Outcome of Therapies for Membranous Glomerulonephritis During Three Waves of COVID Pandemic

Abstract

There is lack of clarity on immunosuppressive therapy in glomerular diseases and concomitant corona-virus infection. We retrospectively evaluated 36 patients with primary membranous nephropathy from January 2020 to December 2021 who had received immunosuppression during this period. Diagnosis of COVID-19 was made based on self-reported history of being COVID positive. History of hospitalization and oxygen therapy was noted. Four patients developed COVID-19 in this cohort, and all were infected only once. Two patients had asymptomatic disease and two were hospitalized for severe COVID-19 and had complete recovery. In immunocompromised patients, there is a high risk of infection. This observational study is an attempt to bridge the gap that immunosuppression can precipitate COVID-19 infection.

Keywords: *Primary membranous nephropathy, Rituximab, Serum PLA2R*

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Introduction

Primary membranous nephropathy (PMN) is characterized by the deposition of circulating autoantibodies to the autoantigens in the basement membrane of the podocytes: the M-type phospholipase A2 receptor (PLA2R) and the thrombospondin type 1 domain-containing 7A (THSD7A).[1] PMN is characterized by an overall dysregulated immune phenotype and a decreased proportion of regulatory T cells in untreated patients.[2] B-cell dysfunction plays a role in the pathogenesis of PMN.[3] Initial therapy for PMN is supportive, with immunosuppressive therapy being recommended for persistent proteinuria.[4] Immunosuppressive therapy includes cyclic therapy (cyclical steroid/cyclophosphamide regimen) or selective B-cell-depleting agent like rituximab. Calcineurin inhibitors are also used for PMN.[5] Patients with glomerular disease who are treated with immunosuppressive therapies may be at a heightened risk of infections {Corona-virus disease-2019 (COVID-19) or other infections}.[6] The closest parallels exist with kidney transplantation and rheumatological diseases.[7] Some schools are of the opinion that the use of long-acting immunosuppressive agents should be avoided in patients with glomerular disease with a theoretical risk of severe COVID-19 in those on immunosuppression.[8] There is lack of clarity in pandemic-related modifications to the treatment of glomerular disease. Thus, we retrospectively evaluated the outcome of 36 PMN patients who were given immunosuppression during three COVID-19 waves.

Methods

This retrospective observational analysis was performed at a tertiary care hospital in North India. The study was approved by the ethics committee of the hospital. We identified all consecutive PMN (tissue or serum PLA2R positive) adult patients (aged 18 years and older) from January 2020 to December 2021. Patients who were negative for PLA2R were excluded. The date of the biopsy was considered as month 0 (date of diagnosis) and data was recorded thereafter at 3, 6 and 12 months. Serum creatinine, albumin, hemoglobin, 24hr urine protein, comorbidities, complications, and immunosuppression were recorded. Remission status was evaluated based on the "KDIGO 2021" clinical practice guidelines for the management of glomerular diseases for complete and partial remission.[9]

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Diagnosis of PMN made by renal biopsy showing subepithelial projections along the capillary walls on methenamine silver stain by light microscopy (LM), granular deposition of IgG and C3 along the capillary walls on immunofluorescence (IF) microscopy, and tissue PLA2R positivity or/and serum PLA2R positivity.

Quantitative serum anti-PLA2R antibody estimation was performed on the baseline sera by ELISA using a commercial kit according to the manufacturer's protocol. As per the institution's protocol, every patient underwent a rapid antigen/reverse transcriptase-polymerase chain reaction for COVID-19 before renal biopsy and treatment. The patients who were negative for COVID-19 and had a diagnosis of PMN were treated with injection rituximab (two doses of inj. rituximab at an interval of 15 days at a dose of 1 g) or cyclic therapy. All patients were asked about symptoms and subsequent positivity for COVID-19. Those having a history of COVID-19 illness were inquired about oxygen therapy, hospitalization, and outcome.

Definitions (KDIGO 2021)[9]

Complete remission: Reduction of proteinuria to <0.3 g/day or PCR <300 mg/g, stable serum creatinine and serum albumin >3.5 g/dL.

Partial remission: Reduction of proteinuria to 0.3–3.5 g/day or PCR 300–3500 mg/g, and a decrease of >50% from baseline.

Relapse: Proteinuria >3.5 g/day or PCR > 3500 mg/g after complete remission has been achieved.

Resistant MGN: Proteinuria >3.5 g/day or PCR >3500 mg/g or a decrease of <50% from baseline after the first line of immunosuppressive therapy of sufficient dose and duration.

Results

Baseline characteristics

There were 36 patients with PMN who received immunosuppression. The mean age was 49.3 ± 15.0 years, and 66.6% (24) were males. Thrombotic events were seen in three patients (two patients had acute pulmonary embolism, and one had deep vein thrombosis of the left lower limb). One young female had associated papilledema. The baseline characteristics of the study population are described in Table 1. Renal biopsy was done in 34/36 patients (two patients were on anticoagulation for venous thrombosis), and 33 were tissue PLA2R-positive and one was THSD7A-positive. Serum PLA2R was done in 20 patients and was positive in 12 patients (these 12 patients were both serum and tissue PLA2R-positive).

