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Case Report

A Patient with Subacute Bacterial Endocarditis and Positive PR3-ANCA: A Case Report and Literature Review

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Abstract

Patients with subacute bacterial endocarditis (SBE) may present with multisystem disorders mimicking autoimmune diseases, such as an antineutrophil cytoplasmic antibody (ANCA) - associated vasculitis (AAV). In this report, we present a 72-year-old female patient with streptococcal SBE who developed multiple inflammatory abnormalities, including ANCA positivity, which was complicated by the occurrence of leukocytoclastic vasculitis, glomerulonephritis, acute myocardial infarction, heart failure, and subarachnoid haemorrhage. The patient had previously known mitral valve regurgitation. Repeated transthoracic echocardiography showed a floating lesion in the area of the mitral valve corresponding to chronic vegetation and confirmed the suspicion of SBE. Antibiotic treatment resulted in the decline of inflammatory parameters and complete recovery of renal function. Conservative treatment of acute myocardial infarction and neurorehabilitation were successful. Repeated ANCA tests were negative. Previously reported cases showed that ANCA-positive SBE could involve multiple organs. Distinguishing between AAV and SBE can sometimes be very difficult because of their clinical and serological similarities. Such a wide clinical presentation requires intensive monitoring of these patients. In conclusion, if systemic vasculitis is suspected, it is necessary to exclude diseases that mimic vasculitis, such as SBE.

Keywords: Antineutrophil Cytoplasmic Antibodies; Glomerulonephritis; Mitral Valve Regurgitation; Subacute Bacterial Endocarditis; Vasculitis

Introduction

Infective endocarditis is an inflammation of the endocardium that is caused by bacteria, viruses, or fungi and can present with various clinical manifestations. Patients with predisposing heart disease are the most commonly affected, especially those with abnormal heart valves. Subacute bacterial endocarditis (SBE) usually develops gradually, with a clinically variable course, and a wide range of manifestations including fever, constitutional symptoms, a newly developed heart murmur, anaemia, purpura, neurological disorders, heart failure, impaired cardiac conduction, and acute renal failure. Among the most common causes are the viridians streptococci. Since SBE has a large number of nonspecific symptoms, patients are often sent to various specialists to diagnostically exclude neurological, malignant or autoimmune diseases, such as vasculitis [1]. Anti-neutrophil cytoplasmic antibodies (ANCA) may be present in 24% to 33.3% of SBE [2,3]. These are circulating IgG antibodies that were first described, in 1982, in patients with segmental necrotizing glomerulonephritis [4]. They are directed against enzymes present in the azurophilic granules of neutrophils, such as serine proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA) [5]. Both antibodies are highly specific (87-91%) for ANCA-associated vasculitis (AAV) [6]. A basic feature of AAV is necrotizing vasculitis, with few or no immune deposits in the endothelium, which predominantly affects small blood vessels [5]. The aim of this study is to review a patient with SBE who presented with rare clinical manifestations mimicking AAV.

