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RESEARCH

Infections and causative microorganisms in patients with ANCA-associated vasculitis

ANCA ile ilişkili vasküliti olan hastalarda görülen enfeksiyonlar ve neden olan mikroorganizmalar

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Abstract

Purpose: The aim of this study was to detect infections requiring hospitalization in patients with ANCA-associated vasculitis (AAV).

Materials and Methods: This is a single-center, retrospective study conducted in Turkish patients with AAV. Infection episodes requiring hospitalization, reproducing pathogens, laboratory findings, immunosuppressive treatments given for the treatment of vasculitis, and the relationship with the infection were evaluated.

Results: Seventy-four patients diagnosed with AAV were included in the study. Hospitalization due to infection was observed in 36 of the patients. The coexistence of diabetes mellitus (DM) was found to be significantly higher in the infected patient group. Cyclophosphamide (CYC) treatment found to increase risk of infection. More than 80% of the infected patient group presented with renal involvement (80.6%). A total of 68 infectious episodes were seen in 36 patients. The most common involvement of infection was the respiratory tract with a rate of 70.6%. Gram-negative bacteria were the most common pathogen, especially *Pseudomonas aeruginosa*. With the effect of the pandemic, SARS-CoV-2 has come to the fore among viral infections. Aspergillosis was the most frequently detected among fungal infections. Besides, aspergillosis was the cause of 85.7% (6 episodes) of fungal infections. Lymphopenia was observed in 76.5% of the infection episodes. 57.4% of infections developed in the first year of the induction therapy. The most frequently used immunosuppressive therapy for the treatment of vasculitis in infectious episodes was CYC (41.2%).

Öz

Amaç: Bu çalışmada ANCA ilişkili vasküliti (AİV) olan hastalarda hastaneye yatış gerektiren enfeksiyonlarının saptanması amaçlanmıştır.

Gereç ve Yöntem: AİV'li Türk hastalarda yapılmış tek merkezli, retrospektif bir çalışmadır. Hastanede yatış gerektiren enfeksiyon atakları, üreyen patojenler, laboratuvar bulguları, vaskülit tedavisi için verilen immünsüpresif tedaviler ve enfeksiyon ile ilişkisi değerlendirildi.

Bulgular: AİV tanısı alan 74 hasta çalışmaya dahil edildi. Hastaların 36'sında enfeksiyon nedeniyle hastaneye yatış görüldü. Enfekte hasta grubunda diabetes mellitus (DM) birlikteliği anlamlı olarak yüksek bulundu. Siklofosfamid (SP) tedavisinin enfeksiyon riskini artırdığı bulundu. Enfekte hasta grubunun %80'den fazlası böbrek tutulumu ile başvurdu (%80,6). Otuz altı hastada toplam 68 enfeksiyon epizodu görüldü. En sık enfeksiyon tutulumu %70,6 ile solunum yolu idi. Gram-negatif bakteriler, özellikle *Pseudomonas aeruginosa* olmak üzere en yaygın patojendi. Pandeminin de etkisiyle viral enfeksiyonlar arasında SARS-CoV-2 ön plana çıktı. Aspergilloz, mantar enfeksiyonları arasında en sık saptanandı. Ayrıca aspergilloz, mantar enfeksiyonlarının %85,7'sinin (6 atak) nedeniydi. Enfeksiyon ataklarının %76,5'inde lenfopeni gözlendi. Enfeksiyonların %57,4'ü indüksiyon tedavisinin ilk yılında gelişmiştir. Enfeksiyöz ataklarda vaskülit tedavisinde en sık kullanılan immünsüpresif tedavi SP (%41,2) idi.

Sonuç Vaskülit tedavisi sırasında enfeksiyonları yönetmek çok önemlidir. Lenfopeni, böbrek tutulumu, DM ve immünsüpresif tedavi enfeksiyon riskini artıran

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Conclusion: Managing infections during the vasculitis treatment is crucially important. Lymphopenia, kidney involvement, DM and immunosuppressive therapy are factors that increase the risk of infection. Clinicians should take preventive measure especially for respiratory tract infections and gram-negative bacteria as pathogens.
Keywords: ANCA-associated vasculitis, infection, immunosuppression, lymphopenia

faktörlerdir. Klinisyenler patojen olarak özellikle solunum yolu enfeksiyonları ve gram negatif bakteriler için önleyici tedbirler almalıdır.

