Annals of Case Reports
Zhi R, et al. Ann Case Rep: 8: 101527
www.doi.org/10.29011/2574-7754.101527
www.gavinpublishers.com

Case Report

Primary Membranous Nephropathy Associated With Malignancy: A Case Report

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Citation: Rui Zhi NG, Tze Wei CHNG, Chee Yong NG (2023) Primary Membranous Nephropathy Associated With Malignancy: A Case Report. Ann Case Report 08: 1527. DOI: 10.29011/2574-7754.101527.

Received Date: 20 November 2023; **Accepted Date:** 25 November2023; **Published Date:** 28 November 2023

Abstract

Membranous nephropathy is known to be associated with a wide range of conditions such as drugs, infection and malignancy. It is recommended to evaluate for associated conditions regardless of the presence of Anti-Phospholipase A2 Receptor (PLA2R) antibody which is known to be associated with primary membranous nephropathy. Our patient presented with nephrotic syndrome and a high serum anti-PLA2R antibody level. After discovering a rectal carcinoma on our secondary workup, we diagnosed him with secondary membranous nephropathy from malignancy and the patient was referred to a surgeon who resected the rectal cancer. Despite the cancer going into remission after the surgery, there was no improvement in the proteinuria or serum anti-PLA2R antibody level. We reconsidered the possibility of primary membranous nephropathy and treated him with immunosuppression. Follow up after treatment with immunosuppression showed improvement in the serum anti-PLA2R antibody level and proteinuria, and he has since gone into partial remission.

Introduction

Membranous nephropathy is a common cause of nephrotic syndrome in adults, accounting for about 20% of the cases [1]. In around 80% of patients with membranous nephropathy, there is no underlying cause and 20% are associated with medications or other diseases such as malignancy [2]. We report a case of membranous nephropathy associated with malignancy that ultimately turned out to be primary membranous nephropathy.

Case Report

A 75-year-old male with a history of hyperlipidemia, presented with testicular and bilateral lower limbs swelling of 2 days duration. He was found to have a systolic blood pressure of 183mmHg. Serum creatinine was 75umol/L with no baseline serum creatinine available for comparison. Serum albumin was 21g/L, urinalysis showed 13 red blood cells per high-power field, 6 white blood cells per high-power field and a urine protein creatinine ratio of 10.16g/g. Fasting plasma glucose was 4.8mmol/L and hemoglobin A1C was 5.5%. C3 level was 1.18g/L and C4 level was 0.17g/L. Serum and urine electrophoresis did not reveal a monoclonal band. He tested negative for the hepatitis B virus surface antigen, hepatitis C virus and human immunodeficiency virus. Testing for anti double-stranded DNA antibody, anti-proteinase 3, anti-myeloperoxidase antibodies were negative. Antinuclear antibody titre was borderline at 1:160. Anti-PLA2R antibody was positive at 840.54 RU/ml.

Kidney biopsy (Figure 1) revealed normal thickness of capillary walls and subtle vacuoles in the glomerular basement membrane on light microscopy. Immunofluorescence showed 3+ granular staining in the glomerular basement membrane for IgG and 2+ granular staining in the glomerular basement membrane for C3. PLA2R staining was weakly positive segmentally. Electron microscopy revealed subepithelial electron dense deposits.

