Reviewer’s report

Title: An unusual case of glomerulonephritis in a patient with Non-Hodgkin Mucosal Associated Lymphoid Tissue (MALT) B-cell lymphoma

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Reviewer: Joachim Velden

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Yeo et al. report a case of newly occurring diffuse endocapillary proliferative glomerulonephritis (GN) in a patient with recurrent B-NHL of MALT type. The GN is considered unusual due to a lupus-like full-house immunofluorescent phenotype. ANA and anti-dsDNA antibody titers were mildly elevated. There were no other clinical signs of systemic lupus erythematosus (SLE), no signs of complement consumption and no detectable cryoglobulinemia. Serum protein electrophoresis and immunofixation revealed a paraproteinemia with monoclonal IgG kappa. Clinical remission of the GN was achieved after 1 cycle of R-CHOP therapy for the B-NHL, after which also ANA and anti-dsDNA became undetectable.

Although this co-occurrence of a lupus-like GN with a recurring MALT lymphoma is interesting, the case study has major deficiencies, as detailed here below.

1) to 5) Major compulsory revisions:

Since the lupus-like phenotype of the GN is a principal point of this case report, the pathomorphological findings need more illustration, including the following points:

1) p.5: Figure 2 only shows the kappa light chain immunofluorescence. Please show the glomerular immunofluorescence findings for all other positive components (IgG, IgA, IgM, C3, C4, C1q and lambda light chains) in order to demonstrate the full-house pattern and the relationship between kappa and lambda light chain stainings.

2) p.5: Intraluminal deposits are reported in the text, but not recognizable in the electron microscopy images (Fig. 3 and Fig. 4). Please show an electron microscopic image in which the intraluminal deposits are present.

3) The scientific background is presented and discussed in an imprecise and incomplete fashion. The authors’ statement that kidney involvement in NHL is most commonly due to direct lymphoma infiltration of the renal parenchyma may hold true for autopsy series such as studied by Richmond et al. 1962, which is of great historical value, but this is a purely morphological observation, which may fall short of nowadays clinical reality in the era of live kidney biopsy diagnostics. Richmond et al. reported clinically relevant (measurable) kidney involvement in <1% of all patients with kidney lymphoma. Importantly, Richmond et al. made no
statement about glomerulonephritis in their study (the term glomerulonephritis is not at all used by them). In my experience as a renal pathologist, in kidney biopsies from NHL patients glomerulonephritis is generally more frequent than lymphomatous infiltration. Likewise, myeloma cast nephropathy, light chain amyloidosis (AL) and monoclonal immunoglobulin deposition disease (MIDD) are much more commonly found in kidney biopsies than intrarenal lymphoma. The latter manifestations of plasma cell myeloma/plasmocytoma and other B cell neoplasms are not discussed by Yeo et al. Monoclonal gammopathy is a common and potentially under-recognized cause of membranoproliferative glomerulonephritis (Sethi et al. 2010 CJASN 5:770-782).

4) On page 5, the electron microscopic findings are described: “Electron microscopy showed glomerular capillary lumina that were severely narrowed or occluded by marked infiltration by macrophages and neutrophils associated with subendothelial and intraluminal deposits that appeared moderately electron dense (Figure 3). Most of the deposits had a granular, amorphous texture with the exception of several that contained delicate randomly oriented thin fibrils (Figure 4). Several capillaries also displayed partial mesangial interposition and duplication of glomerular basement membrane enclosing the subendothelial and mesangial electron dense deposits.” This description fits a pattern of membranoproliferative GN (MPGN). However, on page 8 the authors state: “The absence of a MPGN pattern or an immunotactoid glomerulonephritis picture, which is often the histology compatible with cryoglobulinemic glomerulonephritis, also refutes such a diagnosis.” This is inconsistent, and moreover misleading since many cases of cryoglobulinemic GN do not show organized deposits by electron microscopy.

5) The Discussion part needs substantial improvement and reduction. This is to propose the authors to focus on a sound argumentation concerning the pros and cons of the differential diagnosis of lupus nephritis, which in the present manuscript is neither concise nor conclusive. The authors should concentrate on this as their major message. In contrast, the pathogenesis of lupus nephritis and HIV-associated immune complex GN with lupus-like features is beyond the scope of this case report.

6) to 11) Minor essential revisions:

6) Please indicate normal ranges and/or pathological cut-off values for ANA, anti-dsDNA, kappa/lambda ratio. It is redundant to indicate blood cell counts both in /uL and x10^9/L, use only one of them.

7) p.4: BLOOD leukocyte count.

8) p.4: Glomerular endothelial cell proliferation is not obvious from Fig.1. The terms endothelial damage and activation might be more appropriate.

9) p.6: “The absence of extraglomerular immune deposits involving tubular basement membranes and vessel walls would be unusual in severe lupus nephritis.“ This does not exclude lupus nephritis and is not a helpful differential
diagnostic criterion.

10) p.7: MPGN has been the most commonly reported histological TYPE OF GLOMERULONEPHRITIS, with the prevalence ... 

11) p.7: KOWALEWSKA et al showed ...

Discretionary Revisions:

12) p.5: It is stated that “a few of the glomeruli also had nodular mesangial expansion. This material stained eosinophilic, weakly PAS-positive, trichrome-orange and nonargyrophilic.” If these findings are relevant to the discussion and differential diagnosis, they should be imaged and shown in a figure.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.