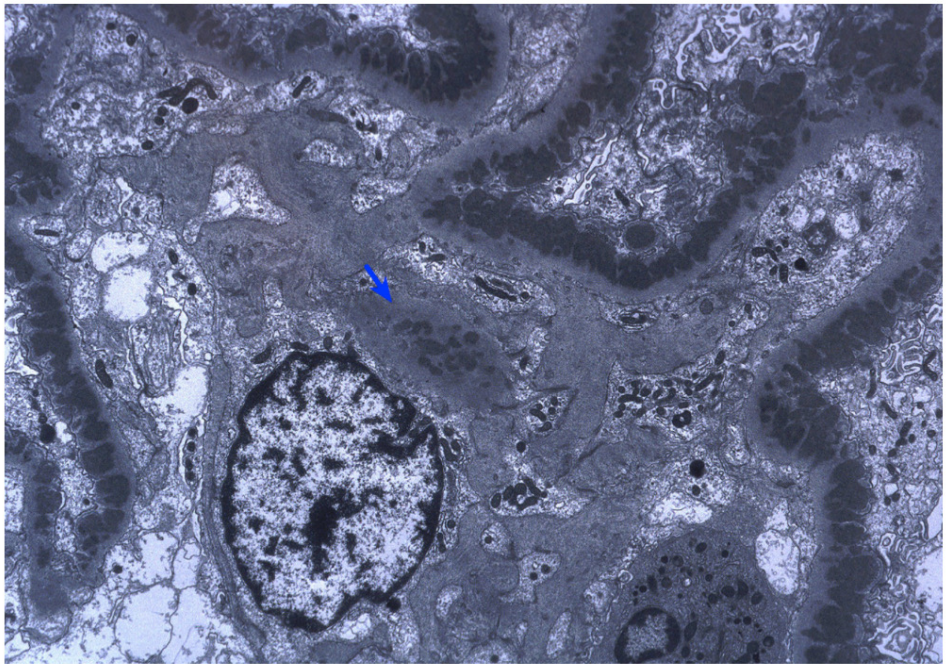
PRIMARY MEMBRANOUS

Exclusive Subepithelial deposits

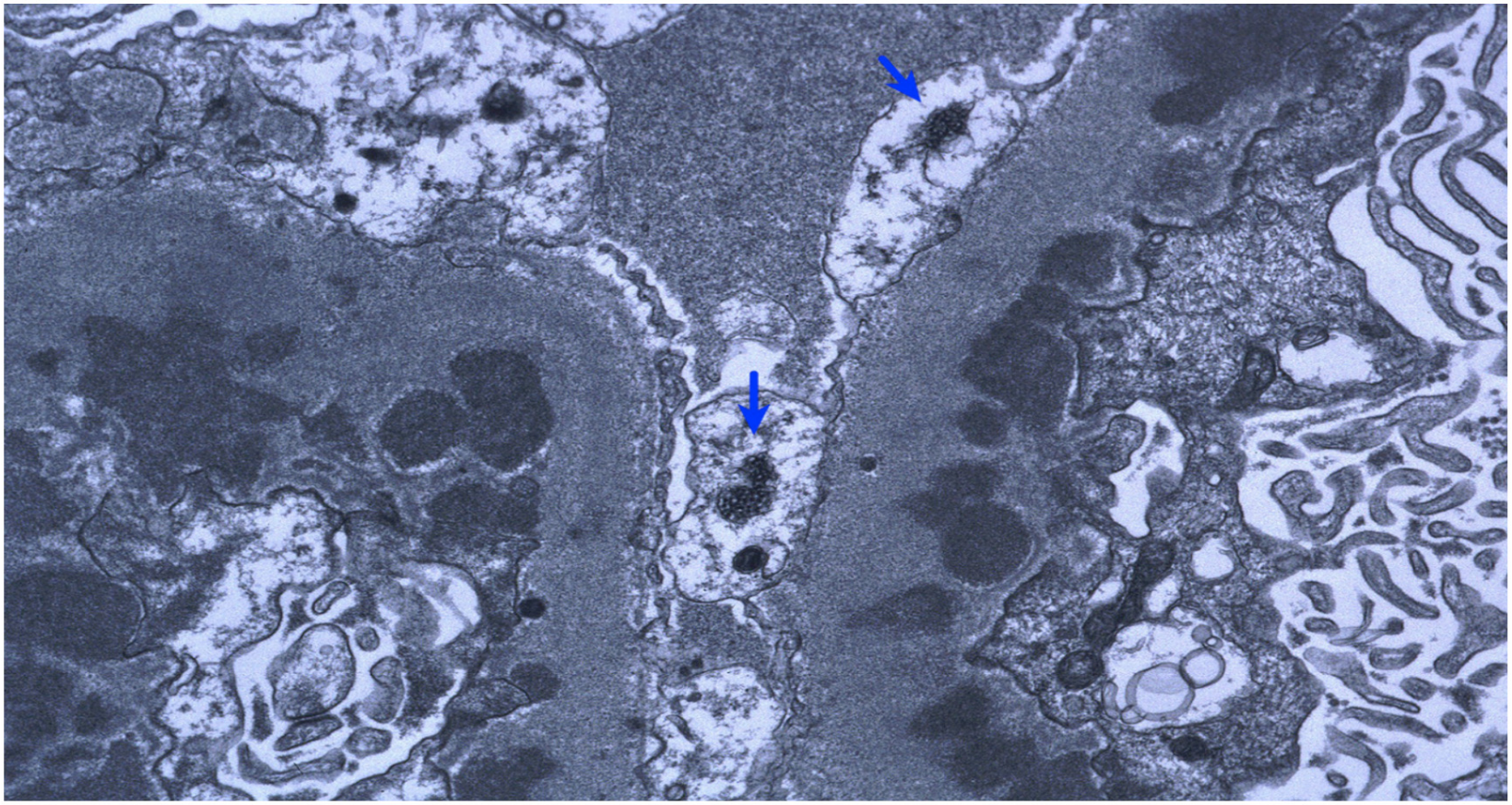