Table 1: Baseline characteristics of the study population

Variable		*n*=36
Age (yrs), Mean±SD		49.3±15.0
Males, N (%)		24 (66.6)
Hemoglobin (g/dL) Mean±SD		12.8±2.0
Serum albumin (g/dL) Mean±SD		2.1±0.6
Serum creatinine (mg/dL) Median (IQR)		0.8 (0.69-1.05)
eGFR (mL/min/1.73 m^2)# Median (IQR)		106 (88.5-115)
24-hr Urine protein (g/24 hr) Median (IQR)		5.4 (4.1-8.6)
Hypertension/Diabetes mellitus, N (%)		7 (19.3%)/3 (8.3%)
Thrombotic event*/Papilledema, N (%)		3 (8.3%)/1 (2.7%)
Tissue±serum PLA2R/THSD7A Positive, N		35/1
New Diagnosed Cases/Old Diagnosed Cases, N		33/3
Follow-up duration (months), Mean (Range)		13.3 (4-25)
Therapy Received, N (%)	Cyclic therapy♦	19 (52.7%)
	Inj. Rituximab	14 (38.3%)
	Partially Treated	3 (8.3%)
Response to therapy, N (%)	Full Remission	11 (30.5%)
	Partial Remission	16 (44.4%)
	Resistant MGN	6 (16.6%)
	Death	2 (5.5%)
	Progression to ESKD∼	1 (2.7%)

eGFR, Estimated glomerular filtration rate; PLA2R, Phospholipase A2 receptor; THSD7A, Thrombospondin type I domain-containing 7A; ∼ESKD: End-stage Kidney Disease; IQR, Interquartile range. * Thrombotic events include two cases of pulmonary embolism and one case of deep vein thrombosis in the left leg. # Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration equation: $eGFR=eGFR_{cr}=142\times\min(S_{cr}/\kappa, 1)^{\alpha}\times\max(S_{cr}/\kappa, 1)^{1.200}\times0.9938^{Age}\times1.012$ [if female]. Cyclic therapy♦ cyclical steroid/cyclophosphamide regimen

Treatment details

Thirty-three patients were newly diagnosed with PMN, whereas three patients had relapse of the previously treated PMN. Cyclic therapy and rituximab-based immunosuppression were used in 22 and 14 patients, respectively. Three patients of cyclic therapy were treated for 4 months. The average follow-up duration was 13.3 months. The response to treatment was seen in 75% of the patients (44.4% partial response and 30.5% full response). Lack of response was seen in three patients on cyclic therapy and three patients on rituximab and they received second-line immunosuppression.

COVID-19 and immunosuppression

Overall, seven patients among 36 had history of COVID-19 (three patients acquired COVID-19 prior to diagnosis of PMN and were excluded) [Table 2]. Among four patients who developed COVID-19, two of them had mild symptoms and developed the disease after the completion of treatment. They were treated with supportive treatment only, and no immunosuppression was given. Two patients had severe COVID-19, one patient

Table 2: Characteristics of patients who develop COVID-19 post immunosuppression

Patient	Age	Sex	Immunosuppression used	Days following immunosuppression for SARSCOV- 2 PCR positive	Co-morbidity	Symptoms Severity	Hospitalization	90 Day Outcome
1	50	F	Cyclic therapy♦	6 months after stopping immunosuppression	No	Mild	No	Alive
2	43	M	Rituximab	15 days after first dose of injection Rituximab	CLD CTP C	Severe	Yes	Expired
3	50	M	Cyclic therapy♦	3 months after stopping immunosuppression	No	Mild	No	Alive
4	58	F	Cyclic therapy♦	4 months on cyclical steroid/ cyclophosphamide regimen	No	Severe	Yes	Alive

COVID-19; Corona virus disease-2019, CLD CTP C: Chronic Liver Disease Child–Turcotte–Pugh class C. Cyclic therapy♦ cyclical steroid/ cyclophosphamide regimen

developed the disease while on therapy (four cycles) and she was started on steroids, and after recovery from COVID-19, she completed her cyclic therapy. The second patient was a diagnosed case of alcohol-related chronic liver disease (anti-HCV antibodies/HbsAg-negative) and PMN. He developed severe COVID-19 after 15 days of inj. rituximab. He was given only supportive care during the hospital stay and improved. He developed acute on chronic liver failure as a terminal event 8 days after discharge and was again admitted and expired. Overall, mortality was seen in two patients (another patient died at home).

Discussion

We evaluated the clinical profile and outcomes of 36 patients with PMN on immunosuppression during three COVID-19 waves in the last 2 years of the COVID-19 pandemic. Only four patients developed COVID-19 in this study, and two had severe disease requiring hospitalization, pointing towards the safety of immunosuppression in this group. We did not find any difference in mortality in the three waves, albeit the numbers were small. There is no study to date regarding immunosuppression and COVID-19 in PMN. According to recommendations from the Canadian Society of Nephrology COVID-19 rapid response team, treatment is provided according to current best practice guidelines in patients with acute glomerulonephritis.[10] The response to treatment was seen in 75% of the patients (44.4% full response and 30.5% partial response), which is comparable to the studies done in past regarding the treatment response in these patients.

This is the first study to look into the outcome of PMN during COVID-19 waves. This study included real-world data based on current practices of managing PMN at a tertiary center. The limitations of this study include its retrospective design, single-center data, and small sample size. The vaccination status of patients was also not available, which could very well be the reason for less COVID-19 in this cohort, In conclusion, this study was an attempt to bridge the gap that immunosuppression can precipitate COVID-19 infection. However, we need larger studies for the definite answer. As new strains are emerging regularly and COVID-19 will be there for times to come, we need disease-specific guidelines for their management.

Ethical approval

The research was approved by the ethics committee of the hospital, "ECR/533/INST/HP/2014/RR-17".

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Conflicts of interest

There are no conflicts of interest.

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