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Case Study

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MEMBRANOUS NEPHROPATHY COMPLICATED WITH ACQUIRED HEMOPHILIA. PRESENTATION OF A RARE MEDICAL CONDITION

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ABSTRACT

A 63-year-old female patient presented with a large ecchymosis on her limbs, torso and buttocks. Few days prior to this event she suffered from facial cellulitis accompanied by suborbital and lower limb edema. That time she was diagnosed with membranous nephropathy and was discharged on angiotensin receptor blocker (Losartan). This time her coagulation factor VIII activity was decreased, and she was having heavy proteinuria. Her renal biopsy showed diffuse glomerular basement deposits of immunoglobulin G (IgG). A diagnosis of acquired hemophilia and concurrent membranous nephropathy was made. She was transfused with fresh frozen plasma and fibrinogen and immunosuppressives and was given rituximab. After one week of treatment the ecchymosis disappeared.

KEY WORDS: Membranous nephropathy, acquired hemophilia, ecchymosis, hematoma.

BACKGROUND

Membranous nephropathy (MN) is the most observed cause of heavy proteinuria worldwide. It can be primary and secondary. Its more common primary form (~70% cases), is a slow autoimmune process leads to heavy proteinuria. Remainder 30% of the cases can occur secondary to various infections, autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), urticarial vasculitis, thyroiditis, Sjogren syndrome, systemic sclerosis, and cancers. It can occur after the use of certain drugs also. Both types present with same features although the course of the two types and treatments strategies may vary due to their different pathophysiology.

As a result, distinguishing between primary and secondary MN is important which is based on the patient's history and clinical symptoms and on investigations such as immunofluorescence and electron microscopy analysis of a renal biopsy and serology. In this case, 63-year-old female shows repeated ecchymosis and coagulation disorder associated with heavy proteinuria. Later she was found to be positive for Epstein Barr Virus infection and was diagnosed as MN. This is not a commonly seen combination, and after replacing coagulation factors and immunosuppressive therapy, the patient's condition improved.

CASE PRESENTATION

A 63-year-old female patient complained of a “skin spots” on her limbs, torso, and buttocks. On history taking, she told that two months before admission, she had facial redness and swelling in suborbital area. Later within few days, swelling or edema rapidly progressed to lower limbs and trunk. She was given antibiotics and Chinese herbal medicine after which the edema was relieved. After few days of this event, she noticed bruising (ecchymosis) on her upper and lower limbs, which gradually expanded and later involved her torso and buttocks also. This was accompanied by severe fatigue but was not associated with fever, gingival bleeding, hematochezia, or joint swelling.

Physical Examination

On her initial Physical examination, her temperature was 36.2 ℃, heart rate 84 beats per minute, breathing 20 per minute, blood pressure 131 / 84mm Hg. No anemia, jaundice, or lymphadenopathy was noted. At the time of examination, the ecchymosis spread nearly all over the body. Heart and lung were normal on auscultation, and no hepatosplenomegaly was observed. There was no edema in both legs. Figure 1-A to C.

