Author’s response to reviews

Title: Case report: Scleroderma with crescentic glomerulonephritis

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Author’s response to reviews: see over
Reviewer's report

Title: Case report: Scleroderma with crescentic glomerulonephritis

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Reviewer: PETER HEWINS

I am familiar with the literature and believe that this case meets one of the 7 criteria for evaluation in the journal: An unexpected association between diseases or symptoms.

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: No

Does the case report have diagnostic value?: No

Will the case report make a difference to clinical practice?: Yes

Comments to authors:

General

The authors present an unusual case of crescentic glomerulonephritis complicating systemic sclerosis. This is an uncommon concurrence and the case demonstrates that presumptions about the cause of impaired kidney function can be misleading, even where there is ‘classical’ associated renal syndrome (scleroderma renal crisis in this instance). Consequently, adequate investigation is paramount in patients with renal failure, especially those with rapidly deteriorating kidney function. As such this report should be of interest to a general audience, particularly those involved in the care of patients with systemic sclerosis. ---------------------------------------------------------------

Revisions necessary for publication

I believe that at present, the explanatory and diagnostic value of this case report is limited and that the following deficiencies should be addressed by the authors to correct this:

1) It would be helpful to briefly outline and/or reference diagnostic criteria for scleroderma and systemic sclerosis. Given the presence Raynaud’s phenomenon, acroosteolysis and Scl 70 autoantibodies in this patient, limited
cutaneous systemic sclerosis may more accurately describe her condition. Diagnostic precision is especially relevant here since one might speculate that this patient has some form of overlap syndrome with features of systemic sclerosis and SLE. It would also be useful to mention or reference features of systemic sclerosis which are associated with scleroderma renal crisis (e.g. prednisolone usage). For example see Vonk MC et al Ann Rheum Dis 2007;66;1129-1131 and Penn H et al Q J Med 2007; 100:485-494.

Reply: Text of the article has been revised with inclusion of criteria for limited and diffuse form. This patient has got involvement of lungs and skin and with the occurrence of renal involvement in 1 year a diagnosis of diffuse scleroderma is more likely. Her ds DNA was was negative. So she is not likely to be a case of overlap syndrome. (The original case sheet was revised to arrive at these results.

2) Blood pressures (at initial presentation and 11 months later when presenting to the nephrologist) and the presence or absence of fundoscopic evidence of accelerated phase hypertension should be described.

Reply: Her initial BP was 140/90 and she was started on ACE inhibitors. In 2004 when she presented to the nephrologist her BP was 160/100 and fundus examination did not reveal evidence of accelerated hypertension.

3) It would be opportune to emphasize the utility of estimated GFR (eGFR) which is becoming widely reported alongside serum creatinine. Although the MDRD formula was not designed with reference to an Asian population, it is probably still useful: eGFR in this instance was 38 ml/min at presentation, demonstrating that in fact the patient already had significant kidney dysfunction at that time. Accordingly, it would worth pointing out that there were good grounds for performing a kidney biopsy at presentation (after controlling BP) and to have done so might well have altered the outcome. eGFR formulas are not intended for use in acute renal failure.

Reply: From the time of initial presentation in Aug 2003 to June 2004 she was under the care of Rheumatologist. In 2004 she was seen by the nephrologist and as she had severe renal impairment not responding to ACE inhibitors kidney biopsy was done.

4) I assume that further autoantibody tests were not performed, however, it would very helpful to briefly discuss additional tests that could have assisted diagnosis in this instance. Anti-dsDNA antibody testing would be particularly informative since these autoantibodies are closely associated with proliferative lupus nephritis and although the patient does not fulfil diagnostic criteria for SLE, it is clear that some patient’s present with lupus nephritis in the absence of other features. Again this raises the possibility of an overlap syndrome involving systemic sclerosis and SLE. Furthermore, anti-PR3 and anti-MPO antibody testing (by immunoassay) would have helped to clarify the inconclusive results of the ANCA immunofluorescence. I appreciate that these tests may have been unavailable in this instance but it appropriate to indicate that supplemental immunoassay testing is recommended for all patients with suspected small vessel vasculitis and in particular for all sera with an antinuclear antibody (ANA) that could mask an ANCA. (See “International consensus statement on testing and reporting of antineutrophil cytoplasmic antibodies (ANCA)” Savige J et al. Am J Clin Pathol 1999; 111:507-13 or Paspaliaris B et al J. Clin. Pathol.
Additionally, testing for circulating anti-glomerular basement membrane antibody is important in patients presenting with acute renal failure that may be due to glomerulonephritis. Further antibody testing has already been done by the rheumatologist. Anti RO, LA, Sm, RNP, anti ds-DNA antibodies were negative. In Brunei, C-ANCA and P-ANCA testing by immunofluorescence are not available.

