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Original Article

Coronavirus Disease 2019 Outcomes in Amyloid A Protein Amyloidosis Secondary to Rheumatic Conditions and Signs of Post- Coronavirus Disease 2019 Proteinuria Progression

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Abstract

Background: We aimed to investigate coronavirus diease 2019 (COVID-19) outcomes in patients with amyloid A protein (AA) amyloidosis secondary to rheumatic diseases and discuss factors associated with disease course.

Methods: A retrospective cohort was formed from adult patients with a diagnosis of AA amyloidosis. In patients with a positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction (PCR) test, rates of hospitalization, intensive care unit admission and mortality due to COVID-19 were collected from medical records. Data regarding to demographics, comorbidities, laboratory tests, medical treatments, adherence to previous treatments during COVID-19 and treatment administered for COVID-19 were collected from hospital databases and patient reviews.

Results: In 96 patients with AA amyloidosis, 16 had COVID-19 with a positive PCR. Ten (62.5%) patients were hospitalized, 2 (12.5%) were admitted to ICU, 1 (6.25%) was died. Hospitalized patients tended to be older. Comorbidities seemed to be more frequent in hospitalized patients. None of the patients had rapid progression to end-stage renal disease post-COVID-19. Seven patients had pre-COVID-19 and post-COVID-19 proteinuria levels. Three had notable increase in proteinuria after COVID-19 in 2 of which amyloidosis treatment was revised accordingly.

Conclusion: Despite high rates of hospitalization in AA amyloidosis patients, mortality was observed only in 1 patient. Progression of proteinuria requiring treatment adjustment may be an issue in these patients.

Keywords: COVID-19, amyloidosis, outcomes, rheumatic diseases, renal disease

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected millions globally since December 2019. Although in the majority of cases, the cases disease course is mild or asymptomatic, a considerable number of patients suffer from a severe disease with complications such as acute respiratory distress syndrome (ARDS), cytokine storm, and thrombosis leading to hospitalization and even death.[1,2] Male gender, older age, obesity, and chronic comorbid conditions like diabetes mellitus, chronic cardiac, respiratory, liver diseases, and reduced kidney functions have been reported as some of the factors associated with COVID-19-related death.[3] Similarly, in patients with chronic rheumatic conditions, those aforementioned general risk factors have also been related to a worse prognosis, alongside disease-specific factors such as disease activity and certain medications (particularly B cell-depleting agents and glucocorticoids with a dose over 10 mg/day prednisolone equivalent).[4,5]

Amyloid A protein (AA) amyloidosis is a devastating complication of chronic rheumatic conditions caused by long-term ongoing and/or recurring chronic inflammation leading to extracellular deposition of serum amyloid A, an acute phase reactant of the pentraxin family, fibrils in various organ systems.[6] Amyloid A protein amyloidosis develops in the course of rheumatic diseases most commonly in rheumatoid arthritis,

juvenile idiopathic arthritis, seronegative spondyloarthritis spectrum disorders, and periodic fever syndromes.[7,8] Major organ involvements comprise the kidneys, gastrointestinal system, and heart, resulting in morbidity and mortality due to chronic organ failure, even organ transplantation in some cases, with a significant deterioration in life expectancy.[7,9-11] Since concomitant chronic organ diseases are reported to be risk factors for poor COVID-19 outcomes in rheumatic patients, patients with AA amyloidosis may also be prone to a worse disease course.

Progression to end-stage renal disease (ESRD) in AA amyloidosis generally takes years; however, disease course may accelerate, ending in rapid progression to ESRD, a phenomenon recently defined as "amyloid storm", particularly after an infectious trigger.[12] The hyperinflammation caused by SARS-CoV-2 had already been considered to have the potential to provoke AA amyloidosis formation.[13,14] Currently, it is unknown whether COVID-19 initiates such an amyloid storm in patients who have AA amyloidosis in the first place.

Mainstay approach in the management of AA amyloidosis is to aggressively suppress chronic inflammation caused by the underlying rheumatic disease. Colchicine and anticytokine agents inhibiting interleukin (IL) 1, IL 6, and tumour necrosis factor alpha (TNFα) pathways are commonly preferred treatment agents. Among these, colchicine and IL 1, 6 inhibitors had been investigated and used in the management of COVID-19 during the pandemic, due to having the potential to control the cytokine storm induced by SARS-CoV 2, with controversial results in the literature.[15-23] As most of the AA amyloidosis patients would already be under treatment with these agents at the time of COVID-19 infection presumably, it is intriguing whether this would prevent the development of cytokine storm resulting in favorable outcomes.

