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Successful Treatment of a Case of Crescentic Glomerulonephritis in a patient with Primary Peritoneal Carcinoma

A case report

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Abstract

Crescentic glomerulonephritis (CGN) has been associated with several solid tumor malignancies. Only a few cases of nephropathy have been reported in association with tubo-ovarian/peritoneal malignancies. We describe a case of 55 years old female who developed combined immune complex-mediated glomerulonephritis and pauci-immune necrotizing crescentic vasculitis simultaneously with the diagnosis of tubo-ovarian/peritoneal cancer. The baseline estimated glomerular filtration rate (eGFR) was 13 ml/min. The patient received two doses of Rituximab and three doses of pulse corticosteroids, leading to significant improvement in renal function and the disappearance of her proteinuria. The eGFR improved to >60ml/min, and her proteinuria gradually resolved after 10 weeks of treatment. She was in a position to be given a combination chemotherapy treatment for tubo-ovarian/peritoneal cancer because of normalization of her CA-125 after three months of therapy.

Keywords: tubo-ovarian/peritoneal cancer, Glomerulonephritis, Vasculitis, Chemotherapy.

Introduction

Glomerulopathy in the field of cancer was first described in 1922.[1] Glomerulonephritis has been reported in patients with solid tumors, and only a few cases have been reported in patients with tubo-ovarian/peritoneal cancer.2 The most common form of secondary glomerulonephritis is membranous nephropathy (MN), which is most commonly presented as nephrotic syndrome. The prevalence of malignancy with MN ranges from 1% to 22%.3 The glomerular lesions are considered paraneoplastic; however, the exact pathogenesis remains unclear in most cases. Renal impairment is a limiting factor in the prescription of chemotherapy, especially nephrotoxic agents, and thus can compromise the survival of patients. Herein, we describe the case of a woman diagnosed with metastatic tubo-ovarian/peritoneal cancer and severe acute kidney injury due to crescentic glomerulonephritis.

Case report

A 55-year-old woman was hospitalised for epigastric pain, weight loss, abdominal distension and poor oral intake. She had a past medical history of hypertension (treated with amlodipine) and hypothyroidism (treated with levothyroxine replacement). Ten years prior to the current presentation, the patient complained of abdominal pain and distention with abdominal mass in the imaging; she had undergone a total abdominal hysterectomy with bilateral salpingo-oophorectomy surgery. The postoperative histopathology report was consistent with serous cystadenoma with borderline malignancy. The postoperative CA-125 was carefully followed up for one year after the surgery, but the patient stopped her follow-up. During the current presentation, PETCT was done, and the patient was found to have supraclavicular, mediastinal, paraaortic, iliac and inguinal lymph nodes with moderate pleural effusion and ascites. She underwent a cervical lymph node biopsy which was consistent with a new diagnosis of metastatic high-grade serous tubo-ovarian/peritoneal carcinoma: CK7: Positive (strong & diffuse), CA-125: Positive (strong and diffuse), WT1: Positive, P16: Positive (Strong and diffuse.) ER: Positive (Strong and diffuse) PR: Negative. Her CA-125 was 1056 KIU/L (normal 0-35 KIU/L). During her hospitalization, she was found to have acute kidney injury (AKI), as she was found to have a serum creatinine of 217 umol/L (normal 45-84 umol/L) on presentation, and the serum urea was 10.9 mmol/L (normal 2.8-8.1 mmol/L). Her electrolytes were normal. The urine dipstick showed blood 3+, protein 1+, and positive leucocytes. Urine microscopy showed no casts or crystals. The urine culture showed significant growth of