Case Report/Case Presentation

A 72-year-old female patient has been treated for arterial hypertension and hyperlipidaemia for a long time. She was treated with bisoprolol, perindopril, acetylsalicylic acid, and rosuvastatin. At the age of 51, she underwent a left thyroid lobectomy due to thyrotoxicosis. For years, she has been experiencing pain in her cervical and lumbar spine, as well as polyarthralgia. Multiple times, she underwent rheumatologically diagnostic tests, but not enough elements were found to support the existence of an inflammatory rheumatic disease. Since 2013, a holosystolic murmur was heard at the cardiac apex. In 2016, she was diagnosed with moderate mitral valve regurgitation and prolapse of a degenerative posterior leaflet. An elective coronarography showed no pathological changes in her epicardia blood vessels. Since November 2017, laboratory findings have shown that she has anaemia. At the beginning of January 2018, she was hospitalized in the Department of Physical Medicine and Rehabilitation, where she went to physical rehabilitation due to worsening polyarthralgia. During this period, she developed a fever, with symptoms of an acute upper respiratory tract infection for which she was symptomatically treated. Laboratory findings then indicated an increased erythrocyte sedimentation rate (ESR 45 mm/3.6ks), elevated C-reactive protein (CRP 42.9 mg/L), anaemia (Hb 113 g/L, ferritin 237 ng/ml), with normal creatinine and urea values. Urine sediment examination showed erythrocyturia (E 8). Clinical examination revealed cutaneous efflorescence on her extremities and she was suspected of having leukocytoclastic vasculitis. Rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, antinuclear antibodies (ANA), PR3-ANCA, MPO-ANCA, and anticardiolipin antibodies (ACA) were all normal. The value of complement C4 was reduced (0.090 g/L), while complement C3 was within reference values. Hypoalbuminemia (42.6 g/L) and hypergammaglobulinemia (gamma globulin 30.3 g/L) with increased immunoglobulin G (IgG 22.68 g/L) were seen on serum protein electrophoresis. A 24-hour urine analysis showed mild proteinuria (312 mg/dU), with reduced creatinine clearance values (45 ml/min). Pathohistological analysis of skin lesion biopsies confirmed hypersensitivity (leukocytoclastic) vasculitis. After completing physical rehabilitation, she was discharged for home treatment. Given her continued sub febricity lasting one month and her constitutional symptoms (malaise, arthralgia, weight loss), she was hospitalized, in February 2018, in the Department of Rheumatology and Clinical Immunology. At admission, she was sub-febrile (37.4°C) with a grade II/VI holosystolic murmur best heard over the cardiac apex. Purpuric lesions were present on the skin of her lower extremities. Laboratory analysis of the blood and urine showed microcytic anaemia (Hb 96 g/L, MCV 80.9 fL, Fe 6, ferritin 340 ng/ml) and elevated C-reactive protein (59.8 mg/L), with impaired renal function parameters (urea 9.1 mmol/L, creatinine 156 µmol/L) and pathological urine sediment (plenty of leukocytes, lots of erythrocytes, plenty of bacteria, negative for nitrates, 2 granulated cylinders, 1 finely granulated cylinder). A chest X-ray showed only an enlarged heart shadow. Immediately, on her first day of hospitalization, treatment was initiated with a combination of amoxicillin and clavulanic acid for a suspected urinary tract infection. Body temperature spikes up to 38°C were recorded daily at the beginning of hospitalization. The flu virus test was negative. A blood culture was done immediately upon admission and viridians group streptococci were isolated. The antibiogram revealed sensitivity to penicillin's, cephalosporins, vancomycin, teicoplanin, and clindamycin. Therefore, the initial treatment with amoxicillin and clavulanic acid was continued. The microbiological analysis of her pharyngeal swab was normal. Considering her continuing sub febricity, predisposing heart disease, meaning the changes on her mitral valve, as well as her positive blood culture, she was suspected of having SBE, which was not confirmed by transthoracic, or transesophageal echocardiogram. Repeated blood cultures on the third, fourth, fifth, sixth, and seventh day