Herein, we aimed to investigate COVID-19 outcomes in patients with AA amyloidosis secondary to rheumatic diseases and discuss possible factors to be associated with the disease course. To our best knowledge, this is the first study to evaluate COVID-19 course in AA amyloidosis patients.

Main Points

- Comorbidities are risk factors for poor coronavirus disease 2019 (COVID-19) outcomes in rheumatic diseases.
- Amyloid A protein (AA) amyloidosis is a major complication of rheumatic conditions and may increase the risk for poor COVID-19 outcome.
- Ten of the AA amyloidosis patients were hospitalized due to COVID-19.
- Mortality was observed in a single patient.
- Three patients had a notable increase in proteinuria requiring treatment adjustment.

Material and Methods

A 2-center retrospective cohort was formed from adult patients who had been followed with a diagnosis of biopsy-proven AA amyloidosis due to underlying chronic rheumatic diseases by authors. Between October 1st and 15th, 2021, patients of this cohort retrospectively investigated for a SARS-CoV 2 polymerase chain reaction (PCR) test result between March 11, 2020 and October 1, 2021 from the Public Health Management System (HSYS) to which all cases with a PCR test were registered during the pandemic in our country.

Data regarding demographics, comorbidities, laboratory tests, medical treatments, and biopsy results revealing AA amyloidosis were collected from hospital databases. In patients with a positive SARS-CoV-2 PCR test, rates of hospitalization, intensive care unit (ICU) admission, and mortality due to COVID-19 were collected from medical records and HSYS. Furthermore, PCR-positive patients were reached via telephone, and data regarding COVID-19 symptoms, adherence to previous

Table 1. Clinical characteristics of patients with amyloid A protein amyloidosis and coronavirus disease 2019

	N = 16
Age, years, median (minimum–maximum)	46.0 (33.0-87.0)
Gender, male, number (%)	11 (68.8)
Underlying rheumatic disease, number (%)	
FMF	10 (62.5)
FMF with spondyloarthritis	5 (31.2)
Chronic recurrent multifocal osteomyelitis	1 (6.3)
Patients with at least one comorbidity, number (%)	13 (81.3)
Comorbidities, number (%)	
Hypertension	12 (75.0)
Chronic renal disease	9 (56.3)
End-stage renal disease	7 (43.8)
Diabetes mellitus	2 (12.5)
Coronary artery disease	2 (12.5)
Gout	2 (12.5)
Nephrotic range proteinuria	14 (87.5)
Others	5 (31.3)
Tissue biopsy confirming AA amyloidosis, number (%)	
Kidney	10 (62.5)
Minor salivary gland	3 (18.8)
Gastrointestinal tract	2 (12.5)
Kidney and gastrointestinal tract	1 (6.3)
Immunosupressive and anticytokine treatments, number (%)	
Colchicine	15 (93.8)
IL 1 blockers	28 (75.7)
Anakinra	9 (56.3)
Canakinumab	6 (37.5)

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; COVID-19, coronavirus disease 2019; FMF, familial Mediterranean fever; IL, interleukin.

treatments during COVID-19 infection, and treatment administered for COVID-19 were collected upon verbal consent.

Approval from Ankara Bilkent City Hospital Ethics Committee prior to conduction was obtained (Approval Number: E2-21-775; Date: September 1, 2021). Informed consent was obtained from the patients who agreed to take part in the study. An official permission was also obtained from the Ministry of Health.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 22.0 software (IBM SPSS Corp.; Armonk, NY, USA). Normality of continuous variables was evaluated with Shapiro-Wilk test and with plots and histograms visually. Continuous variables were presented either with median (minimum-maximum or interquartile range [IQR]) or mean ± standard deviation, according to normality). Categorical variables are presented with numbers and percentages. The Mann–Whitney U-test or Student's *t*-test was used for comparison of continuous variables, according to normality of distribution. For the evaluation of categorical variables, the Pearson's Chi-Squared test was used. *P* values <.05 were considered statistically significant.

