Response to Comment on; Newly Diagnosed Glomerulonephritis During COVID-19 Infection Undergoing Immunosuppression Therapy, a Case Report

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Dear Editor,

I have read the article entitled "Comment on; Newly Diagnosed Glomerulonephritis During COVID-19 Infection Undergoing Immunosuppression Therapy, a Case Report." By Mubarak *et al.*, I want to congratulate the authors for this successful editorial letter, and make some contributions.

In this comment Mubarak *et al.* have been noted some point that we clarify them in the following:

1- Mubarak *et al.* mentioned that our case did not have any respiratory symptoms related to glomerulonephritis (GN), but it is notable that our case had diffuse alveolar hemorrhage in his computed tomography report and it could related to systemic vasculitis.[1]

2- It is a reality that differentiation between these two entities (crescent & pseudocrescent) can be very hard and challenging, but not in our case which reveals clear crescentic features of gloms in figures.

The term crescent is used for a lesion consisting of extracapillary hypercellularity, composed of a variable mixture of cells. Fibrin and fibrous matrix may be present; 10% or more of the circumference of Bowman's capsule should be involved.[2] In our case parietal epithelial cells show proliferation and make cellular crescent, although in some glom's podocyte hyperplasia is seen also and it's not in conflict with the diagnosis of crescentic GN.

True crescents and pseudocrescents even may coexist in the same glomerulus.[3]

The presence of fibrinoid necrosis, karyorrhexis, glomerular basement membrane rupture and red blood cell casts to be helpful indicators of crescent formation while the absence of these findings with the presence of protein resorption droplets admixed with the hypertrophied and hyperplastic podocytes, significant tubular intracytoplasmic protein resorption drops, microcystic tubular dilatation, thyroid type tubular atrophy and a predominance of solidified or disappearing-type global glomerulosclerosis suggests collapsing glomerulopathy.[4]

In contrast with your comment, there were no protein resorption droplets in our pictures and also cellular vacuolation was not specific for pseudocrescent formation.

The glomeruli in the case also show capsular rapture (Figure 1A), fibrinoid necrosis (Figure 1B), and karyorrhexis (Figure 1C); which define the diagnosis of crescentic GN.

Collapsing lesions are more commonly global than segmental and are often accompanied by severe tubulointerstitial injury with microcysts and hypertrophic tubular epithelial cells swollen.[5]

Many various IHC markers like CD68, CK, Nestin, CD44, WT1, and ki67 can be helpful in challenging case for differentiation between crescent and pseudo crescent,[3,4,6] but in this case the diagnosis was clear by morphology and IHC study just achieved for responding your comment and as expected, confirmed our diagnosis.

In collapsing glomerulopathy, hyperplastic podocytes showed complete loss of normal podocyte phenotype utilizing known markers of podocytes (CALLA, GLEPP1, Podocalyxin, Synaptopodin, WT1, P27, and p57) were decreased while Cyclin D1, Cyclin E, Cyclin A, Ki-67, Desmin, Cytokeratin, and CD68 were increased.[4,7]

We use the markers of cytokeratin, CD68, and Ki67 (Figure 2) and no accentuated staining compatible for hyperplastic podocytes was seen. Usually in true crescents, no cell expresses cytokeratin and numerous CD68-positive hyperplastic dysregulated podocytes in a glomerulus showing a pattern of collapsing GN.[3]

It should be mentioned that contrary to previous reports, podocytes are indeed involved in human

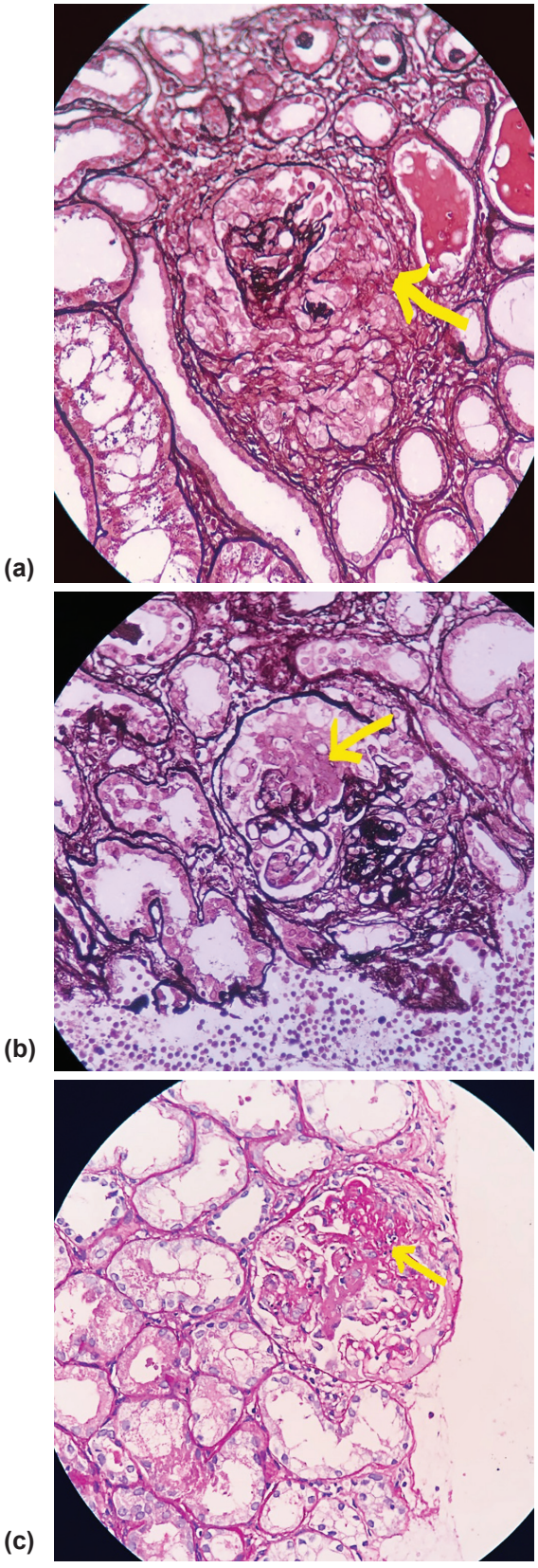

Figure 1. It shows true crescents with a) capsular rupture (Jones staining × 400); b) fibrinoid necrosis (Jones staining × 400); and c) karyorrhexis (PAS staining × 400).