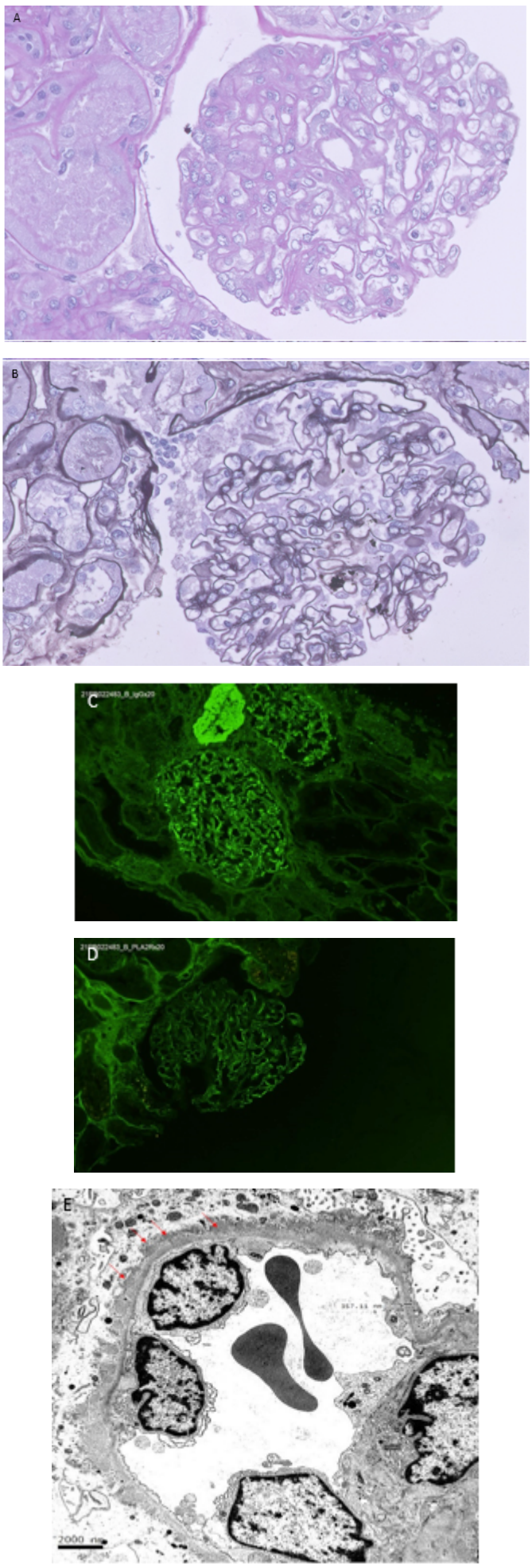

Figure 1: (A) Kidney biopsy findings of membranous nephropathy. Light microscopy hematoxylin and eosin stain shows normal thickness of capillary walls. (B) Silver stain shows subtle vacuoles in the glomerular basement membrane though definite spikes are not identified. (C) Immunofluorescence shows granular staining of IgG along the glomerular basement membrane and (D) weakly positive anti-PLA2R staining along the glomerular basement membrane. (E) Electron microscopy shows subepithelial electron dense deposits.

We proceeded with age-appropriate malignancy screening after the diagnosis of membranous nephropathy as recommended by the KDIGO guidelines [3]. A Contrasted Tomography (CT) scan of the thorax, abdomen and pelvis with intravenous contrast was done which showed a polypoidal rectal mass and segmental emboli in the right lower lobe pulmonary arteries.

We started treatment dose of enoxaparin with a plan for an indefinite duration as the pulmonary embolism is likely from the underlying membranous nephropathy. A colonoscopy was performed by the colorectal surgeon which showed a rectal tumor. Histology of the rectal tumor was villiform adenomatous large bowel tissue with high grade dysplasia. Subsequently gastroenterology attempted endoscopic mucosal resection of the rectal tumor. However, it was friable with contact bleeding and could not be elevated by submucosal injection raising the possibility of malignancy and submucosal invasion. The patient had episodes of bleeding likely from the rectal tumor necessitating the stopping of enoxaparin. The patient then underwent robotic assisted laparoscopic ultra-low anterior resection with defunctioning ileostomy. Intraoperative histology was rectal adenocarcinoma moderately differentiated. Enoxaparin was restarted on post op day 4 as the hemoglobin was stable and there was no signs of bleeding. Oral options of warfarin and apixaban were discussed with the patient and he eventually decided on apixaban. On follow up with the colorectal surgeon, the patient remained in cancer remission and no further treatment for the rectal carcinoma was required.