Results

Out of a total of 96 patients with biopsy-proven AA amyloidosis secondary to chronic rheumatic conditions, 16 identified to have COVID-19 with a positive PCR. The demographic and clinical characteristics of AA amyloidosis patients with COVID-19 were presented in Table 1. Median (min-max) age was 46.0 (33.0-87.0), and 68.8% of the patients were male. The underlying rheumatic disease was familial Mediterranean fever (FMF) in 15 cases, accompanied by spondyloarthritis in 5, and chronic recurrent multifocal osteomyelitis in 1. The most common comorbidity was hypertension (75.0%), followed by chronic renal disease (56.3%) and end-stage renal disease (ESRD) (43.8%). 87.5% of patients had nephrotic range proteinuria. None of the patients had chronic heart failure or a chronic respiratory condition. The most frequently preferred treatment agents were colchicine (93.8%), followed by IL-1 blockers (75.7%).

COVID-19 symptoms, outcomes, treatment agents, and adherence to amyloidosis treatment were given in Table 2. The most common COVID-19 symptoms were malaise (71.4%), fever (57.1%), and cough (57.1%), followed by arthralgia (42.9%), myalgia (42.9%), and dyspnea (42.9%). Ten (62.5%) patients were hospitalized, 2 (12.5%) were admitted to ICU, and 1 (6.25%) died. The lost patient was an 87-year-old male who had multiple comorbidities, including hypertension, coronary artery disease, chronic renal failure, and was under colchicine and anakinra treatment. All patients who were receiving IL-1 blockers continued their treatment during COVID-19 course, and only 2 (14.3%) patients discontinued colchicine treatment during the infection period.

Table 2. Symptoms, outcomes, and medical treatments in amyloid A protein amyloidosis patients with coronavirus disease 2019

	N = 16
COVID-19 symptoms on admission, number (%)*	
Fever	8 (57.1)
Malaise	10 (71.4)
Cough	8 (57.1)
Dyspnea	6 (42.9)
Hemoptysis	0 (0)
Myalgia	6 (42.9)
Arthralgia	6 (42.9)
Abdominal pain	1 (14.3)
Diarrhea	3 (21.4)
Headache	4 (28.6)
Anosmia	2 (14.3)
Ageusia	2 (14.3)
COVID-19 symptom duration, days, median (minimum–maximum)*	9.5 (5.0-15.0)
COVID-19 outcomes	
Hospitalization, number (%)	10 (62.5)
Length of hospital stay, days	9.5 (3.0-26.0)
Intensive care unit admission, number (%)	2 (12.5)
Mortality, number (%)	1 (6.3)
COVID-19 treatments, number (%)*	
Favipiravir	12 (85.7)
Hydroxychloroquine	1 (7.1)
Glucocorticoids	5 (35.7)
LMWH	2 (14.3)
Adherence to medical treatment for AA amyloidosis and underlying rheumatic disease during COVID-19, number (%)*	
Colchicine discontinuation	2 (14.3)
IL-1 blocker discontinuation**	0 (0)

*Out of 14 patients, 2 cannot be reached and interviewed. **Out of 12 IL-1 blocker users who can be reached and interviewed. COVID-19, coronavirus disease 2019; IL, interleukin; LMWH, low molecular weight heparin.

When demographics, clinical and treatment characteristics, and COVID-19 symptoms were compared between hospitalized and non-hospitalized patients (Table 3), hospitalized patients tended to be older (median (min-max), 36.5 (23.0-53.0) vs. 46.5 (33.0-87.0), *P* = .093). Furthermore, comorbidities seemed to be more frequent in hospitalized patients, particularly hypertension (50.0% vs. 90.0%, *P* = .074). Anosmia and ageusia were less frequent in hospitalized patients (*P* = .078 for each).