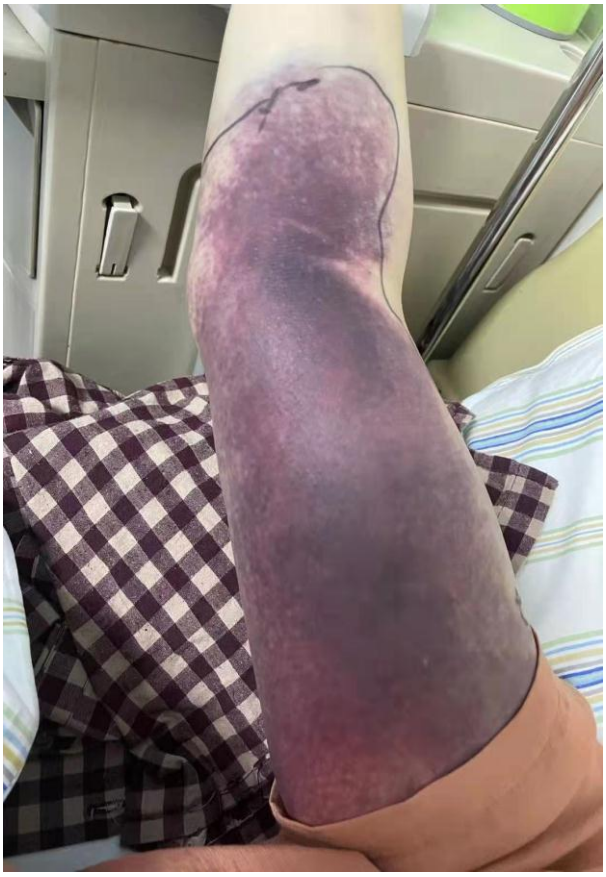

Figure 1-A.

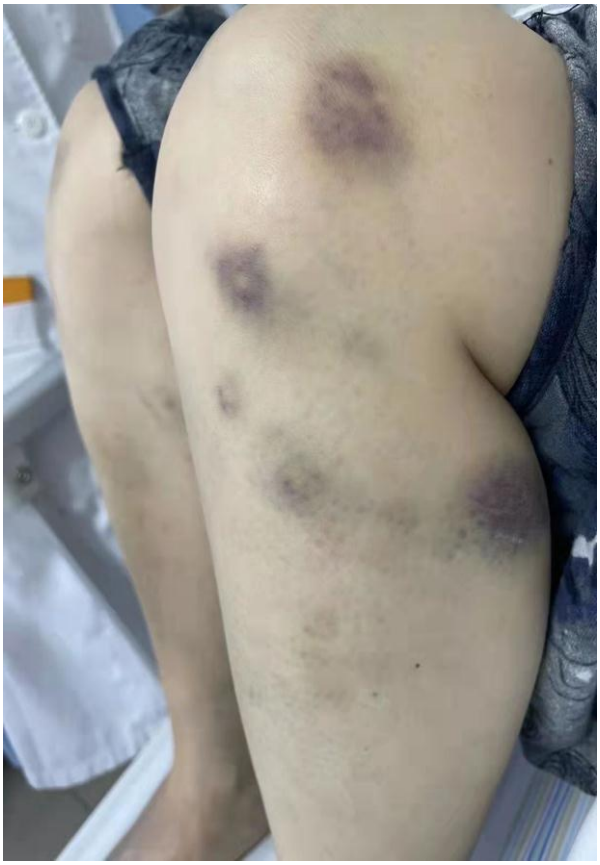

Figure 1-B.

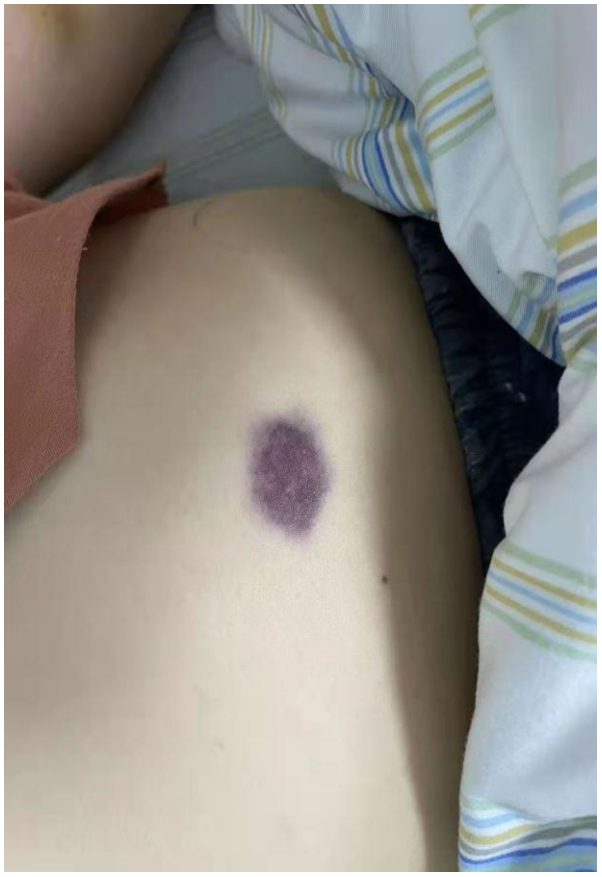

Figure 1-C

Figure 1: Areas of ecchymosis on various parts of the body of patient on presentation.

