UNIVERSITI TEKNOLOGI MARA

ANTI-GBM GLOMERULONEPHRITIS

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Introduction:

Anti- GBM is a rare, life-threatening disease, which characterized by production of autoantibodies towards glomerular membrane. It is diagnosed by high presence of anti-GBM in blood and renal biopsy finding. It poses a diagnostic challenge and may delay treatment if the antibody was negative. In this report, we illustrate an unusual case with clinical and histological finding of anti-GBM disease without evidence of circulating anti-GBM antibody and suspicious of plasma cell dyscrasia from renal biopsy finding.

Case presentation:

65 years old lady with underlying Anaplastic lymphoma in complete remission since 2008, pulmonary fibrosis secondary to radiotherapy, Diabetes mellitus and hypertension was referred to our nephrology clinic with sudden worsening kidney function and normochromic normocytic anemia. She presented with lethargy and reduce oral intake for one-month duration. No angina symptoms. She denied bleeding tendencies. She had no history of reduce urine output. No history of taking traditional medication or Non-steroidal anti-inflammatory drugs (NSAIDs). No history of gastro-intestinal losses. Denied hematuria or frothy urine. No symptoms suggestive of renal stones. She has no family history of kidney disorder. She also denied lymph node swelling and B- symptoms.

On physical examination, she appears pale. Blood pressure was 152/62 mmHg, pulse rate of 86 beats per minute and 99 percent oxygen on room air. There was no lymph node palpable. No signs of uremia. Cardiovascular, respiratory and abdominal examination was unremarkable. There was no organomegaly. However, she has pitting edema up to mid shin.

Investigation showed normochromic normocytic anemia (Hb 73 g/dL), acute renal failure with increase of creatinine more than 50 percent within 5 months (from 45 to 450 ummol/L), hypoalbuminemia (30 g/L), and virology screening was negative for hepatitis B and C and human immunodeficiency virus (HIV). Urinalysis showed packed filled red blood cells and 24-hour urine protein of 1.2g/day. Kidney, ureter and bladder ultrasound showed normal size and echogenicity, no evidence of obstructive uropathy and normal Doppler. Percutaneous renal biopsy was then performed and showed crescentic glomerulonephritis with linear pattern on immunofluorescence staining. Histo-morphology and immunofluorescence are in keeping with anti- glomerular basement membrane (GBM) disease. There is marked interstitial nephritis with conspicuous population of plasma cells. Congo red stain was negative for amyloid.

She was then admitted for further investigation of glomerulonephritis and treatment. During admission, she complaint of fever and upper respiratory tract infection for 2 weeks. She was treated as community acquired pneumonia and was given intravenous Augmentin for 1 week. Other than that, she also appears overloaded as her urine output reduced but no uremic symptoms. She was treated as anti-GBM glomerulonephritis. Urgent hemodialysis was done and started on Intravenous Methylprednisolone 500mg daily for 5 days. Plasma exchange was started on day 2 of admission and continues for 5 cycles. Once completed methylprednisolone was change to oral prednisolone 60mg once daily. She was then discharged and seen as outpatient. Again, she had to be admitted due to worsening renal function and requires urgent hemodialysis. She had

regular hemodialysis while in the ward and second cycles of plasma exchange was done for another 5 days. She was also started on oral cyclophosphamide 25mg daily.
Other investigation includes peripheral blood film showed anemia of chronic disease and leukocytosis most likely due to steroid. Anti-nuclear antibody (ANA) and anti-double stranded antibody (dsDNA) was negative; anti neutrophilic cytoplasmic antibody (ANCA) and Anti glomerular basement membrane was also negative (2.8). Serum electrophoresis showed polyclonal increase in gamma globulin and no abnormal free light chain ratio (kappa free light chain: 123, lambda free light chain 286, kappa/lambda ratio 0.43). She also had a computed tomography of thorax, abdomen and pelvis to look for mass however no mass was found. At present, after 5 months of immunosuppression, there was no renal recovery. She was referred to renal nurse for long-term renal replacement therapy.