extended-spectrum beta-lactamase-producing Escherichia Coli with (>100.000 CFU). She was commenced on intravenous Piperacillin/Tazobactam antibiotic. However, she did not complete the course of antibiotics as she only had mild symptoms, her inflammatory markers were not raised, and the urine sample was taken. In contrast, the patient had a urinary catheter, but the renal functions declined slowly. She also was found to have nephrotic range proteinuria with a urine protein to creatinine ratio (UPCR) of 436 mg/mmol (normal less 15 mg/mmol) and urine albumin to creatinine ratio (UACR) of 312 mg/mmol (normal 0-3.5 mg/mmol). Serum creatinine increased to 257 umol/L despite hydration and appropriate urinary tract infection treatment. In light of her metastatic disease, AKI, and heavy proteinuria, a thorough workup was performed to seek possible additional causes of the AKI. She had normal complements, negative hepatitis B and C serology, and negative HIV serology. The serum protein electrophoresis and urine protein electrophoresis showed no abnormal serum protein bands or free light chains in the urine, respectively. The ANA was positive (titer 1:320) but negative anti-dsDNA antibody. All extractable nuclear antigens profile was negative. She had positive IgG antibodies for Cytomegalovirus and Epstein-Barr virus but negative IgM for both viruses. The CMV, adenovirus, and EBV tested negative on a polymerase chain reaction. Regarding her anti-neutrophil cytoplasmic antibodies (ANCA), the cytoplasmic and perinuclear forms were both positive, the anti-proteinase 3 (PR3) was expected, but MPO was borderline positive (titer was 24 U/ml, normal from 0.00 – 20.00 U/ml). A clinical diagnosis of rapidly progressive glomerulonephritis was made, and a kidney biopsy was performed. The light microscopy report was consistent with crescentic glomerulonephritis (GN) with positive staining for IgG, IgA, C3, and C1q. Later, further histopathologic examination of the kidney tissue by electron microscopy revealed features consistent with immune complex-related GN with mesangial and subendothelial deposits electron microscope (EM) with extensive effacement of podocyte foot processes. The patient received a diagnosis of AKI secondary to crescentic GN, likely due to pauci-immune GN with concomitant immune complex-mediated GN. She received pulse intravenous (IV) methylprednisolone 500mg daily for three days with appropriate calcium and vitamin D supplementations, then started on oral prednisone 30mg daily with a gradual taper over 8 weeks and was finally maintained on prednisone 5mg daily. Additionally, she received IV Rituximab 1gm once weekly for 2 weeks. Rituximab infusions were without any Anaphylaxis and infusion-related reactions. Two months later, the UPCR was 43 mg/mmol, and UACR was 27.6 mg/mmol. Serum creatinine decreased to 98 umol/L, and her

eGFR was 50ml/min. The remission of her proteinuria and significant improvement in her renal functions allowed for complete dose chemotherapy to be administered. She continued to show significant improvement in her renal functions (serum creatinine was 78 umol/L, eGFR: 66.5ml/min) and had a good response to chemotherapy (CA-125: 30.2 KIU/L). Verbal and written consent for publication purposes was taken from the patient.

Discussion

Historically, solid tumor malignancies, most commonly associated with nephropathy are pulmonary and gastric carcinomas.[3] Membranoproliferative (MPGN) injury pattern has been described in association with solid tumors of the lung, kidney and stomach. Melanoma, breast carcinoma, and thymoma have also been rarely reported in association with MPGN"3. Crescentic glomerulonephritis (CGN) has been associated with several solid tumor malignancies.3 Only a few cases of nephropathy have been reported in association with tubo-ovarian/peritoneal malignancies.3 Nephropathy seems to occur irrespective of the tubo-ovarian/peritoneal tumor diagnosis, either during a relapse, two years after the first diagnosis or simultaneously. The underlying glomerular lesions are reported to be membranous nephropathy, MPGN, AA amyloidosis, minimal change nephropathy, and mesangial-proliferative glomerulonephritis.4 In the case of nephropathy associated with tubo-ovarian/peritoneal tumors, the treatment includes the administration of corticosteroids, surgery and chemotherapy.5 Our patient was not fit for initial debulking surgery as the disease was metastatic. Corticosteroids and rituximab were prescribed, resulting in complete nephropathy remission. Chemotherapy paclitaxel and carboplatin could be prescribed one month after her cancer diagnosis. The pathogenesis of secondary nephropathy has not been clearly defined, but a cell-mediated immune response has been postulated; the secretion of a tumoral factor and/or the appropriate production of lymphokines by T-cells to suppress tumor growth could increase glomerular permeability.6 Clinically, it is difficult to differentiate primary MPGN from secondary MPGN associated with solid tumors. Lefaucheur et al. 7 reported two risk factors differentiating paraneoplastic MPGN from primary MPGN. These include an age of over 65 years and a history of smoking 20 pack-years. Our patient was a no-smoker.Beck et al. 8 identified circulating autoantibodies in most cases of adult primary MPGN. These autoantibodies were not found in cases of secondary MPGN.4 .7 Lefaucheur et al. reported an increased number of inflammatory cells (more than eight cells per glomeruli) on the kidney biopsy of patients with paraneoplastic MPGN as compared to patients with primary MPGN. In our case, biopsy showed