Eleven patients had 24 hour urine protein excretion measured within 6 months prior to COVID-19 infection with a median (IQR) excretion of 1200.0 (2038.0) mg. Among them, 7 also had 24 hour urine protein excretion measured after 3 months of recovery from COVID-19 with a median (IQR) value of 1547.0 (1381.0) mg/day. When pre-COVID-19 and post-COVID-19 proteinuria levels of these 7 patients were

Table 3. Comparison of demographics, clinical properties, coronavirus disease 2019 symptoms, and treatment agents between outpatients and hospitalized patients

	Non-hospitalized N = 6	Hospitalized N = 10	*P*
Age, years, median (minimum-maximum)	36.5 (23.0-53.0)	46.5 (33.0-87.0)	.093
Gender, male, number (%)	4 (66.7)	7 (70.0)	.889
Patients with at least one comorbidity, number (%)	4 (66.7)	9 (90.0)	.247
Comorbidities, number (%)			
Hypertension	3 (50.0)	9 (90.0)	.074
Chronic renal disease	2 (33.3)	7 (70.0)	.152
End-stage renal disease	2 (33.3)	5 (50.0)	.515
Diabetes mellitus	0 (0.0)	2 (20.0)	.242
Coronary artery disease	0 (0.0)	2 (20.0)	.242
Gout	1 (16.7)	1 (10.0)	.696
Nephrotic range proteinuria	5 (83.3)	9 (90.0)	.205
Others	2 (33.3)	3 (30.0)	.889
Immunosuppressive and anticytokine treatments, number (%)			
Colchicine	6 (100.0)	9 (90.0)	.424
IL 1 blockers	6 (100.0)	6 (60.0)	.869
Anakinra	3 (50.0)	3 (60.0)	.696
Canakinumab	3 (50.0)	3 (30.0)	.424
Adherence to medical treatment for AA amyloidosis and underlying rheumatic disease during COVID-19, number (%)*			
Colchicine discontinuation	0 (0.0)	2 (25.5)	.186
IL 1 blocker discontinuation**	0 (0.0)	0 (0.0)	
COVID-19 symptoms on admission, number (%)**			
Fever	3 (50.0)	5 (62.5)	.640
Malaise	5 (83.3)	5 (62.2)	.393
Cough	3 (50.0)	5 (62.5)	.640
Dyspnea	2 (33.3)	4 (50.0)	.533
Hemoptysis	0 (0.0)	0 (0.0)	
Myalgia	4 (66.7)	2 (25.0)	.119
Arthralgia	4 (66.7)	2 (25.0)	.119
Abdominal pain	1(16.7)	0 (0.0)	.231
Diarrhea	1 (16.7)	2 (25.0)	.707
Headache	2 (33.3)	2 (25.0)	.733
Anosmia	2 (33.3)	0 (0.0)	.078
Ageusia	2 (33.3)	0 (0.0)	.078

*Out of 12 IL-1 blocker users who can be reached and interviewed. **Out of 14 patients, 2 cannot be reached and interviewed. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; COVID-19, coronavirus disease 2019; FMF, familial Mediterranean fever; IL, interleukin.

compared, no significant difference was observed (median (IQR): 1200.0 (2038.0) vs. 1547.0 (1381.0), $P=1.0$). However, 3 patients had an increase in proteinuria levels of more than 500 mg after COVID-19 and persisted in 2 of them, for which amyloidosis treatment was tailored accordingly (switched from anakinra to canakinumab in 1, canakinumab interval reduced from once every 2 months to once a month in the other).

Discussion

In our study comprising AA amyloidosis patients with underlying rheumatic diseases, we identified 16 out of 96 patients who had COVID-19. About 62.5% of the patients were hospitalized due to COVID-19 and mortality was observed in a single patient who was an elder with multiple comorbidities. No significant risk factor was observed for hospitalization, yet older age and frequency of comorbidities, particularly hypertension, were more common in hospitalized patients. Unlike western literature, nearly all of our cases had FMF as the underlying cause as expected, since the country is endemic for periodic fever syndromes. The majority of the patients adhered to their background treatment during the infection. Three patients had a notable increase in proteinuria after COVID-19, in 2 of which amyloidosis treatment was revised accordingly.

Comorbid diseases have been reported as major factors associated with worse outcomes in COVID-19. Hypertension, chronic renal disease, nephrotic level proteinuria, and ESRD were among the most frequent comorbid conditions in our study group. Williamson et al. revealed that age, hypertension, and reduced kidney function are associated with COVID-19-related mortality in the general population.[3] Likewise, in patients with rheumatic diseases, age, hypertension, and chronic renal disease are associated with poor outcomes in COVID-19.[5,24,25] Particularly, age over 60 years has been revealed to be strongly associated with a worse prognosis both in the general population and in patients with rheumatic diseases.[3,5,24,25] In our patients with COVID-19, we observed a high rate of hospitalization (62.5%) and ICU admission (12.5%), which is coherent since AA amyloidosis patients generally have an increased disease burden with multiple comorbidities such as hypertension, chronic renal disease, and proteinuria in addition to the underlying rheumatic condition. When hospitalized and non-hospitalized patients were compared, the age was older and comorbidities were more frequent in hospitalized patients. In fact, the only patient who was lost due to COVID-19 was an elder with multiple comorbidities.

