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EDITORIAL ARTICLE

Are the renal ANCA-associated vasculitides histologic patterns changing after Covid pandemic?

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Background

Last year we published in Frontiers in Nephrology a retrospective study comparing incidence, severity and histology of 61 cases of ANCA-associated vasculitis (AAV), encompassing two well defined periods: from 2008 to 2019, prior to Covid pandemic (n= 37) and 2020 to 2022, during pandemic isolation (n= 24)[1].

During the first year of the pandemic and through the second, we not only noticed a higher incidence of renal vasculitis but also an increase in its severity in terms of declining renal function and patient's outcome, leading to the need for more renal replacement therapy and a noteworthy higher mortality index (figure 1).

YEAR	N
2008	2
2009	1
2010	2
2011	1
2012	5
2013	2
2014	2
2015	3
2016	5
2017	5
2018	4
2019	5
2020	5
2021	15
2022	4
2008-2022	61

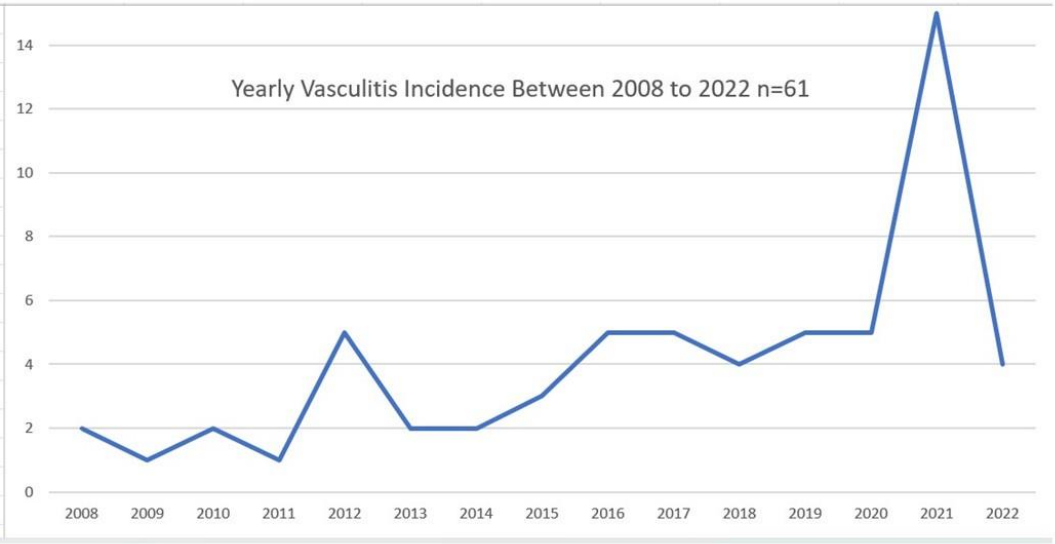

Figure 1: Renal Vasculitis Incidence Between 2008 to 2022 (n= 61)

Despite the particular interest of those findings, we noticed that the renal pathology findings of an important percentage of our pandemic AAV cases were different compared with the prior pandemic cases. There was a significant increase of small immunoglobulin G (IgG) and C3 deposits in mesangium by immunofluorescence and electron microscopy analysis[1], reaching more than 40% of our cases. On the other hand, in the twelve-year interval prior to pandemic, the pauci-immune pattern of immunofluorescence decreased from 81% in pre-pandemic cohort to 54% in the two year-period of pandemic[1].

Reports from other places

Our literature review from the pandemic period revealed that only a few authors found several autoimmune diseases associated to Covid vaccination, such as rheumatoid arthritis, ANCA-associated vasculitis, and lupus erythematous[2].

Meanwhile, several case reports of post-Covid AAV raised the question that they might be related to the viral infection[3-8], after vaccination[9-15], or in a more sophisticated theory, involving an infection-driven neutrophil-regulation during a long stress period[16-17].

Even though a report from Israel stated that they did not find any increment of vasculitis during pandemic[19], another retrospective trial from Spain has established an increase of anti-basement membrane antibodies glomerulonephritis (ABMG) since the pandemic, with almost 30% of those cases testing positive to ANCA serology[20], with a few isolated case-reports addressing the same findings[21]. In addition, anti-basement membrane cases were also described as isolated reports from different places, signaling that the pathogenic role of the virus and/or the vaccine could be possible[22-24].