mixed inflammatory cell infiltrate consisting mainly of lymphocytes and a few neutrophils, which is consistent with the paraneoplastic origin of glomerulonephritis. Beck et al. 8 explain the possible mechanisms, whereby solid tumors may be associated with MPGN. These include: (a) in-situ immune-complex formation in which antibodies are formed against a tumor antigen that is localized in the subepithelial location or to podocyte antigen that is identical or similar to the tumor antigen, (b) tumor antigens may form circulating immune complexes that are subsequently trapped in glomerular capillaries, and (c) external factors such as infections with oncogenic viruses or altered immune function that can cause both the malignancy and MPGN.

The degree of proteinuria varies among patients with myeloperoxidase (MPO) vasculitis but is usually subnephrotic. 9. 10 Proteinuria of 1g per day or less in patients with ANCA-associated vasculitis (AAV) is most likely the consequence of fibrosed glomeruli or tubular fibrosis in an individual who may or may not be in remission. Higher amounts of proteinuria, including proteinuria of more than 3g/day, may be more common in patients who present later in the course of the disease and who have had previous necrotizing glomerulonephritis.11 In our patient, although the biopsy had a limited number of glomeruli, all glomeruli were intact and showed a mild increase in the mesangial matrix. All glomeruli showed cellular crescents with segmental fibrinoid necrosis in the tuft. There were no signs of endocapillary hypercellularity or thrombosis on light microscopy. Capillary walls showed normal thickness with no spikes or double contours. There was no tubular atrophy or interstitial fibrosis. Further examination by EM revealed numerous small subendothelial deposits in the basement membrane with extensive effacement of podocyte foot processes with mesangial expansion and mesangial deposits. In some patients with AAV with high amounts of proteinuria, there may be a second concurrent glomerular disease or an atypical histologic pattern like a glomerular immune-complex deposition.12.13 The nephrotic range proteinuria was most likely due to the extensive foot processes effacement found on histopathologic analysis of the renal biopsy.

Conclusion

We describe the case of a patient diagnosed with tubo-ovarian/peritoneal cancer and associated with glomerulonephritis and vasculitis. Clinical history, physical examination, laboratory data, and kidney biopsy revealed the correct diagnosis. Corticosteroids combined with Rituximab resulted

in an improvement in renal functions, and the patient was able to receive a combination of chemotherapy paclitaxel and carboplatin for tubo-ovarian/peritoneal cancer. The treatment of paraneoplastic glomerulonephritis requires a multidisciplinary approach to monitor both cancer and glomerular lesions.

Authors' Contribution

AZ, AN and IAB managed the case. MR provided the details of histopathology. AZ, AN and MR drafted the manuscript. IAB critically reviewed the manuscript. All authors approved the final version of the manuscript.

