Synopsis of Nephritic Syndrome and Membranoproliferative Glomerulonephritis (MPGN)
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Your patient is an 18 year-old woman who is seen for the complaint of occasional vomiting, back pain, swollen ankles, and oliguria. She has a 4-year history of arthritic joint pain. She previously tested positive for serum antinuclear antibody (ANA). On examination she has a blood pressure of 160/90 mmHg. Urinalysis is significant for hematuria, and serology shows high BUN and creatinine levels. To confirm your clinical suspicion, you schedule her for renal biopsy and immunofluorescence evaluation. Results of the biopsy show a tram-track appearance of the glomerular basement membrane and sub-endothelial deposits of immune complexes.

1. It is apparent that the patient has renal disease. Which of the two patterns of renal disease, nephrotic or nephritic, is supported by the given findings?

2. What is the classic triad of nephritic syndrome?

3. What is the mechanism of severe hypertension and oliguria in nephritic syndrome?

4. Hematuria of nephritic syndrome is known as glomerular hematuria. How do we distinguish between hematuria of glomerular origin and those that originate from lower urinary tract locations?

5. What is the mechanism of red cell cast formation in nephritic syndrome?

6. What are the major causes of nephritic syndrome?

   P ____________________________________________
   I ____________________________________________
   G ____________________________________________
   Rapidly progresses ____________________________
   to
   H ____________________________________________
   A ____________________________________________
   M ____________________________________________

   Hematuria!

   PIG Rapidly Progresses to HAM!
   "If slaughterhouses had glass walls, everyone would be vegetarian."
   Sir Paul McCartney
   PETA Organization, UK

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Question 7 Refers to the previous clinical vignette:
7. Which of the listed conditions that we covered with the mnemonic of “PIG RAPIDLY PROGRESSes to HAM” is the most likely cause of her symptoms?

   Hint: the tram-track appearance of the glomerular basement membrane and subendothelial deposits of immune complexes!

Supplemental Drill Questions
8. What is the other commonly used term for rapidly progressive glomerulonephritis?

9. What is the hallmark of nephritic syndrome?
10. What is the hallmark of nephrotic syndrome?

11. It is apparent that the procedure for collecting 24-hour urine samples for measuring protein levels is quite difficult for patients as well as being more time-consuming and expensive. What is the commonly used alternative test for this purpose?

12. Single dipstick (spot) urinalysis tests are reported in four grades of 1+, 2+, 3+ and 4+. What does this reporting mean and what is the reason that proteinuria of more than 3.5 is known as nephrotic range proteinuria?

13. A patient has a single spot urine test of 2+; what does this mean?

14. What is the function of mesangial cells?

15. What does the following diagram remind you of and how is it related to nephritic syndrome in general and MPGN in particular?

*Hint: Supreme pizza with lots of items!*

<table>
<thead>
<tr>
<th>Type I MPGN</th>
<th>Type II MPGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• AKA. Mesangiocapillary proliferative glomerulonephritis</td>
<td>• AKA. Mesangial proliferative glomerulonephritis</td>
</tr>
<tr>
<td>• The more common type</td>
<td>• No immune complexes involved</td>
</tr>
<tr>
<td>• Immune complexes activate the classical complement pathway</td>
<td>• Pathogenesis is related to uncontrolled activation of the alternate complement pathway</td>
</tr>
<tr>
<td>• Subendothelial and mesangial deposits</td>
<td>• Dense homogenous deposition along the glomerular basement membrane and in the mesangium</td>
</tr>
<tr>
<td>• Thickening of the capillary walls and interposition of mesangial cytoplasm into the peripheral capillary loops</td>
<td>• Mesangial cell proliferation</td>
</tr>
<tr>
<td>• Mesangial cell proliferation</td>
<td>• Dense deposits largely diminish kidney’s filtering ability</td>
</tr>
</tbody>
</table>

16. Would you be able to identify hypercellularity of the glomeruli in light microscopy of other causes of nephritic syndrome besides poststreptococcal glomerulonephritis?