SECONDARY MEMBRANOUS

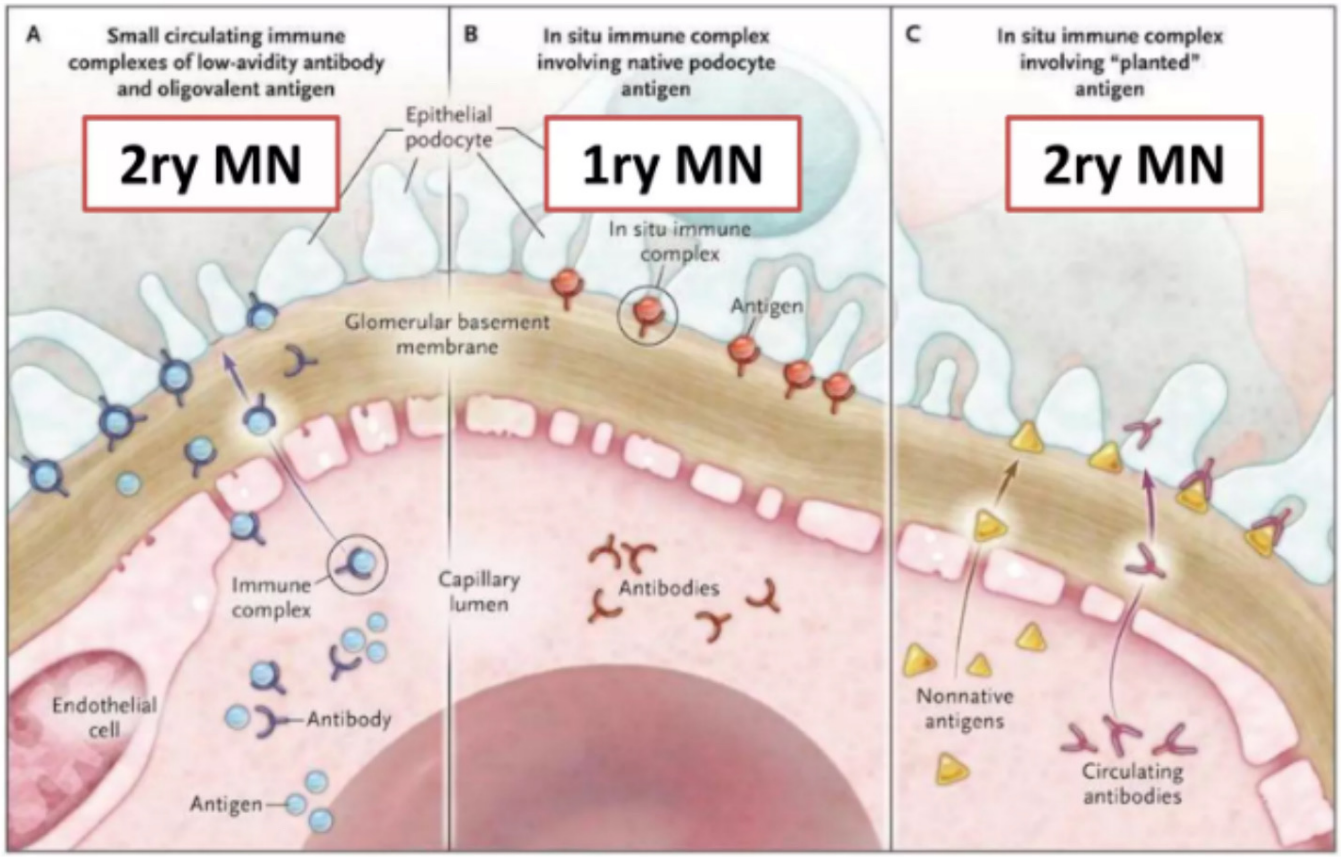
Subepithelial deposits with few mesangial deposits (blue arrow)