from the start of antibiotic treatment, were sterile. New laboratory results showed hypocomplementemia (C3 0.76 g/L, C4 0.050 g/L) and an increase in proteinuria (1336 mg/dU), with a decrease in creatinine clearance (34 ml/min). Cytological analysis of urine sediment revealed plenty of erythrocytes, of which 30-40% were dysmorphic, and a urine culture of Mycobacterium tuberculosis acid-fast bacilli was negative. An abdominal ultrasound showed no abnormalities except for echogenic parenchyma of the right kidney. In the meantime, since a positive PR3-ANCA (108 AU/ml, positive finding > 25 AU/ml, tested by the MIA Luminex method) was confirmed, with dysmorphic erythrocytes present in the urine, AAV was suspected. However, she refused to have a kidney biopsy. Due to her persistent spikes in body temperature, in agreement with the infectologist and cardiologist, crystalline penicillin was added to her treatment plan. Not long after, her condition was complicated by the onset of chest pain, shortness of breath and an increase in cardio selective enzymes (hs-Troponin I 157741.1), so she was transferred to the Coronary Intensive Care Unit due to acute coronary syndrome and symptoms of heart failure that included dyspnoea, orthopnoea, and congested jugular veins. Since she continued to be febrile, in addition to the crystalline penicillin, gentamicin was added and she became afebrile. On the fourth day, after being transferred, neurological manifestations developed such as a headache and weakness in her right arm. A multiple-layer computed tomography (MSCT) of the brain showed a subarachnoid haemorrhage in the front parietal area on the left. A magnetic resonance angiography (MRA) of the brain blood vessels was normal. The urea and creatinine levels were increased (urea 13.6 mmol/L, creatinine 206 μmol/L). Two weeks after her first echocardiogram, a repeated transthoracic echocardiography showed a floating lesion in the area of the mitral valve corresponding to chronic vegetation and confirmed the suspicion of SBE. Repeated brain MSCT showed resorption of the previously presented subarachnoid haemorrhage. She was treated with crystalline penicillin for a total of six weeks, after which cardiac surgery was advised, but the patient refused cardiac surgical care. She underwent neurorehabilitation, with complete recovery of the neurological deficit. The patient became afebrile. Laboratory results showed a decline in inflammatory parameters (CRP 9.9 mg/L) and recovery of renal function, but anaemia of inflammation was still present (Hb 97 g/L). Repeated ANCA tests were negative.

Discussion/Conclusion

SBE and AAV may clinically manifest with the same symptoms, which include fever, constitutional symptoms, purpura, glomerulonephritis, and elevated levels of acute inflammatory reactants. Similar clinical manifestations most likely are due to the deposition of circulating immune complexes in the blood vessel endothelium and micro embolization [7]. Embolization is the probable cause of myocardial infarction in our patient. The exact connection between infection and the occurrence of ANCA is unknown. Persistent injury to blood vessels by bacterial antigens may activate endothelial cells and induce the expression of cytoplasmic proteins, resulting in the formation of autoantibodies [8]. In our patient, the presence of specific PR3-ANCA was seen, while microbiological analysis of a blood sample isolated Streptococcus viridians, one of the most common causes of infective bacterial endocarditis [1]. This case is similar to a study done by a Chinese group of authors that showed 39 patients with infective endocarditis, 13 of whom were ANCA positive. In all 13 patients, PR3-ANCA was present. The prevalence of microbial isolates from blood samples was significantly higher in patients with ANCA-positive infective endocarditis and in 90% of cases; the cause was streptococci [3]. Constitutional symptoms and elevated values of acute inflammatory reactants (CRP and ESR) have been reported in almost all patients with ANCA-positive infective endocarditis [2,3,9-11]. However, due to the constitutive symptoms and different clinical manifestations, in addition to infective endocarditis and vasculitis, it is also necessary to think about other connective tissue diseases and antiphospholipid syndrome. Namely, immunosuppressive therapy in infectious endocarditis would be devastating. On the other hand, delay in immunosuppressive therapy in vasculitis and other mentioned conditions could also have bad outcomes. In reviewing the literature, we found that most patients with ANCA-positive infective endocarditis have been found to have hypocomplementemia [12-15]. Our patient initially had low values of complement C4 and then of complement C3, which favours the activation of the classical complement pathway triggered by the production of autoantibodies. Leukocytoclastic vasculitis was determined by the presence of purpura on the lower extremities of our patient. In a study by Langlois et al., approximately 25% of patients with ANCA-positive infective endocarditis were found to have purpura on their limbs [2]. Our patient was diagnosed with mitral valve regurgitation, with prolapse of the posterior leaflet, which is a predisposing risk factor for infective bacterial endocarditis. A similar incidence can be seen in studies by Ying et al., as well as Chirinos et al., in which 40% and 37.5% of subjects with ANCA-positive infective endocarditis had mitral valve damage, respectively. Aortic valve involvement was present in 30% and 62.5% of patients, respectively, while both valves were affected in 30% and 12.5% of patients, respectively [3,7]. Distinguishing between AAV and SBE can sometimes be very difficult, since damage to the endocardium, as well as the appearance of discrete vegetation can also be part of the clinical spectrum of systemic vasculitis [7,16]. Heart failure has been reported in several patient cases [7,17,18]. According to a study by Mahr et al., approximately 50% of patients undergo cardiac surgery [9]. Increases in nitrogen compounds in the blood, haematuria, the presence of dysmorphic