17. What is the basement membrane?

18. What is basal lamina and how does it differ from the basement membrane?

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**MPGN**

- MPGN is an uncommon cause of nephritic syndrome that mostly affects children and young adults.
- There are two major types of MPGN, mesangiocapillary glomerulonephritis (known as Type I), and mesangial proliferative glomerulonephritis (known as Type II).
- Causes: Idiopathic or familial predispositions.
- Type I MPGN is due to abnormal immune response and sub-endothelial antibody and immune complex deposition.
- In either Type I or II, mesangial cells increase in number.
- Type I, as its name implies, is by far the most common and most commonly tested one on the USMLE and COMLEX examinations.

**Note:** Type III MPGN is uncommon and is characterized by the concomitant presence of sub-endothelial and subepithelial deposits.
19. What is the location and function of the basal lamina?

_____________________________________

20. What are the 3 layers of the basal lamina and how do they help to differentiate the basement membrane from the basal lamina?

_____________________________________

21. What are the major chemical ingredients of the laminal layers?

_____________________________________

22. What staining technique is most helpful in highlighting the basement membrane for visualization in light microscopy because of the presence of glycoproteins (e.g. heparan sulfate)?

Hint: The color scheme of the above picture must have been a pink-red color!

23. An 18 year-old patient with a recent history of streptococcal sore throat presents with sudden onset of hematuria and hypertension. Within 4 days his condition worsened and his 24-hour urine protein exceeded 3.5 grams. A renal biopsy was performed. Results were significant for crescentic urinary spaces. What is your most probable diagnosis?

_____________________________________

Type I MPGN characteristic microscopic findings are increased number of mesangial cells, thickened basement membrane, extension of mesangium in between the epithelial and endothelial cells, narrow lumen of the vessels, and widespread mesangial and subendothelial deposits of immune complexes.

Type II MPGN presents with proliferation of mesangial cells, lack of subendothelial deposits, and thickened basement membrane (see the above diagram). The thickened basement membrane may be due to combined growth of mesangial matrix and basement membrane.

24. What are the two major microscopic findings of MPGN I?

_____________________________________

25. You might have heard of the term “tram track” in conjunction with MPGN; what does it really mean?

_____________________________________

The answer will be evident soon!

26. What other staining method will highlight the basement membrane?

_____________________________________

*The dumbbell-shaped structure in the left capillary is a red blood cell!
Your patient is an 18 year-old woman who is seen for the complaint of occasional vomiting, back pain, swollen ankles, and oliguria. She has a 4-year history of arthritic joint pain. She previously tested positive for serum antinuclear antibody (ANA). On examination she has a blood pressure of 160/90 mmHg. Urinalysis is significant for hematuria, and serology shows high BUN and creatinine levels. To confirm your clinical suspicion, you schedule her for renal biopsy and immunofluorescence evaluation. Results of the biopsy show a tram-track appearance of the glomerular basement membrane and sub-endothelial deposits of immune complexes.

27. Which of the following serological findings would you also expect in this patient?
A. Low levels of serum complement 3 (C3)
B. High levels of serum complement 3 (C3)
C. High levels of IgG auto-antibody against C3 convertase that over-activates the alternative complement pathway
D. Low levels of C1-esterase enzyme that over-activates the classic pathway
E. Low levels of serum complement 2 (C2)

28. Formerly we said that it is postulated that complement deficiency plays an important role in the pathogenesis of MPGN. What complement deficiency is most commonly involved in this situation?

29. What is the prognosis of MPGN?

30. Which of the two patterns of nephritic or nephrotic syndrome would you expect to see in MPGN?

31. Does nephritic or nephrotic pattern of MPGN present in a rapidly or slowly progressive manner?

32. Which of the two MPGNs is called dense deposit disease?

33. Although the tram-track appearance is characteristic of MPGN, it is not as apparent in one of the two types; in which type is it less apparent?