Anahtar kelimeler: ANCA ile ilişkili vaskülit, enfeksiyon, immünsüpresyon, lenfopeni

INTRODUCTION

ANCA-associated vasculitis (AAV) are systemic inflammatory diseases affecting significantly small blood vessels. The respiratory tract and the kidneys are the most common organs affected. Considering the clinicopathological features, AAV encompasses three disease phenotypes; granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA).[1]

With modern immunosuppressive treatments, survival of patients with AAV has increased significantly.[2] Nevertheless, infections in AAV patients are an important cause of morbidity and mortality, especially in the first year of the diagnosis.[3,4] Major treatment modalities like CYC or rituximab (RTX) combination with glucocorticoids create substantial immunosuppression. Glucocorticoid therapy is also among the immunosuppressive treatments that cause infection.[5] These remission induction therapies cause infection with increased immunosuppression. Treatment of active vasculitis may also delayed due to coexisting infection. This shows that the first year following the diagnosis is the most difficult period for the management of AAV. Severe infections are a common problem in AAV that would affect up to 40% of patients.[4]

The hypothesis of our study is that; are sociodemographic features, comorbidities, disease-related characteristics (duration of disease, treatments, types of involvement) associated with the presence of infection requiring hospitalization in AAV patients? In this retrospective study we aimed to investigate the infectious profile in patients with AAV. We analyzed the characteristics of the infection and the factors associated with the infection in patients with AAV.

MATERIALS AND METHODS

Study design

This single center retrospective study includes AAV patients followed between December 2015 and December 2021 at Cukurova University Faculty of Medicine, Rheumatology Division. The study protocol was approved by Cukurova University Faculty of Medicine Ethics Committee (Date: 3.12.2021, Reference number: 117/55). Patients diagnosed as AAV according to 2012 revised Chapel Hill consensus conference vasculitis classification criteria based on clinical, laboratory, pathological diagnosis were included in the study[6].

AAV was diagnosed according to the Chapel Hill classification criteria and disease phenotypes as GPA, EGPA, MPA. Of the 74 patients included in the study, 36 had infections requiring hospitalization. Patients requiring hospitalization were enrolled in the study. Hospitalization was applied to the patients those were resistant to oral antibiotic therapy, needed oxygen, or thought to have serious infections as a result of immunosuppressive therapy. Each hospitalization for infection was considered an episode. Data of microorganisms and infection markers reproduced in each episode were collected from the hospital database and the patients' files. Patients with hypotension, tachypnea or needing respiratory support were followed up in the intensive care unit.

Age, gender, disease duration, kidney involvement, comorbid diseases, immunosuppressive treatments taken during infection and treatments given for vasculitis until infection were recorded. Renal involvement was determined according to disease-related proteinuria, urine sediment, creatinine value or kidney biopsy results. We evaluated not only the presence of renal involvement during hospitalization, but also the presence of renal involvement from diagnosis to the period of study enrollment. In our study, the presence of DM, hypertension, coronary

artery disease and chronic obstructive pulmonary disease which are common in the community, were determined as comorbid diseases. All immunosuppressive treatments during the vasculitis treatment were recorded separately. In addition, the immunosuppressive treatment for vasculitis in each episode of hospitalized patients due to infection was recorded. CYC, RTX, mycophenolate mofetil (MMF), methotrexate (MTX), azathioprine and methylprednisolone are immunosuppressive drugs used in the treatment of vasculitis. CYC was administered with a dose of 500 mg/m^2/month 6-12 courses intravenously. None of the patients received oral CYC treatment. RTX 375mg/m^2/week was administered intravenously every 6 months for 4 weeks (1 cycle). MMF was given orally at a dose of 2-3 g/day, and azathioprine at a dose of 2 mg/kg/day. Patients on MTX therapy received the treatment at a dose of 10-25 mg/week.

Infections were categorized as bacterial, fungal, viral and mixed. The infection focus was classified as respiratory tract, urine, blood, skin, mix and the others. Cultures taken according to the focus of infection at each hospitalization and infection markers were examined. Blood culture, urine culture, sputum culture, broncholaveolar lavage, wound culture, galactomannan in serology, Cytomegalovirus polymerase chain reaction (CMV PCR), tuberculosis PCR, SARS-CoV-2 PCR results were evaluated. In addition, the presence of leukopenia and lymphopenia in the same period of patients with infection were recorded. Leukocyte values below 4000/mcL and 1000/mcL were evaluated as leukopenia and lymphopenia, respectively.