One of the well-known complications of COVID-19 is a hyperimmune response, so-called "cytokine storm", induced by SARS-CoV 2 leading to multiorgan failure and eventually to death in some cases. By binding to toll-like receptors, viral proteins induce inflammasome and caspase-1 activity. Caspase 1 cleaves inactive pro-IL-1β to active IL-1β, a potent mediator for lung inflammation and fibrosis in COVID-19.[26] Furthermore, IL-1β mediates IL-6 synthesis, a key proinflammatory cytokine in COVID-19 cytokine storm.[27]

Virus infected monocytes, macrophages and dendritic cells further induce expression of IL-6 and other proinflammatory cytokines. It had been reported that severe COVID-19 patients have higher plasma levels of cytokines such as IL-1β, IL-6, and IL-10 and different concentrations of the aforementioned may predict mild, moderate, and severe cases.[28,29] There is an association between cytokine storm and development of ARDS, disseminated intravascular coagulation and multiorgan failure.[30] Accordingly, anti-inflammatory agents like colchicine and even more potent anticytokine agents like anakinra and tocilizumab had been used during the pandemic. Since aggressive suppression of ongoing chronic inflammation is mandatory in management of AA amyloidosis, majority of our patients were already under colchicine and IL-1 blocker treatment when infected with SARS-CoV 2 and most of whom complied with their therapy during the infection. This may be related to the fact that despite a high rate of hospitalization, mortality was relatively low which was observed only in a single patient.

AA amyloidosis patients typically progress to ESRD in years with insufficient suppression of chronic inflammation. However, acceleration in clinical course can be observed in some cases, recently defined as "amyloid storm", which defines rapid progression to ESRD within weeks, and infections were reported to be the major culprits triggering this phenomenon.[12] Furthermore, it has been hypothesized that the cytokine storm induced by SARS-CoV-2 may provoke overproduction of serum amyloid A, which can potentially result in systemic AA amyloidosis.[14] *In vitro* research has supported this hypothesis and speculated that AA amyloidosis may be a long-term complication of COVID-19.[13] In our study, none of our surviving patients progressed to ESRD in such a short time and among our 7 AA amyloidosis patients in whom both pre-COVID and post-COVID 24 hour urine protein excretion levels were obtainable, we did not observe such acceleration. However, among these 7 patients, 3 of them had a marked increase in proteinuria (>500 mg in 24 hour sample) in 2 of them, treatment revision was required accordingly.

Cranial nerve involvement leading to ageusia and anosmia is an intriguing aspect of COVID-19 which generally indicate a favorable disease course.[31-34] The most common COVID-19 symptoms in our cohort were malaise, fever, cough, arthralgia, and myalgia. Two of our patients had anosmia and ageusia, and neither of them was hospitalized, nearly reaching statistical significance suggesting a favorable disease course in accordance with the current literature.

The very small sample size was the major limitation of our study, which detained us from reaching conclusive results rather than presumptions. Furthermore, the retrospective nature of the study and the fact that most of the data was obtained from medical records were also notable limitations. Finally, the vaccination status of the patients at the time of COVID-19 infection was not evaluated. Nevertheless, we believe our results are impactful since, to our best knowledge, this is the first study regarding COVID-19 outcomes in patients with AA amyloidosis secondary to rheumatic diseases.

All in all, despite the high rates of hospitalization observed in AA amyloidosis patients with COVID-19, mortality was observed in only in 1 patient. Being under Il-1 blockade at the time of infection may be related to favorable survival. The progression of proteinuria requiring treatment adjustment may be an issue in these patients. Further studies with a larger population are mandatory to elucidate the impact of COVID-19 on AA amyloidosis patients and to better demonstrate the role of associated factors.

Ethics Committee Approval: This study was approved by the Ethics Committee of Ankara Bilkent City Hospital (Approval Number: E2-21-775; Date: September 1, 2021).

Informed Consent: Informed consent was obtained from the patients who agreed to take part in the study.

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