中文題目：人工血管感染之菌血症誘發 C3 腎絲球腎炎

英文題目：C3 Glomerulonephritis Associated with Ralstonia mannitolilytica bacteremia from Indolent Port-A Infection

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Introduction

C3 glomerulopathy (C3G), a concept introduced in 2010, is a rare emerging entity of kidney disease consequent to dysregulation of alternative complement cascade. The incidence rate was estimated to be one to three cases per million [1]. Aside from genetic variants in complement regulatory proteins, associations with infection and monoclonal gammopathy have also been reported in case series and cohort studies. The defining diagnostic criteria by pathology are presence of dominant C3 staining by more than 2 orders in magnitude in comparison to minimal to no staining of immunoglobulins on immunofluorescence microscope. Although patterns of C3G on light microscope vary, most of the injuries presents as membranoproliferative (MPGN) pattern. Based on the location of the deposits under electron microscopy, C3G may be further subclassified as dense deposit disease (DDD) or C3 glomerulonephritis (C3GN) [2]. Given the rarity of this disease, we think it is worthwhile to report this this case of C3 GN presenting manifesting as rapidly progressive glomerulonephritis superimposed on chronic kidney disease attributable to port-A infection and monoclonal gammopathy of unknown significance (MGUS) with cryoglobulinemia.

Case report

A 58-year-old female with a history of breast cancer status post left mastectomy with adjuvant chemotherapy, diabetes mellitus type 2, hypertension, chronic kidney disease and cryoglobulinemia with cutaneous vasculitis, peripheral neuropathy and polyarthritis, presented with acute kidney injury in conjunction with nephrotic-range proteinuria and full-blown nephritis in recent 3 months. Admission for comprehensive exams was arranged. During admission, other than low grade fever on occasions, vital signs were stable whereas physical examination was unremarkable except for purpura and pitting edema on bilateral legs. Significant findings from the hemograms were isolated C3 hypocomplementemia, monoclonal IgGκ gammopathy, cryoglobulinemia, hypercalcemia, hypoproliferative microcytic anemia with sufficient ferritin level, Ralstonia mannitolilytica bacteremia, dysmorphic urinary RBC, and

nephrotic-range proteinuria. Under the tentative diagnosis of multiple myeloma with cryoglobulinemic glomerulonephritis, we ordered bone marrow biopsy which reported decreased erythroid series without clonal plasmacytosis. Given inconclusive results from the prior exams, we proceeded to renal biopsy and discovered sampled glomeruli were in MPGN pattern with fibrocellular crescents, dominant C3 deposition in mesangium and capillary wall and dense deposits in subendothelial space, compatible with C3GN. Prompt plasmapheresis, pulse methylprednisolone, followed by maintenance prednisolone were initiated after preliminary renal pathology report has been obtained. Due to persistent Ralstonia mannitolilytica bacteremia on serial blood cultures, she also received antibiotics and port A removal. Albeit significant improvement of glomerular filtration rate under the above measures, her daily urinary protein loss was consistently in nephrotic range (Fig. 1). Hence oral cyclophosphamide was later added on. Unfortunately, she failed to comply to scheduled outpatient visits and was lost to follow-up in the end.

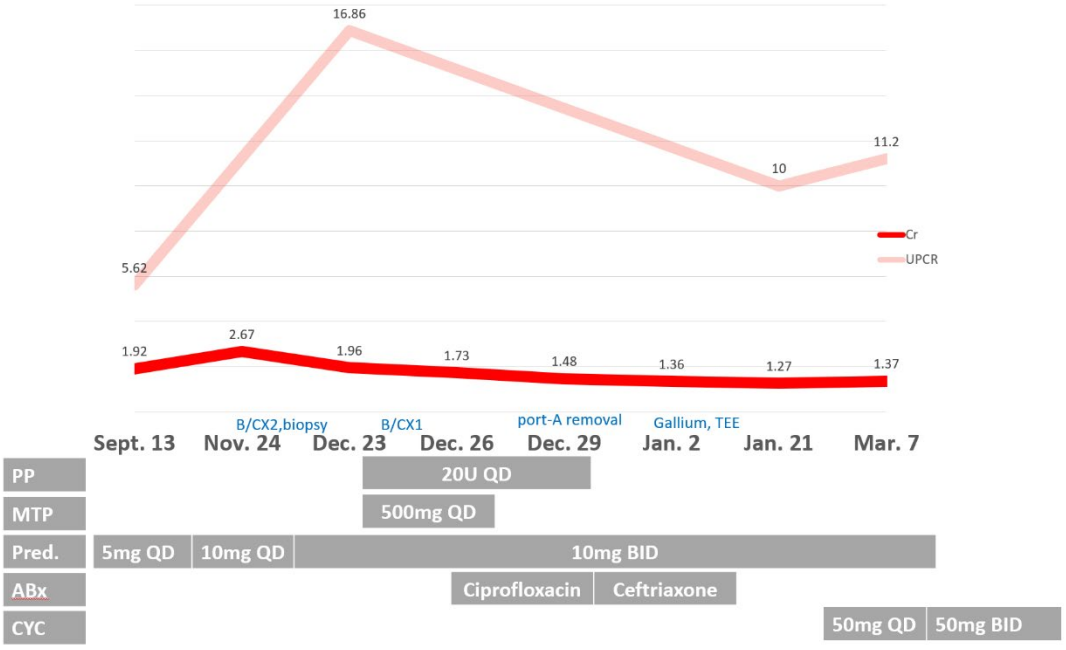

Fig. 1 Treatment regimen and renal outcome of the index patient

Discussion

Renal outcomes of C3G as reported from one review article was poor, as approximately 30-50% of patients slowly (in decades) progress to ESRD in published series [3]. A large US cohort with diagnosis of C3G showed the most common clinical

manifestation was proteinuria, hematuria but stable kidney function while one-quarter of them presented with chronic kidney disease upon diagnosis [4]. Nonetheless presentations with nephrotic syndrome or a rapidly progressive glomerulonephritis have also been described [5, 6]. Another cohort of C3G reported by Mayo Clinic had monoclonal immunoglobulin in serum or urine demonstrated in 37.9% of the patients and recent infection in 28.9% of the patients [7]. The hypothesis for association between C3G and dysparaproteinemia was postulated via persistent activation of the alternative complement pathway by monotypic immunoglobulin as inhibitors against complement regulator proteins indirectly [8]. Though more studies are needed to support this hypothesis. On the other hand, C3G occurring in the setting of infection may be caused by unmasking of a latent underlying complement abnormality by infections [7, 9]. In our patient, the unrevealed diagnosis of IgGκ monoclonal gammopathy may be attributable to cryoglobulinemia and C3GN in chronic kidney disease, which progressed to a full-blown nephritic and nephrotic syndrome aggravated by indolent port-A infection in Ralstonia mannitolilytica bacteremia.

Conclusion

In summary, C3G belongs to one of the complement-mediated glomerulonephritis which also encompasses C4 glomerulopathy and aHUS. This case reminds us that looking for the underlying diseases that causes and unmasks C3G is as important as treating the glomerulonephritis itself. On the other hand, benefits of genetic analysis for all cases of C3G are not proven yet but should be done in familial cases.

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