Investigation

Renal biopsy results were consistent with chronic kidney disease and renal immunohistochemistry bowman's capillaries showed diffuse granular deposition of IgG (3 +), IgG1 (2 +), IgG2 (2 +), IGg3 (2 +), IGg4 (4 +), C3 (3 +), kappa light chains (3 +) and lambda and (3 +). PLA2R, IgM, IgA, C1q, and C4 were all negative. Extractable Nuclear Antigen Antibodies (ENA) Panel was negative. (Figure 2 A and B)

Urine kappa light chain level was 36mg / L (reference value: < 19mg / L), urine light chain 21.5 mg / L (reference value: < 50mg / L), blood kappa light chain 2.31 mg / L (reference value: 1.7-3.7g / L), urine light chain 1.5 mg / L (reference value: 1.35-2.65g / L), ratio 1.54 (reference value: 1.35-2.65)

Auxiliary examination: Factor VIII antibody: 3.84 (reference value: 0-0.6); Complete set of endogenous coagulation factors: plasma coagulation factor VIII: 4.4% (reference value: 0-0.0); Hepatitis B surface antibody: 89.50mlU/mL (reference value: 0-0.6); Hepatitis B core antibody: 4.0s/co (reference value: 0-0.6).

Renal function: Urea: 6.43mmol/l; Creatinine: 66.1 μmol / L; uric acid (UA): 373.6 μmol↑; Chlorine (C1 -): 111.5mol/l ↑

Blood routine analysis: WBC: 5.90 × 10^9/L; Red blood cell: 3.07 × 10^12/L↓; Hemoglobin: 97.0g/l ↓; Platelet: 181 × 10^9/L; Eosinophil absolute value: 0.00 × 10^9/L↓; Hematocrit: 29.8%; ESR: 20 mm / h; von Willebrand factor antigen: 174.10

Anti GBM antibody test: negative (-)
EB virus DNA: was positive (+) 5.272 copies / ml;

Immunoglobulin complete set: immunoglobulin G (IgG): 4.68g/l ↓;

Liver function Test: ^ blood lipid test: alanine aminotransferase: 11U / L; Aspartate aminotransferase: 15U / L; Total bilirubin: 4.7umol/l ↓; Total protein (TP): 50.1g/l ↓; Albumin (ALB): 25.5g/l ↓; WBR: 1.04; Low density lipoprotein (LDL-C): 3.43 mmol / L ↑; Lipoprotein (a) (LP (a)): 500.7mg/l ↑; Glucose (Glu): 4.83 mmol / L;

Shoulder joint plain scan: It was done to assess the cause of swelling in the axilla. showed right axillary and anterior chest wall soft tissue edema; Mild injury of the right rotator cuff (mainly supraspinatus and subscapular tendon), and right axillary mass with peripheral enhancement likely to be a hematoma.

Urinalysis urinary sediment for occult blood: positive (+); Urine protein: positive (+ +); Red blood cells: 114.60 / UL; Epithelial cells: 70.30 cells / UL; Tube type: 38.32 / UL; Pathological type: 9.92 / UL; Small round cells: 65.9 cells / UL; Urine protein electrophoresis: urine β2 microglobulin 953.7ug/l (reference range: 0-300); 0 mg / L (reference range < 30); 00 mg / L (reference range: < 12.0); 70 mg / L (reference range: < 9.4); Urinary transferrin 737.00 mg / L (reference range: < 2.12); Urine immunoglobulin 905.00 mg / L (reference range: < 9.6); Urine protein electrophoresis: results; Small molecular protein: 7.9%; Medium molecular protein: 79.9%; Macromolecular protein: 12.2%.