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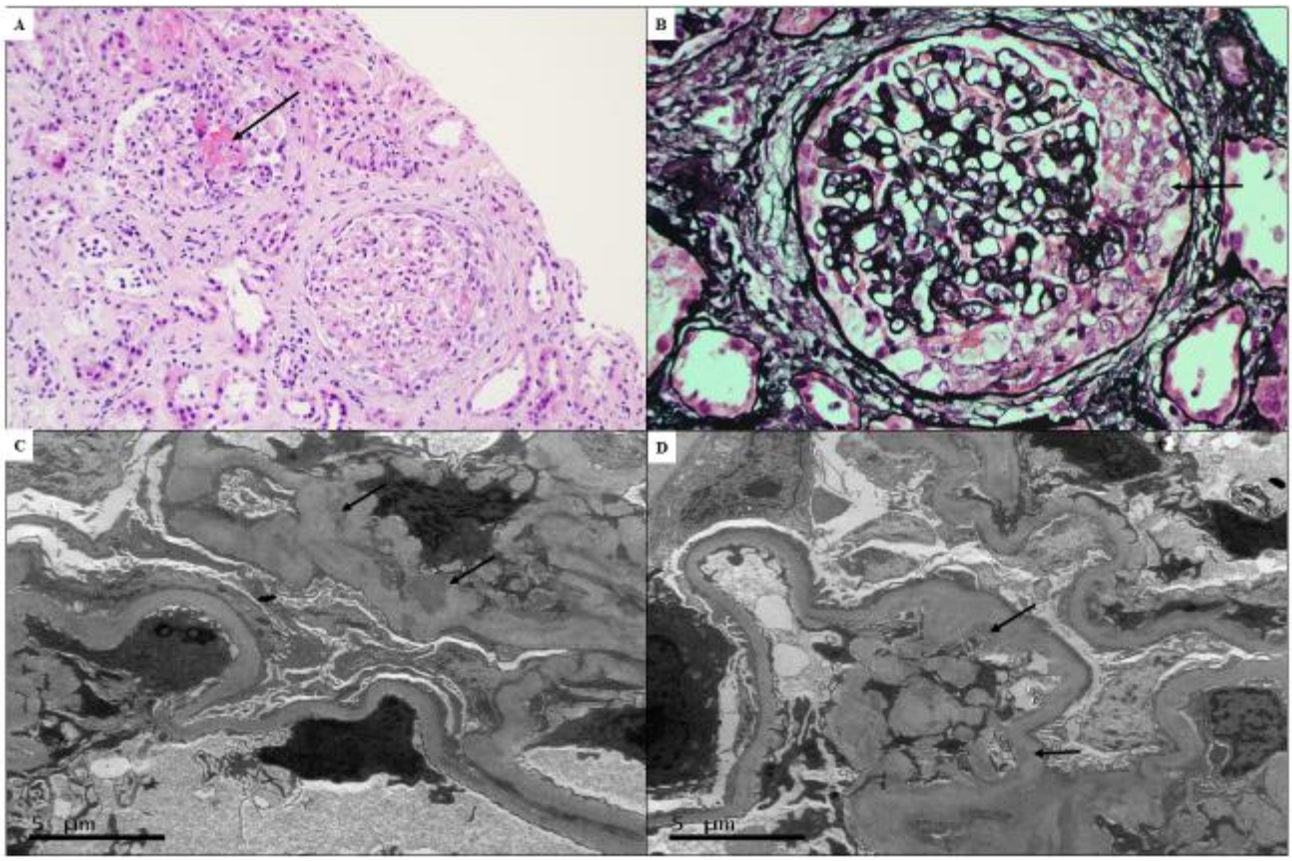

Figure1: A: shows two glomeruli, one with fibrinoid necrosis (arrow) and the other with a cellular crescent (H&E stain). **B:** higher magnification of a glomerulus with a cellular crescent (Jones stain). **C and D:** Electron micrograph highlighting mesangial and subendothelial deposits, respectively (arrows). There is also extensive foot process effacement of podocytes. Magnifications: Image A: 200X, Image B: 400X, Image C: 12,000X, Image D: 10,000X.