5) Crescentic glomerulonephritis describes the pathological correlate of the clinical syndrome rapidly progressive glomerulonephritis but neither term defines the immunopathogenesis which it is essential in define in order to select appropriate therapy (Jennette JC Nephrol Dial Transplant 2001 16(suppl 6): 80-82 and Jennette JC Kidney International 2003 63: 1164-1177). Pathologically the lesion can be categorized as pauci-immune, immune complex mediated or anti-GBM (linear glomerular staining) mediated. I recommend that the authors
briefly describe or tabulate important causes of crescentic nephritis. In the
developed world, ANCA-associated vasculitis is the leading cause followed by
anti-GBM nephritis with other causes including lupus nephritis and crescentic
IgA nephritis (Henoch-Schoenlein purpura). It might be helpful for the authors to
indicate to what extent they believe this pattern is representative in their
country.
One anticipates that post infectious GN and MPGN/cryoglobulinaemic GN
associated with hepatitis C infection may be more prevalent in some regions.
Reply. A short note on classification and treatment of crescentic glomerulo
nephritis has been added. Brunei is a small country with a population of around 3,00,000.
we occasionally see crescentic glomerulonephritis the underlying etiology being
ANCA-associated vasculitis, Anti GBM disease and SLE.
6) Furthermore, the current histopathologic description is rather inadequate
making it difficult to determine the precise diagnosis. It is conventional (and
informative) to describe the % of glomeruli affected by crescents and it would
be particularly helpful to describe the presence or absence of glomerular
hypercellularity and its composition (mesangial proliferation is mentioned in the
legend), glomerular thrombosis or necrosis, subepithelial deposits (crescentic
variants of membranous nephropathy) and the pattern of immunostaining (e.g.
linear or granular). Are the glomerular lesions predominantly segmental or
global?
Reply. The histopathological specimen has been revised by our pathologist.
95 % of the glomeruli showed crescents and the lesions are global. The glomerular
hypertrophy was mainly mesangial with occasional polymorphs. No comment was made on
subepithelial deposits as electron microscopy was not available in our center. Immunoperoxide staining
was mainly granular.

7) There should be some additional short comment about the treatment of
crescentic nephritis. The isolated use of methylprednisolone is rarely
successful except possibly in post-infectious GN. For diseases such as ANCA-vasculitis,
anti-GBM disease and proliferative lupus nephritis, combination therapy with
corticosteroids and cyclophosphamide is typically required. Plasma exchange is
used as an adjuvant therapy in selected cases (anti-GBM disease and severe
ANCA-vasculitis) and newer alternatives including mycophenolate mofetil and
Rituximab (ANCA-vasculitis and lupus nephritis) are currently being assessed in
randomized trials.
Reply: Treatment of crescentic glomerulonephritis includes Methyl prednisolone,
cyclophosphamide and plasma pheresis. In the present case patient did not respond to
methylprednisolone and as the biopsy showed mainly fibrous crescents other
immunosuppressives were not tried.

8) Another important differential diagnosis to mention in this case is bilateral renal
artery stenosis (RAS) which should be considered in all patients presenting with
deteriorating kidney function after ACEI therapy. Indeed acute renal failure due to
RAS but mistaken for scleroderma renal crisis, has been described (Morris K et
Reply: In our patient doppler study of the renal arteries was not suggestive of
renal artery stenosis.
9) Finally, it would be appropriate to mention nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy) a recently described condition with features of systemic sclerosis that develops in patients with advanced kidney disease, apparently in association with gadolinium exposure. The risk appears to be greatest in individuals with a GFR <30 ml/min and restricted use of gadolinium enhanced MRI has been recommended. 

Reply Our patient has not undergone any MRI studies using gadolinium.


The current background could be revised and abbreviated to accommodate some of these points.

What next?: Revise and resubmit
Quality of written English: Acceptable