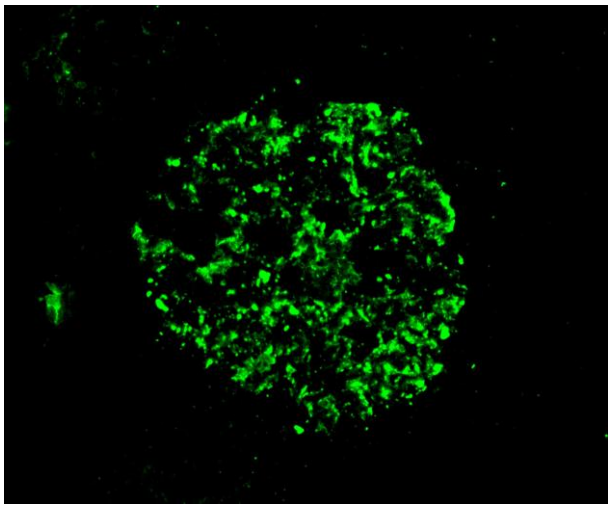

Figure 2A: Immunofluorescence showing diffuse deposition of IgG.

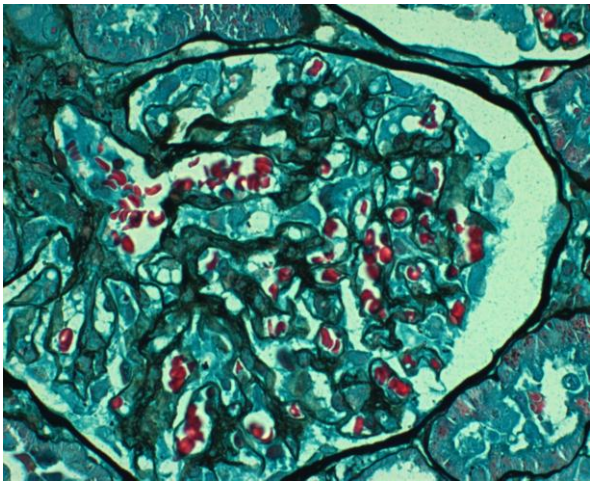

Figure 2B: Masson staining. capsule wall and basement membrane is slightly thickened with a small amount of stratification. The volume of the remaining glomeruli is generally increased, the mesangial cells and mesangial matrix are slightly increased.

DIAGNOSIS

After careful investigations and assessment, diagnosis of membranous nephropathy with acquired hemophilia was on the top of the list. In addition concurrent Epstein Barr virus infection was also considered. Other comorbidities, including mild anemia and grade 2 hypertension with hypertensive heart disease, were also diagnosed.

TREATMENT

The patient was given immunosuppression therapy with methylprednisolone and tacrolimus) while Candesartan was given to control blood pressure. To control bleeding, she was transfused with coagulation factor VIII, and fresh frozen plasma.

OUTCOME AND FOLLOW-UP

The patient's condition improved after treatment. However, to further confirm the diagnosis of membranous nephropathy, the concentration of tumor markers, PLA2R and FK506 is still awaited. Therefore, the patient was advised for a follow-up visit to the nephrology department after which the dosage of tacrolimus will be adjusted.

DISCUSSION

Membranous nephropathy (MN), as the name indicates, involves thickening of the glomerular basement membrane (GBM), and it affects all glomeruli (global) and involves the whole glomerulus (diffuse). In its primary form, which is autoimmune, it is caused by autoantibodies directed against phospholipase A2 receptor (PLA2R) or, sometimes, thrombospondin type-1 domain-containing 7A (THSD7A).[1,2] The secondary type is associated with various drugs usage, infections, various cancers, and many autoimmune diseases. These autoimmune diseases include rheumatoid arthritis, SLE, multiple sclerosis, temporal arteritis, Sjogren's syndrome, AIHA, pulmonary hemorrhage nephritis syndrome, myasthenia gravis, hyperthyroidism, and autoimmune