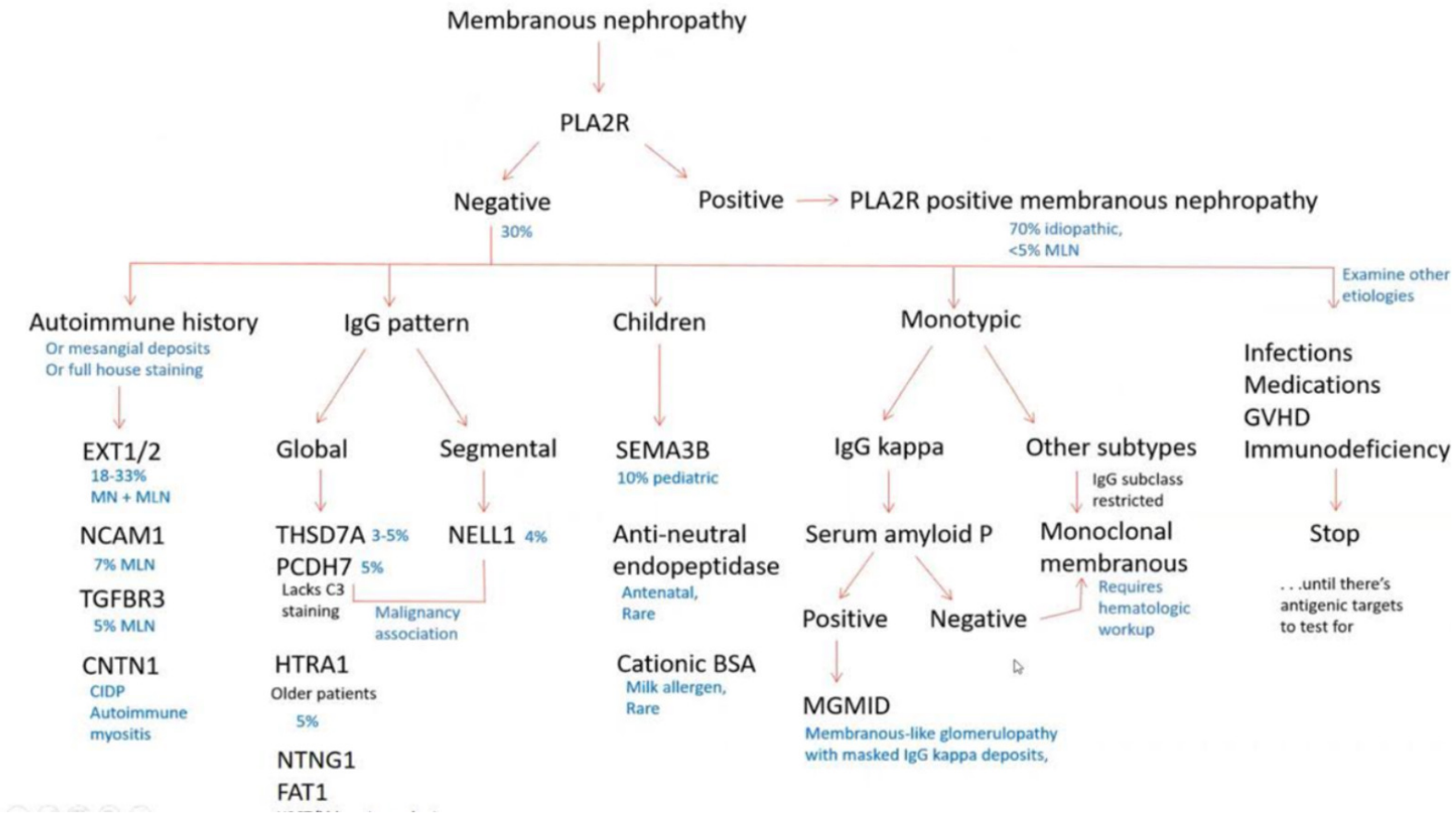


MLN (Membranous lupus nephritis)-Tubuloreticular aggregates (blue arrows) in the cytoplasm of endothelial cells