After the rectal carcinoma was resected, the patient remained in nephrotic syndrome with albumin still low at 18g/L and urine protein creatinine ratio hung up at 7.55g/g and 6.13g/g three and six months after the operation respectively. Anti-PLA2R antibody level was 828.32 RU/ml five months after cancer resection, similar to the level at diagnosis which was 840.54 RU/ml. eGFR was still preserved at 68ml/min/1.73m2. Angiotensin receptor blocker dose had already been optimised. After discussing with the surgeon who confirmed that the patient remained in cancer remission, we decided to treat with immunosuppression as the patient is at risk of progressive loss of kidney function. In view of his history of malignancy, we decided to treat with prednisolone

and cyclosporine, targeting a cyclosporine trough of 125-225ng/ml as recommended by the KDIGO guidelines [3] 7 months after immunosuppression was started, his albumin improved to 31g/L and urine protein creatinine ratio decreased to 3.48g/g. Anti-PLA2R antibody levels decreased to 53.62 RU/ml five months after treatment. Prednisolone was weaned off after six months while cyclosporine is being gradually tapered.

Discussion

This case shows that the presence of a concurrent malignancy may not mean that the membranous nephropathy is secondary to the malignancy. We initially thought that this patient had membranous nephropathy secondary to the cancer because he presented with sudden onset nephrotic syndrome with the concurrent diagnosis of malignancy which is known to be associated with membranous nephropathy.

However, we thought it was unusual for secondary membranous nephropathy to have such high anti-PLA2R antibodies and for PLA2R staining to be present in the kidney biopsy. A case series [4] had shown that though tissue staining for PLA2R has a sensitivity of 75% (95% CI 65-84%) and a specificity of 83% (95% CI 72-90%) for primary membranous glomerulopathy, PLA2R staining was also present in 25% of patients who had concurrent malignancy hence PLA2R staining of the kidney biopsy may not accurately differentiate between primary and secondary membranous nephropathy. Also, anti-PLA2R antibodies are associated with 70% of patients with primary membranous nephropathy [5], hence this patient's high titre of serum anti-PLA2R antibodies did not fit into the picture of a secondary membranous nephropathy.

Since then, a retrospective review of patients with malignancy associated membranous nephropathy [6] has shown some patients who attained cancer remission achieved remission of membranous nephropathy while none of the patients without remission of cancer did. This suggests a causal relationship between the two diseases. However, there was another group of patients who had persistent membranous nephropathy following cancer remission. They only achieved remission of membranous nephropathy after immunosuppressive therapy, similar to what was seen in our case.

A prospective study showed that in PLA2R associated primary membranous nephropathy treated with immunosuppression, serological remission precedes clinical remission and the decline in titres was noted as early as at the end of the first month in >50% of cases [7]. Among serological responders, 54.1%, 37.5%, 62.5%, 79.1%, and 95.6% achieved negative anti-PLA2R at 1, 2, 3, 4, and 5 months, respectively. In our patient, the anti-PLA2R antibody levels remained high five months after curative resection, making it is less likely for cancer to be the cause of membranous nephropathy. To help determine if a PLA2R positive membranous nephropathy associated with a cancer is PLA2R antibody driven or cancer driven, we can trend the anti PLA2R within 5 months after cancer treatment. If there is no decrease in anti PLA2R titre during this period, it will be more likely to be a primary membranous nephropathy and hence immunosuppression should be considered after a discussion with the oncologist.

Conclusion

From our case and the above-mentioned studies, we find the following factors may help to differentiate whether a PLA2R positive membranous nephropathy associated with cancer is PLA2R antibody driven or cancer driven. They are the serum anti-PLA2R antibody titre at diagnosis, the clinical and serological response to treatment of the cancer and to immunosuppression if given.

Ethical statement: Not applicable

Support/Funding: None.

Conflicts Of Interest: The authors have no conflicts of interest to disclose.

Patient Protections: The authors declare that they have obtained written informed consent from the patient reported in this article for publication of the information about him that appears within this case report.

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