Statistical analysis

The variables were investigated using visual and analytical methods (i.e., Kolmogorov–Smirnov test, skewness, and kurtosis) to determine whether their distribution was normal. All parameters were presented as mean ± standard deviation (SD), median (25th-75th percentile) or percentage. The patients were divided into two groups: patients with infection and patients without infection. Continuous variables were analyzed using Student's T test or Mann-Whitney U test. We summarized the categorical variables as numbers and percentages and compared the groups using the Chi-square test or Fisher's exact test. Statistical significance was defined as $p < 0.05$. We performed a logistic regression model to show the relationship between infections and comorbidity, kidney involvement and treatment. Factors included in the multivariate regression model were selected for their clinical relevance among variables yielding p-values smaller than 0.25 in the univariate analyses. Multiple variable model was selected by a forward-looking stepwise procedure. All calculations were performed in the Statistical Package for the Social Sciences version 20. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

RESULTS

Seventy-four patients with AAV (52.7% female; mean age 52.14 ± 12.9 years) admitted between December 2015 and December 2021 were included in the study. Disease duration was 5.6 ± 4.3 years. Disease phenotype classification was 66 (89.2%) GPA, 5 (6.8%) EGPA, 3 (4.1%) MPA. The characteristics of the patients are shown in Table1.

Table 1. Patients' characteristics

AAV patients, *n*	74
Age (years) mean ± SD	52.14±12.9
Female, *n* (%)	39(52.7)
Types of AAV, *n*(%)	
GPA	66(89.2)
MPA	3(4.1)
EGPA	5(6.89)
Kidney involvement, *n*(%)	53(72.6)
Lung involvement, *n*(%)	74(100)
Comorbidities, *n*(%)	
Diabetes mellitus	18(24.3)
Hypertension	25(33.8)
Coronary artery disease	4(5.4)
Chronic obstructive pulmonary disease	4(5.4)

AAV: ANCA-associated vasculitis, GPA: Granulomatosis with polyangiitis , EGPA : Eosinophilic granulomatosis with polyangiitis , MPA: Microscopic polyangiitis

No correlation was found between the age, gender and hospitalization of the patients. There was no statistically significant association between hypertension, coronary artery disease, chronic obstructive pulmonary disease and hospitalization due to infection. A statistically significant correlation was found between presence of DM and hospitalization due to infection (p=0.021). There was no statistically significant relationship between kidney involvement and the presence of infection (p=0.097). However, the percentage of patients with renal involvement who had infection was higher than those who did not (80.6%-63.2%). Although all our

patients had pulmonary tomography findings such as ground glass, nodules or cavities, none of our patients had fibrosis. CYC therapy for AAV was found to be significant risk of hospitalization due to infection (p=0.001). The characteristics of patients with infection and those without are shown in Table 2. DM, renal involvement, use of CYC and MMF in the treatment were separately included in the logistic regression analysis. The presence of DM and the use of CYC in the treatment increased the risk of infection in a multiple variable model by stepwise method. In our study, the use of CYC increases the risk of infection [OR (odds ratio) = 6.028, %95CI (confidence interval) =2.026-17.933, p=0.001]. Additionally, presence of DM has been associated with an increased risk of infection (OR=4.471, %95 CI=1.232-16.229, p=0.023). Prednisolone use above 7.5 mg was observed in 60 of 68 episodes.

Table 2. Characteristics of patients with and without infection

Characteristics	Patients with infection (*n*=36)	Patients without infection (*n*=38)	P value
Age (years) mean ± SD	52.83±10.6	51.4±14.9	0.65
Female, *n*(%)	17(47.2)	22(57.9)	0.485
Disease types of AAV, *n*(%)			
GPA (%)	34(94.4)	32(84.2)	
EGPA (%)	1(2.8)	4 (10.5)	0.34
MPA (%)	1(2.8)	2 (5.3)	
Kidney involvement, *n*(%)	29**(80.6)**	24**(63.2)**	0.097
Comorbidities, *n*(%)			
Diabetes mellitus	13(36.1)	5(13.2)	**0.021**
Hypertension	13(36.1)	12(31.6)	0.68
CAD	3(8.3)	1(2.6)	0.27
Duration of disease median(25%-75%)	5(2.25-8.75)	5.5(2-7)	0.815
Agents used for AAV			
Cyclophosphamide	28(77.8)	15(39.5)	**0.001**
Rituximab	12(33.3)	13(34.4)	0.93
MMF	7(19.4)	4(10.5)	0.239
Azathiopirine	16(44.4)	20(52.6)	0.481
Methotrexate	8(22.2)	6(15.8)	0.480

AAV: ANCA-associated vasculitis , GPA: Granulomatosis with polyangiitis , EGPA: Eosinophilic granulomatosis with polyangiitis , MPA: microscopic polyangiitis , CAD: Coronary artery disease, MMF: Mycophenolate mofetil