34. Why do we only see the tram-track appearance in the above type of MPGN?

35. The case scenario states that the patient had been tested positive for antinuclear antibodies; what is the significance of this piece of information?

36. Name important autoimmune conditions that are associated with ANA.

37. The gender and age of the patient may increase the suspicion of SLE as our top differential for the ANA antibodies. Assuming that the patient has SLE, is SLE nephropathy a nephrotic or nephritic syndrome?

38. IgA nephropathy is a non-systemic disease that is associated with mesangial IgA deposits. But several systemic diseases are also associated with mesangial IgA deposits. Name the top 4 such diseases.
39. Patients with ankylosing spondylitis are also presented with mesangial deposits. These patients are often young males that, in addition to IgA deposits, may also have another type of immune deposit in their glomeruli and vertebral joints. What is the name of the other immune deposits, and why is this condition more common in young males?

40. Dermatitis herpetiformis is also associated with IgA nephropathy. What is the relationship between herpes and dermatitis herpetiformis?

41. What type of deposits would you expect to see in the glomeruli of a patient with SLE nephropathy?

42. A patient with a history of systemic lupus erythematosus presents with MPGN and glomerular IgA deposits. Which of the two patterns of MPGN would you expect in this patient: Type I or II?

Simplified Classic and Alternate Complement Pathways

**Details of the Classic Complement Pathway**
- The classic pathway shown above is a simplified an oldest version of the classic pathway. The current view of the classic pathway includes the following steps:
  - The classic pathway starts with an antigen-antibody reaction. The antibody is either IgG or IgM.
  - Complement 1 (C1) identifies Fc receptors of the IgG or IgM.
  - C1 is activated and forms C1qrs complex. Note that C1 is a multi-subunit protein containing three different proteins (C1q, C1r and C1s).
  - C1qrs activates C4.
  - Activated C4 breaks down to C4a and C4b.
  - C4b activates C2 to form C4b2a complex.
  - C4b2a complex is also known as C3 convertase.
  - C4b2a activates C3 (note that calcium is necessary for this reaction).
  - Activated C3 breaks down to C3a and C3b fragments.
  - C3b binds to the membrane in association with C4b and C2a. Meanwhile C3a is released into the surrounding area. The resulting C4bC2aC3b is known as C5 convertase. Generation of C5 convertase is the end of the classic pathway.
  - C5 convertase activates MAC complex.
  - Activated MAC has lytic power and attacks cellular membranes of pathogens, makes pores in them, and mediates both pathogenesis and the prevention of immune complex diseases.
Details of the Alternate Complement Pathway

- C3 is made by the liver and is abundant in the blood.
- The pathway is initiated by the spontaneous hydrolysis of C3, that is, C3 (H2O) formation.
- Binding of plasma protein Factor B to hydroxylated C3 allows Factor D to cleave Factor B into Ba and Bb fragments.
- Bb attaches to C3 to form C3Bb (AKA, C3 convertase). The latter cleaves many C3 complements into C3a and C3b.
- C3a dissipates and C3b cleaves C5 to C5a and C5b. C5a dissipates.
- C5b, C6, C7, and C9 together form the MAC complex.

Lectin (Mannose-Binding Lectin) Pathway

- The lectin pathway is the third complement pathway.
- Mannose-binding protein is produced by the liver and can initiate the complement cascade by binding to pathogen surfaces.
- It binds to mannose, glucose, or other sugars or glycoprotein components of micro-organisms.
- It is similar to the classical complement pathway because after activation, it proceeds through the action of C4 and C2 to produce activated complement proteins further down the cascade.
- In contrast to the classical complement pathway, it does not recognize antibodies bound to its target.
- The pathway starts with mannose-binding lectin binding to certain sugars on micro-organisms.

43. What is the consequence of activation of MAC complex in the nephrons?

44. Activation of which of the two complement pathways, classic or alternate, is most likely related to etiology of IgA nephropathy and Type II MPGN?