Possible mechanisms in Membranous Nephropathy

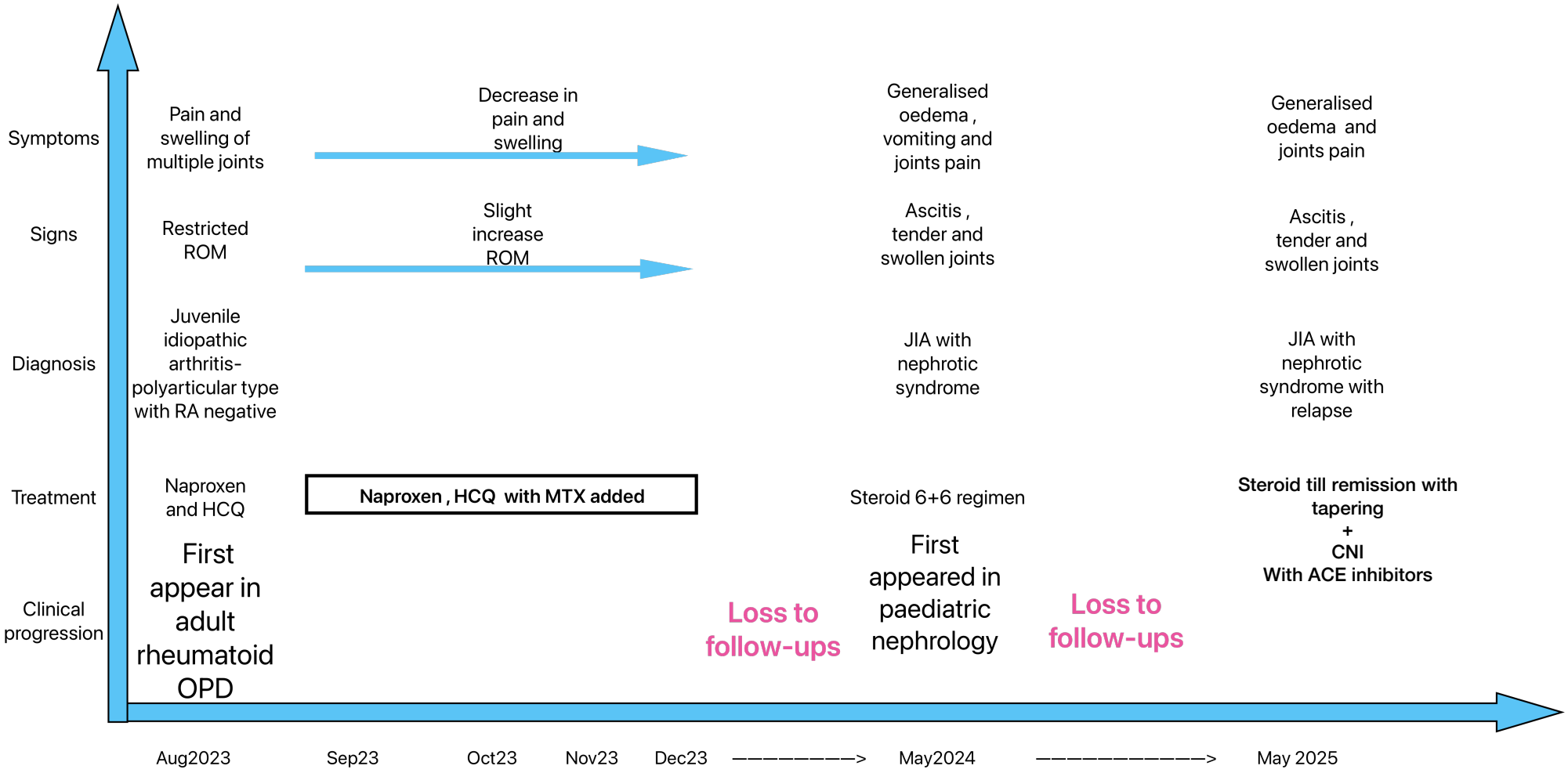



Membranous nephropathy
PLA2R
Negative
30%
Positive
PLA2R positive membranous nephropathy
70% idiopathic,
<5% MLN
Examine other etiologies
Autoimmune history
Or mesangial deposits
Or full house staining
IgG pattern
Children
Monotypic
Infections
Medications
GVHD
Immunodeficiency
EXT1/2
18-33%
MN + MLN
NCAM1
7% MLN
TGFBR3
5% MLN
CNTN1
CIDP
Autoimmune myositis
Global
Segmental
THSD7A 3-5%
PCDH7 5%
Lacks C3 staining
Malignancy association
NELL1 4%
HTRA1
Older patients
5%
NTNG1
FAT1
SEMA3B
10% pediatric
Anti-neutral endopeptidase
Antenatal,
Rare
Cationic BSA
Milk allergen,
Rare
IgG kappa
Other subtypes
IgG subclass restricted
Serum amyloid P
Monoclonal membranous
Requires hematologic workup
Positive
Negative
MGMID
Membranous-like glomerulopathy with masked IgG kappa deposits,
Stop
. . .until there's antigenic targets to test for

What can be done futher?

PLA2R , SEMA3B, NELL1
EXT1/2

- Electron microscopy


Symptoms
Signs
Diagnosis
Treatment
Clinical progression
Pain and swelling of multiple joints
Restricted ROM
Juvenile idiopathic arthritis- polyarticular type with RA negative
Naproxen and HCQ
First appear in adult rheumatoid OPD
Decrease in pain and swelling
Slight increase ROM
Naproxen , HCQ with MTX added
Loss to follow-ups
Generalised oedema , vomiting and joints pain
Ascitis , tender and swollen joints
JIA with nephrotic syndrome
Steroid 6+6 regimen
First appeared in paediatric nephrology
Loss to follow-ups