Infection requiring hospitalization occurred in 36 (48.6%) patients. A total of 68 infectious episodes requiring hospitalization were identified in 36 patients. Twenty out of 36 were hospitalized with 1 episode of infection, 9 with 2 episodes, and 7 patients with multiple episodes of infection. Respiratory tract infection was the most common focus. The most common identified infections were bacterial, followed by viral and fungal infections. Gram-negative bacteria were the most commonly produced microorganisms. These bacteria were *Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumannii* in order of decreasing frequency. Among viral infections, SARS-CoV-2 was the most frequently observed type with 9 episodes. Fungal infections, especially Aspergillosis (in six episodes) were noted in seven of the episodes (10%). Abnormal findings such as halo sign, cavity and consolidation were observed in high resolution computer tomography of 6 cases. Although galactomannan positivity was observed in all of these cases, fungal hyphae were demonstrated by lung biopsy in 2 cases. Sputum culture was demonstrated in 1 case, and *Aspergillus spp.* was demonstrated by bronchoalveolar lavage in 3 cases. The causative microorganisms in infections requiring hospitalization are summarized in Table 3.

Twelve (33.3%) of 36 patients hospitalized due to infection were followed up in the intensive care unit with septic shock or respiratory support need. Eight (22.2%) of the patients who were hospitalized and treated with infection died due to respiratory failure or shock secondary to the infection. Lymphopenia was observed in 52 (76.5%) of 68 infection episodes. Thirty-nine (57.4%) of the infection episodes occurred in the first year of induction therapy. Hospitalized patients were receiving CYC in 28 and RTX in 18 infection episodes. The episodes are summarized in Table 4.

Table 3. Causative microorganisms in infections requiring hospitalization in AAV patients

Infections	Number of episodes (%)
Bacterial agent, n (%)	42(61.8)
Gram positive, n (%)	14(20.6)
Staphylococcus aureus	11
Streptococcus pneumoniae	3
Gram negative, n (%)	25(36.78)
Pseudomonas aeruginosa	10
Klebsiella pneumoniae	9
Acinetobacter baumannii	4
Other	2
Mycobacterium, n (%)	3(4.41)
Mycobacterium tuberculosis	2
Atypical mycobacteria	1
Viral agent, n (%)	14(20.6)
SARS-COV-2	9
Herpes	3
Other	2
Fungal agent, n (%)	7(10.3)
Aspergillus spp	6
Other	1
Mixed organisms, n (%)	5(7.4)

SARS-COV2: Severe acute respiratory syndrome coronavirus 2

Table 4. Evaluation of episodes

Variable	
Episodes of infections (*n*)	68
Bacterial infections (*n*)	42
Viral infections (*n*)	14
Fungal infections (*n*)	7
Mix infections (*n*)	5
Leukopenia, *n*(%)	12(17.6)
Lymphopenia, *n*(%)	52(76.5)
Focus of infection	
Respiratory, *n*(%)	48(70.6)
Urinary tract, *n*(%)	5(7.4)
Blood, *n*(%)	7(10.3)
Infection in the first year of illnes, *n*(%)	39(57.4)
Treatment for AAV during episode of infection, *n*(%)	
Cyclophosphamide	28(41.2)
Rituximab	18(26.5)
Mycophenolate mofetil	3(4.4)
Azathiopirine	9(13.2)
Azathiopirine+Methotrexate	6(8.8)
No treatment	3(4.4)
Prednisolone treatment for AAV during episode of infection, *n*(%)	
<7.5 mg	5(7.4)
7.5-30 mg	24(35.3)
30-100 mg	30(44.1)
>100mg	6(8.8)
No treatment	3(4.4)
Days of hospitalization (Mean±SD)	16.16±4.43

AAV: ANCA-associated vasculitis.

DISCUSSION

Infection is a common complication in patients with AAV. Studies have shown that infections are the main cause of mortality in AAV patients. Infection, rather than uncontrolled vasculitis, is the greatest cause of early mortality.[7,8] Older age and the presence of comorbidity have been shown as risk factors for infection.[9] In our study, no relationship was found between the age, gender and hospitalization. In the study of Ofer-Shiber et al., the presence of comorbidity at the time of diagnosis of AAV was associated with lower patient and kidney survival.[10] In the study of Sakari et al., DM and kidney disease were seen more frequent in patients with vasculitis with infection than in patients without infection.[11] In our study, the presence of coexistent DM seems to be one of the factors increasing the risk of infection.