Discussion:

Anti-GBM disease is a rare autoimmune disease that is caused by autoantibodies directed against the alpha-3 chain of type IV collagen which is found in kidney, lung, (2). It is frequently seen in whites and incidence showed bimodal distribution, the first peak being 20 to 30 years of age with male predominance and second peak at age 50 to 70 years are females (8). Younger patients are more likely to present with pulmonary hemorrhage and crescentic glomerulonephritis and older patients tend to have isolated glomerulonephritis (6). Anti-GBM disease is by far the most severe form of crescentic glomerulonephritis both in terms of clinical presentation and extent of the glomerular involvement (7). Raised anti-GBM antibody level in the blood is pathognomonic in diagnosing anti-GBM disease. Histologically in active phase there will be cellular crescents seen in glomeruli and there will be linear deposition of Ig G along the basement membranes in the kidney. About one third of patients with anti-GBM will have ANCA positive and more likely P-ANCA pattern and higher specificity for MPO.

Our patient was treated as per anti-GBM disease in view of renal biopsy findings and rapid deterioration of kidney function while waiting for anti-GBM level, which came back negative. There are a few cases reported as atypical variant of anti-GBM nephritis in which the clinical presentation and renal biopsy finding are consistent with anti-GBM however there were no circulating anti-GBM antibodies in the blood. Nahr et al collected 20 patients with atypical variant of anti-GBM nephritis and the clinical characteristics are different from the classic anti-GBM nephritis, first, none had clinically evident of pulmonary involvement, second, most patient presented with hematuria, proteinuria and mild renal insufficiency as opposed to rapidly progressive glomerulonephritis in patients with classic glomerulonephritis and third, these patients have better renal survival rates (9). Seven out of 20 had complete remission with normalization of serum creatinine and disappearance of hematuria and proteinuria. Four out of 20 patients progressed to end stage renal disease. However, this finding is in contrast with our patient who came with rapid worsening renal function and RPGN on renal biopsy.

In this case, we also proceeded with plasma cell dyscrasia screening in view of presence of plasma cell in renal biopsy finding. Renal involvement in plasma cell dyscrasia is well-known and can manifest in wide range of renal lesions. However, rapidly progressive glomerulonephritis is not common renal presentation for plasma dyscrasia.

Furthermore, there was no paraproteinemia and M protein seen in the blood. Even though urine free light chain was high but the ratio was normal for renal patient.

Treatment of choice in anti GBM disease is intensive plasmapheresis combined with prednisolone and cyclophosphamide. Plasmapheresis will remove the circulating anti-GBM antibodies and other inflammatory mediators while immunosuppressive agents will help in minimizing new antibody formation. The optimal duration of therapy is unknown. Spontaneous cessation of autoantibody formation can take six to nine months or longer. 40-45 percent of patients will benefit by not progressing to end stage renal disease or death. Recovery more likely in patient who begin treatments before oliguria ensues and rare in patients who require dialysis or who have 100 percent crescent on biopsy.

Stolk et al reported a case of a 55-year-old male who was treated as Good Pasture's disease in the absence of anti-GBM antibody but positive ANCA and this patient responded well to high dose steroid and cyclophosphamide (1). Our case is similar to the patient but without pulmonary hemorrhage and negative ANCA however does not have similar response. This may be explained by creatinine level at presentation and negative ANCA as best predictor of outcome in anti-GBM (4). Bosch et al reported that ANCA positive in Anti-GBM disease has a good prognosis in term of renal recovery as opposed to pure anti-GBM disease (3). Another best predictor of outcome for anti-GBM disease is the severity of glomerular injury (4). One study showed that patient with atypical anti-GBM variant may not responded to conventional immunosuppressive study, four out of 6 patients who received steroid and cyclophosphamide died or progress to end stage renal disease and two patients who received plasmapheresis progressed to end stage renal disease (9). Relapses are uncommon but more relapse seen in patient who are also ANCA positive, it whom it may be due to the reactivation of vasculitis rather than autoantibody (10).

Conclusion:

In conclusion, kidney biopsy may be the best method of diagnosing anti-GBM disease in the appropriate clinical presentation. It is important for early detection and treatment as this may help in preserving patients renal survival. There are very limited data on atypical variant of anti-GBM nephritis and more studies and a larger cohort of patients is needed.

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