hypothyroidism. Many drugs such as sulfanilamide, phenytoin sodium, chloramphenicol, and methyldopa are associated with MN. In addition, many hematological tumors such as CLL, NHL, WM, MDS, MF, erythroleukemia are also associated with MN. The disease generally shows granular sub-epithelial deposits of immunoglobulin G (mainly IgG4) and C3 on immunofluorescence microscopy[3], while on electron microscopy, deposits confined to the subepithelial space of glomeruli or incorporated into irregular projections of GBM-like material ("spikes and domes") are seen. There are no mesangial deposits seen in primary MN. These secondary MNs generally show the same peculiar aspects at immunofluorescence and electron microscopy, but variation can occur due to the associated primary disease. In our case, the 63-year-old patient was suffering from EBV infection and was having coagulopathy. Secondary MN is also commonly associated with viral infections; for instance, it is the most common extrahepatic manifestation of hepatitis B virus (HBV) infection.[4] In a recent study, 64% of patients with HBV-associated MN showed PLA2R overlapped with HBsAg, suggesting a strong association of HBV with anti-PLA2R antibody.[5] In adults, spontaneous remission of proteinuria is rare, and the clinical course is more frequently progressive, and many patients eventually develop chronic renal insufficiency and ESRD.[6] However, in patients with abnormal liver function tests and nephrotic syndrome, the progression to ESRD was more rapid.[7]

MN has been diagnosed in a small number of HCV-positive patients[8] and HIV-positive patients.[9] Other viruses, such as influenza[10], are likely to play a role in the etiology of secondary MN. Detailed clinical and laboratory data and tissue molecular analysis are used to diagnose virus-related MN. Virus-related MN is caused by several processes, including virus tropism in the kidney, generation of aberrant immune complexes, direct cytopathogenic effects, and multiorgan failure.[11] Circulating pla2r antibody can be found in 70-80% of primary membranous nephropathy.[1,12] Pla2r antibody is also positive in this case, which indicates primary membranous nephropathy. Pla2r antibody positive patients can also be seen in membranous nephropathy associated with autoimmune liver disease.[13] The main treatment of primary membranous nephropathy is the use of immunosuppressants. Monoclonal antibody Rituximab can completely or partially eliminate urinary protein and reduce the level of autoantibody pla2r.[14] Other treatments include methylprednisolone and, tacrolimus. The condition of our case could be due to Acquired hemophilia, a hemorrhagic disease that produces antibodies against plasma coagulation factor VIII.[15]

Acquired hemophilia is also known as Acquired hemophilia A (AHA) or acquired factor VIII inhibitor disorder. This is a rare bleeding disorder where patients has no prior history of bleeding disorders.[16] 50% of cases are idiopathic but may be due underlying autoimmune disease producing factor VIII inhibiting antibodies, infections or malignancy.[15] It predominantly affects elderly population without any prior history of bleeding, such as in our case of the 63-year-old female. Other disorders which can cause Acquired hemophilia include lupus, rheumatoid arthritis, multiple sclerosis, Sjogren's syndrome, inflammatory bowel disease, diabetes, respiratory and drugs such as penicillin or interferon.[15,17] Labs will show an isolated increase in PTT with a normal PT, platelet count and thrombin time. This points to either an intrinsic pathway problem (deficient factor VIII) or a factor inhibitor.[18,19]

Management of acquired hemophilia A involves treating the acute bleeding episodes with human factor VIII products (recombinant factor VIII or factor VIII concentrate) and desmopressin with less severe bleeding.[20] Long-term management include controlling the inhibitor activity of autoantibodies[21] using immunosuppressive agents such as steroids, rituximab, cyclophosphamide, intravenous immunoglobulin.[22]

CONCLUSION

In conclusion, the above case presents a rarely documented case of suspected membranous nephropathy with acquired hemophilia. This is an exceptional occurrence, beyond current guidelines, where prompt treatment should be applied to prevent further complications, including end-stage renal failure, uncontrolled bleeding, or intracranial hemorrhage.

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