Possible causes of AAV outbreak during pandemics

Furthermore, it seems to be a genetic predisposition for developing AAV secondary to Covid vaccination, as Loo and collaborators described recently[25], whereas Brilland et al. identified renal transcripts that may influence kidney function prognosis in AAV[26]. Further research may better establish the potential genetic susceptibility for developing AAV, helping to understand how the pathogenic process begins and the importance of epigenetics factors that could contribute to the mechanism of the disease. We believe that some of these factors may be preventable with correct health behavior, including lifestyle habits, avoiding environmental pollution and occupational hazards.

Delving deeper, the fact that there seems to be an association between ABMG and Covid AAV, allows us to propose an antibody mediated mechanism as the principal contributor of the rise of AAV incidence during pandemic. Despite most of our cases did not reveal intense glomerular deposits such as ABMG, the decrease of pauci immune histologic pattern observed during pandemic AAV may support similar pathogenic mechanisms with lower intensity of deposits.

Furthermore, regarding the pathological features described for the pre- and post-pandemic cases of AAV, it is very intriguing for us to see the noticeable increase of post-Covid cases showing non-IgA immune complex deposition (IgG with concurrent C3). "Pauci-immune" AAV can include up to 50% of very minimal-scattered glomerular deposits[27]. However, it was the finding of the four-time increase of immune-complex positive cases from our pre-to-post pandemic series that made an impact on our clinical and pathological impression of the disease. In addition, the role of immune complex deposition with secondary complement local activation in AAV is still unclear regarding its patho mechanism. It is usually explained as a "synergistic event with ANCA to produce more severe glomerulonephritis", since those patients show less platelet count, lower serum C3 and IgG levels, higher serum creatinine levels, and trending toward poorer kidney survival[28]. In a recent publication from Gietzen et al[29], it has been demonstrated through immunohistochemical staining that a significant proportion of cases of MPO-positive AAV with concurrent immuno-complex deposition (IgG) present a positive staining pattern for antibodies against ANCA antigens along the mesangial and some capillary loops deposits in a co-localized manner. Their findings raise the possibility of a pathogenic role of glomerular ANCA "deposits" as a special target for immunocomplex formation at the glomeruli, very likely representing a sub-group of AAV.

Pathogenic mechanisms proposed

From our perspective, we hypothesize that some basement membrane epitopes can be overexposed due to the lytic effect of the ANCA-mediated process over the glomerular tuft (including endothelial cells) and consequently acting as "new target antigens" that can trigger a second-hit event of antibody deposition with the consecutive immune complex formation that can be identified by immunofluorescence and/or electron microscopy. Their variable presence, frequently minimal and mainly absent, probably lays on the efficient labor of inflammatory cells that "clean" this early and very likely small immune-complexes. If we add the factor of Covid-infection, we truly believe that the intensity of this process is amplified in several patients, many of them with other baseline conditions that may contribute to the mechanism of glomerular and capillary wall injury (vascular diseases, diabetes, hypertension, procoagulant states, etc.).

As we previously referred, Covid-infection is the most likely factor that explains the increase of AAV, basically due to persistent systemic inflammation that may unmask severe autoimmunity with pathogenic mechanisms that include molecular mimicry, T-cell activation, neutrophil extracellular trap formation and finally, the release of ANCA antigens[30-31]. Therefore, in this exacerbated autoimmune environment, it is realistic to expect an increase in antibody production

added to this already amplified form of glomerular inflammatory and lytic injury.

Finally, we expect on our prospective follow-up, to define if this trend is permanent or if it returns to pre-pandemic level of epidemiologic characteristics. Our clinical team is already recording and targeting a publication in 2027 (five years after pandemic), to present the characteristics of all new incoming AAV cases to our Institution, and to draw more definitive conclusions based on the analysis of epidemiologic, clinical and histopathological data in longer follow-up.

Conclusion

We observed an important increase in AAV during pandemic time in our province, encompassing more severity of clinical pictures and a few changes in biopsy findings compared to pre-pandemic AAV. Despite the etio-pathogenic way is not clear, we think that viral exposure had a pivotal role in this outbreak, whereas further new cases follow-up will be needed to clarify whether this trend continues or it was just a pandemic direct effect.

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