Generalised oedema and joints pain
Ascitis , tender and swollen joints
JIA with nephrotic syndrome with relapse
Steroid till remission with tapering
+
CNI
With ACE inhibitors
Aug2023
Sep23
Oct23
Nov23
Dec23
May2024
May 2025

Discussion

- Diagnosis can be challenging due to variable and mixed patient presentations and changes in symptoms over time. Early diagnosis is associated with improved outcomes.
- An inter-professional team approach is crucial for improving clinical outcomes and patient quality of life.
- Definitive diagnosis often requires close follow-up and identification of the characteristic clinical, laboratory, and radiologic findings and serial monitoring of various parameters.

Take home message

- Not all steroid sensitive nep syndrome should be treated as simple nephrotic syndrome as they can be associated or manifestation of other systemic or rheumatological illnesses
- All nephrotic syndrome need not biopsy, but as in this case, the patient is a 13 year old, adolescent female, which is with joint pains, so we do need biopsy, even if she is steroid sensitive For ruling our SLE or other rheumatology disorder
- anti nuclear antibody testing should always be confirmed by IFA
- In adolescent girl with joint pain & proteinuria always rule out SLE

Importance of renal monitoring

- Proteinuria and hematuria are early signs of renal involvement in JIA and should be monitored in patients.
- Detailed screening of renal function is necessary to monitor patient with JIA for any signs of kidney disease.


thank you