45. Which of the two complement systems, classic or alternate, is more effective against the lipopolysaccharide of gram-negative bugs?

46. Which of the two immunoglobulins, IgG or IgM, is more effective in binding complements and initiating the complement cascade?

47. Biopsy of the glomeruli and immunofluorescence studies of the deposits in renal diseases show certain patterns of distribution of immune complexes. Which of the following patterns is associated with mesangial deposits?
1. Nephritic
2. Hypertension, Hematuria, and Oliguria
3. Immune complex injury of the glomerular capillary endothelium causes hematuria. Meanwhile, widespread damaged glomerular vessel walls will activate degranulation of the platelets and lead to thrombotic blockade of the vessels and a resulting drop in the GFR and oliguria. Drop in the GFR will aggressively activate the renin-angiotensin system, and this leads to hypertension.

4. Hematuria of glomerular origin presents with red blood cell casts, whereas the hematuria that originates after the renal pelvis does not present with casts.

5. Red cells that pass through injured fenestrations of the glomerular capillaries are damaged and assume dysmorphic shapes. Additionally, they pile up and adhere to each other with protein molecules. As such they assume a stack-like and cylindrical appearance.


7. Membranoproliferative glomerulonephritis.
8. Rapidly progressive glomerulonephritis is also known as crescentic nephritis.
9. Hematuria
10. Proteinuria of more than 3.5 grams per day
11. Single "Spot" urine test (simple dipstick test). Nephrotic range proteinuria is 3 grams per day or more.
12. On a single, "spot" urine collection, it is 2 grams of protein (albumin) per gram of urine creatinine. A healthy liver makes 3 grams of proteins (albumin) per day. If in nephrotic syndrome a patient loses 1 (1+), 2 (2+), or 3 (3+) grams of albumin per day, the liver compensates by making up to 3 grams per day. However, above 3 (4+) grams of protein loss, the liver’s compensatory ability will be lost. Note that even if a patient loses 4, 5 or more grams of protein per day it is going to be reported as 4+.
13. Pre-nephrotic range or 2 grams per day of protein loss. Note: Although the lab reporting may vary from lab to lab, below is a helpful summary table based on the recommendations of the International Society on Nephrology.

<table>
<thead>
<tr>
<th>Grades</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1+ on dipstick or 0.15–1.0 g/24</td>
</tr>
<tr>
<td>II</td>
<td>2+ to 3+ on dipstick or &gt;1.0–3.5 g/24 h</td>
</tr>
<tr>
<td>III</td>
<td>4+ on dipstick or &gt;3.5 g/24 h</td>
</tr>
<tr>
<td>IV</td>
<td>Nephrotic syndrome</td>
</tr>
</tbody>
</table>

14. Mesangial cells, modified smooth muscle cells, occupy a central position within the renal glomerulus. They produce cytokines and prostaglandins, mediate inflammation, produce and remove basement membrane and other matrix substances, uptake immune complexes, and by the virtue of their contraction or relaxation-ability can modify glomerular filtration rate.
15. This diagram is a cartoon version of hypercellularity of the glomeruli in poststreptococcal glomerulonephritis (PSGN). The cells (and their nuclei) are practically all types of cells; endothelial, mesangial, epithelial, neutrophils, etc.
16. Hypercellularity is a common finding of nephritic syndrome, although it may not present with a diffuse pattern as it is seen with PSGN. For instance, in Type I MPGN it is more localized to the mesangial cells.
17. Extracellular matrix found on the basal surface of and secreted by the epithelial cells.
18. The basal lamina and the basement membrane are quite often used interchangeably. However, the term "basal lamina" is usually used in conjunction with electron microscopy, while "basement membrane" is usually used with light microscopy.
19. The basal lamina surrounds and lies underneath sheets of epithelial cells. In the lungs and kidneys it separates two types of cells; namely, the endothelial cells of blood vessels and epithelial cells from each other.
20. The 3 layers of basal lamina are lucida, densa, and reticularis. Some histologists believe that the basal lamina is composed of lamina densa and lamina lucida, whereas the basement membrane is composed of the lamina densa and lamina reticularis. No matter which description of basement membrane and basal lamina you subscribe to, they both have the middle layer, lamina densa, in common!
21. Collagen Type IV and Heparan sulfate (a glycosaminoglycan)