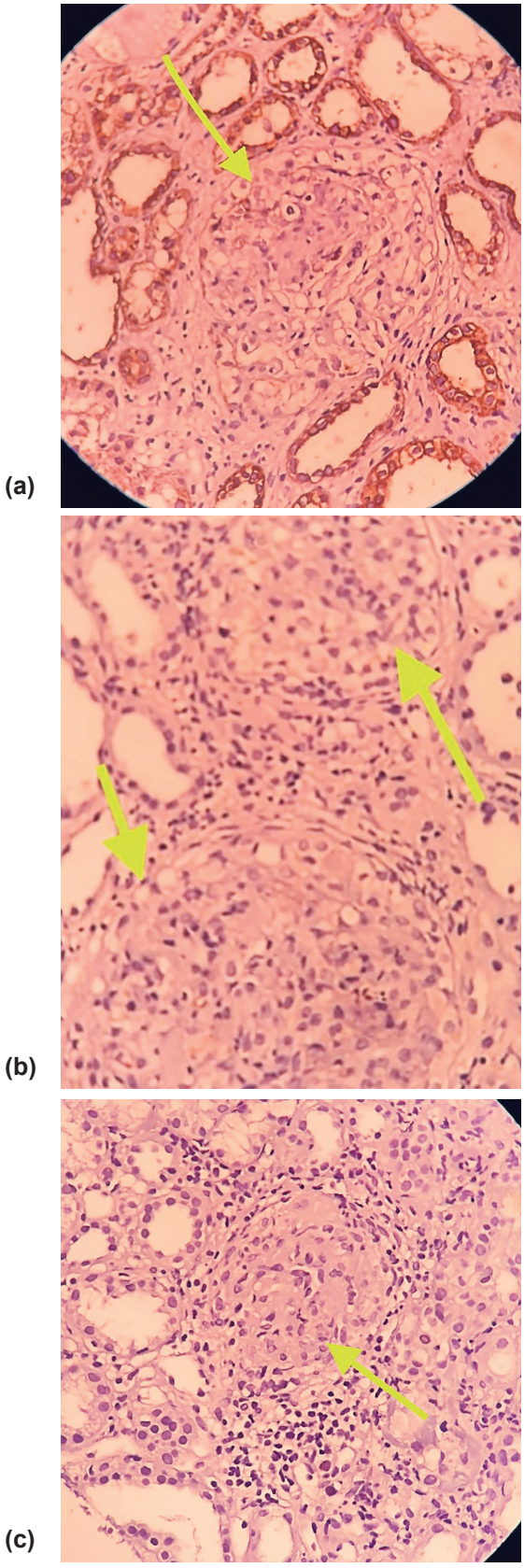

Figure 2. It demonstrates true crescents; IHC staining, a) Cytokeratin (× 400); b) CD68 (× 400); c) Ki67 (× 400).

crescentic GN too and therefore interpretation of IHC study for differentiating crescent from pseudocrescent should be done by cautious.[3] Unfortunately, we don't have access to electron microscopy at our center. Immunofluorescence study was negative in the case, but didn't prepare photos and as you know IF staining is not stable for long time and now, we can't send you the IF photos.

3- It was noted that renal biopsy was given on completion of induction treatment of rapidly progressive glomerulonephritis (RPGN), but in our case; renal biopsy was given before intravenous immunoglobulin or cyclophosphamide administration.

4- It was correctly mentioned that hemoglobin should have been reported in g/dL. It was a mistake. It also noted that C-reactive protein (CRP) is given in qualitative form, which is not a correct presentation of this result. We should mention that In this case CRP is reported as qualitative result in that situation.

5- We tested antineutrophil cytoplasmic antibodies (ANCA) with ELISA and the titration was 50.

6- It is notable that the creatinine level of our case was stable around 5.5 mg/dL during hospitalization. There was no significant change in creatinine to report in our article.

7- In this case, the importance of receiving a strong immunosuppressive drug despite COVID-19 was considered. Despite receiving immunosuppressive agents, the patient did not progress respiratory failure caused by COVID-19. Therefore, this condition considered as health during COVID-19 infection. His renal disease condition will be determined over time.

In the last several weeks, there have been numerous concerns not just from patients but also from other nephrologists on the most effective way to treat immunosuppression in today's environment. Will patients with GN could their doses of immunosuppression or avoid the treatment altogether?[8] When evaluating the effect of immunosuppression on COVID-19 outcomes, nephrologists must take into consideration the possible influence of avoiding immunosuppression on the kidney outcomes at the same time. It still recommended that patients who are at high risk of progression to kidney disease without prompt treatment, initiate regular immunosuppression regimens.[8,9] There is evidence that cyclophosphamide-based regimens is an important immunosuppressive drug for induction therapy in these patients.

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