erythrocytes in the urine and proteinuria have all suggested glomerular kidney disease in our patient. ANCA-positive infective endocarditis affects the kidneys in approximately 31% of patients, and they most commonly present with haematuria [3]. In such patients, histological analysis of biopsied renal tissue may vary from focal segmental glomerulonephritis, with or without fibrinoid necrosis, to diffuse proliferative glomerulonephritis, with extra capillary proliferation [8,12,19,20]. Most patients have immunoglobulin deposits and C3 complement present in their glomerular blood vessels during immunofluorescence staining, which can partially explain the hypocomplementemia in our patients [12,19]. However, in about 13% of patients, immune complex deposits are absent or rare, and histologic imaging is consistent with pauci-immune glomerulonephritis [20]. In such patients, the absence of immunoglobulin deposits could suggest a role for ANCA in the pathogenesis of glomerulonephritis. During hospital treatment, our patient developed a subarachnoid haemorrhage. In a study by Langlois et al., central nervous system involvement in patients with ANCA-positive infective endocarditis was present in about 37% of patients [2], in comparison to AAV, where these manifestations were present in about 10% of the patients [21]. In the same study, neurological lesions in the form of cerebrovascular haemorrhages were present in 4% of the patients. Other neurological manifestations included cerebrovascular ischemic changes, mycolic aneurysms, and amyloidosis-like antipathy [2]. Kishimoto et al. presented a patient with ANCA-positive infective endocarditis, with cerebrovascular haemorrhage and a fatal outcome after mitral valve replacement. Microbiological analysis of the blood culture isolated Streptococcus oralis [22]. Hirunagi et al., also presented a patient with cerebrovascular haemorrhage, in which Aggregatibacter segnis was the microbial pathogen that caused ANCA-positive infective endocarditis [23]. Our patient developed multiple clinical manifestations that otherwise occur in SBE with varying frequency. While searching the available literature, we did not find a presentation describing the simultaneous occurrence of leukocytoclastic vasculitis, glomerulonephritis, acute myocardial infarction, heart failure, and subarachnoid haemorrhage in patients with ANCA-positive SBE. Such a wide clinical presentation requires intensive monitoring of these patients. In conclusion, if systemic vasculitis is suspected, it is necessary to exclude diseases that can mimic vasculitis, such as infective endocarditis. Persistent fever peaks and a positive blood culture for viridians group streptococci were the main determinants that led to the search for infective bacterial endocarditis. Features that would support a diagnosis of infective bacterial endocarditis are a positive blood culture, hypocomplementemia, cardiac vegetation, neurological manifestations, and recovery after receiving antibiotic therapy. This patient was reviewed to remind us that other diseases can be manifested by a clinical picture of AAV, and that in this case, the use of immunosuppressive therapy could have been devastating.

Author Contributions: Dijana Perković developed the theory and was in charge of the overall direction and planning of the presented idea. Ana Vodanović, Ivana Vrandečić, and Jelena Pocedić wrote the manuscript with input and support from Dijana Perković, Antonela Karačić, and Dijana Borić Škaro. All authors helped shape the manuscript, contributed to the final version of the manuscript, and provided critical feedback.

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