22. Periodic Acid Schiff (PAS)

23. Rapidly progressive glomerulonephritis

24. Mesangial and subendothelial deposits of immune complexes, and increased number of mesangial cells.

25. Tram-track refers to the basement membrane in MPGN, which has a tram-track appearance in light microscopy with the help of special staining techniques. With PAS staining, the capillary endothelial lamina and basement membrane show two distinct membranes in light microscopy due to mesangial interposition into the capillary, which gives the loops a tram-track appearance. Do all MPGN types have tram-tracks? Please see below for the answer.

26. Silver staining (methenamine-silver staining) is the second commonly used staining, besides PAS, for highlighting the basement membrane. With this type of staining the glomeruli will assume a silverish-bluish coloration.

27. [A]. Low levels of serum complement 3

28. C3 deficiency is very common in MPGN and is demonstrable in about 75% of the patients.

29. As you might have guessed the prognosis of MPGN is relatively poor despite optimal effects of steroids and immune suppressant therapy. The disease often progresses to end stage renal failure.

30. The best answer is either, but the nephritic pattern is by far the most common pattern. Quite often it starts with a nephritic pattern and progresses to a nephrotic pattern.

31. They both appear in a slowly progressive pattern. This is their distinguishing characteristic against rapidly progressive glomerulonephritis.

32. Type II

33. You don’t see it in Type II and you only see it in Type I MPGN.

34. In Type I the mesangium extends between the podocytes and endothelial cells, whereas in Type II we get a dense homogenous deposition along the glomerular basement membrane and in the mesangium that would not allow the double contour to express itself. In Type II you will see a thick ribbon-like pattern.

35. This supports the fact that MPGN must have an autoimmune etiology!

36. SLE, Sjogren’s, Scleroderma, Polymyositis and Rheumatoid arthritis.

37. SLE presents with either nephrotic or nephritic or a mixed pattern. But the nephrotic pattern is by far the most commonly presented pattern.

38. Henoch-Schonlein Purpura, Systemic lupus erythematosus, Ankylosing spondylitis, and Dermatitis herpetiformis. A few other noteworthy associations are celiac disease, rheumatoid arthritis, and HIV.

39. Ankylosing spondylitis is due to IgA and more importantly, HLA-B27 deposits. This condition is characteristically more common in men, and is accentuated with hyper-testosterone levels in younger men. It is postulated that testosterone facilitates interaction of HLA-B27 with the glomerular or joint tissues.

40. There is no relationship between the two conditions. The presumption of a relationship may be due to the resemblance of the skin rash of dermatitis herpetiformis with that of the rash of herpes. Interestingly, dermatitis herpetiformis is heavily associated with celiac disease and gluten sensitivity.

41. SLE nephropathy may have any combination of IgG, IgM, IgA, and C3 glomerular deposits.

42. The patient with SLE will most likely have a Type II pattern of MPGN. In Type I, immune complexes are due to IgG and IgM, and they activate the classical complement pathway. In contrast, Type II MPGN involves uncontrolled activation of the alternate complement pathway and consumption of C3. Hence, this patient most likely has Type II MPGN due to IgA deposits.

43. Ongoing activation of the complements and MAC complex in the nephrons in nephritic and nephrotic diseases can cause ongoing damage to the kidney’s filtering ability.

44. Given that IgG and IgM are involved in the initiation of the classic pathway, the IgA nephropathy and MPGN Type II must involve the alternate complement pathway.

45. The alternate pathway.

46. IgM is more effective because it has 5 immunoglobulin subunits and thus more binding surfaces.

47. [C]. This pattern resembles fireworks in the sky, or “4th of July pattern!”