Previous studies have shown that infections are more common in patients with renal dysfunction or vasculitis-related kidney involvement[12,13,14]. Although we could not reach a statistically significant result in our study, a higher percentage of kidney involvement was observed in the infected patient group compared to non-infected patients. Further studies with a larger patient groups may yield more meaningful results. Patients with renal involvement require more intensive immunosuppressive therapy to achieve remission compared to patients with limited disease. Kidney involvement is also an additional factor requiring immunosuppressives[15,16]. Considering all these, we can predict that kidney involvement may be a factor in the development of infection in patients with vasculitis.

The responsible pathogens causing the infection and the type of infection vary from society to society. Although there are differences between societies, the most common infection focus in most of the studies has been shown to be the respiratory tract.[14] Respiratory tract infection was the most common infection focus in a study including Chinese patients and the most common pathogens were gram-negative bacteria. Among gram-negative bacteria, *Pseudomonas aeruginosa* and *Acinetobacter baumanni* were found to be the most common.[17] In a study conducted on Swedish patients with AAV, the most common infection focus was reported to be the respiratory tract and the most common pathogen was found to be *Escherichia coli*.[4] In a Japanese study, fungal agents were the leading infection cause.[11] To the best of our knowledge, infection type and cause have not been investigated previously in Turkish patients with AAV. In our study, infection was caused by various pathogens, predominantly gram-negative infections. Similar to the study conducted in the Chinese population, the most common gram-negative bacterium in our study was *Pseudomonas aeruginosa*. With the effect of the COVID-19 pandemic, SARS-CoV-2 has drawn attention among the viral pathogens. In our study, Aspergillosis was the most common pathogen among fungal infections.

Infection has also been associated with use of CYC therapy at any stage of treatment. This relationship may be related to the hypogammaglobinemia and leukopenia, as side effects of CYC. High dose immunosuppression is preferred as induction therapy in patients with high disease activity. In our study, patients receiving CYC treatment were given high-dose treatment with the same treatment protocol. Therefore, the relationship between CYC dose and infection could not be evaluated. Indirectly, it has been shown that infections may develop more frequently in those whose disease progresses more aggressively. The relationship between immunosuppressive therapy and the development of infection complications is known. Studies have shown that infections develop more frequently in patients during periods of immunosuppressive therapy. In the study by Murosaki et al., it was shown that the most common cause of delay in induction therapy and failure to continue treatment was infections that developed during treatment.[18] Infections were reported to be more frequent, especially in the first months of induction therapy and infections were the most common cause of death during this period.[3,17,19,20] In our study, 57% of 68 infection episodes were seen in the first year, which supports previous studies. In a recent study of Xu et al., infections were shown to be the most important cause of mortality in AAV patients in the first year of diagnosis.[21] This showed us that we should be more careful in terms of infection, especially in the first year of induction therapy.

Previous studies as well as in our study lymphopenia were associated with infection.[17,22,23,24] In our study, lymphopenia was observed in 76.5% of infection related admissions. Presence of lymphopenia requires more attention in terms of infection. Although it could not be evaluated with the control group, most of the patients with infection were receiving immunosuppressive therapy. In our study, the most

common immunosuppressive therapy in these episodes was CYC. Since there were only 3 patients developed infection without immunosuppressive treatment, herein it is shown that immunosuppression is an undeniable risk factor for infection.

Pneumocystis carinii has been shown to be a common opportunistic pathogen in AAV patients receiving immunosuppressive therapy[25]. Therefore, trimethoprim-sulfomethoxazole was given prophylactically in all of our patients receiving immunosuppressive therapy, and Pneumocystis carinii pneumonia was not observed in any of our patients.

The strengths of our study are the pathogens that cause infection were examined in detail. There are few studies on this subject and to our knowledge, it is the first study conducted in Turkish population. The study has some limitations. Single-center, retrospective study and small sample size are limiting factors. But it is non-interventional and observational study. In addition, we could not obtain information about disease activity of patients such as the Birmingham vasculitis activity score, vasculitis damage index.

In conclusion, this study demonstrated the importance of safer immunosuppressive therapy and possible pathogens in this group of patients. In our study, the most common focus in infections requiring hospitalization was the respiratory system and the most identified pathogens were gram-negative bacteria. Therefore, these findings should be taken into consideration during antibiotic therapy of AAV patients. Additionally, the frequency of infection can be reduced with prophylactic antibiotic treatment appropriate for the pathogen.[23] Close clinical follow-up may increase treatment success especially in patients with lymphopenia in the first year after diagnosis those receiving CYC treatment. In addition, monitoring infection is important for the prognosis and management of the disease. Factors such as lymphopenia, comorbidity, first year of diagnosis, use of CYC treatment require more attention to the risk of infection. Although our study is instructive, further multicenter studies with larger patient groups required to verify our findings.

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