Acute Renal Failure After Intravenous Use of Immunoglobulin to Treat Myocarditis

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The patient is a 60-year-old female with functional class III/IV (NYHA) heart failure of an immunomediated etiology (autoimmune myocarditis). After unsuccessful therapeutic attempts, intravenous immunoglobulin was used, leading to deterioration in renal function, a rare complication of that therapy. After hemodialysis, the patient's renal function was restored, and the chronic heart failure improved to functional class I.

Myocardites constitute a group of diseases characterized by immuno-inflammatory aggression against the myocardium. The anatomicopathological substrate of this aggression has been classically described as a cellular infiltration of lymphocytes, macrophages, and other leukocytes, with destruction of cardiomyocytes, myocarditis (Dallas criteria)¹. In past years, advances in understanding of the complex pathophysiology of the disease and low sensitivity of the histopathological criteria have forced us to widen the model of aggression to beyond the immune response of the classical cellular type (Th1). Currently, we believe that an immuno-mediated aggression against the myocardium occurs, even when the infiltration of immunologic cells is absent. The characterization of pathogenic autoantibodies specific for more than a dozen autoantigens has led us to a new model². The etiology of those diseases is still obscure. Activation of the immunologic system is known to occur, resulting in different forms of myocardial injury. The pathogenic stimuli that lead to the development of that cardiotoxic aggression are yet to be elucidated.

The current major hypothesis is based on the model of viral infection as the promoter of the immune reaction directed against the heart. Different types of viruses, such as coxsackievirus, parvovirus, adenovirus, cytomegalovirus, Epstein-Barr virus, and parvovirus B19, have often been implicated. However, most clinical studies have shown great variability and low positivity in evidencing the viruses ¹. Other clinical phenomena, such as skin diseases (eg, psoriasis and vitiligo), systemic autoimmune diseases, and even intestinal diseases, such as celiac disease, have been significantly associated with myocardites, suggesting, therefore, a wide and complex pathophysiological model².

The clinical findings of myocardites are highly varied. Their symptoms may range from fever and malaise to cardiac symptoms, such as palpitation, dyspnea, and chest pain. The physical examination, and laboratory and radiological findings are not specific, making the diagnosis difficult, which requires an elevated clinical suspicion.

The most accurate noninvasive diagnostic method is indium-111 antimiysin myocardial scintigraphy⁴. This technique is not available in our country. However, another technique of nuclear medicine that uses gallium 67, a marker of inflammation, has been used despite its lower sensitivity and specificity.

The endomyocardial biopsy, using Dallas histopathologic criteria, has been the standard diagnostic method, despite its low sensitivity. That technique has been boosted by the use of new in situ markers of immune activation, such as MHC class II (HLA-DR) and markers of lymphocytic populations, which increase the accuracy of that invasive diagnostic strategy.

Different groups have characterized pathogenic autoantibodies in that disease. Dozens of autoantigens have been implicated in myocardites, as well as in idiopathic dilated cardiomyopathy. However, the serological tests have partially satisfactory results, using techniques such as enzyme (ELISA) and radioactive (RIA) immunnoassays². Some authors¹ have reported a 96% positivity in patients with myocarditis through biofunctional assays in a culture of murine cardiomyocytes, initiating a new field for the diagnosis of myocarditis: the measurement of specific autoantibodies.

Intravenous immunoglobulin has been used in cardiovascular diseases for a relatively short period, although its immunoregulatory function has been known for more than 2 decades. Different reports about its use in cardiology exist, mainly in peripartum cardiomyopathy, and, as recently reported, in chronic heart failure⁵.

Case Report

The patient is a 60-year-old female of mixed heritage, from the state of Rio de Janeiro, who reported dyspnea for 2 years, and, in the last 6 months, 3 episodes of acute pulmonary edema, despite being treated with an angiotensin-converting enzyme inhibitor (ACEI), a beta-blocker, and furosemide for heart failure.

On admission, the patient was lucid, her jugular pressure was elevated, her blood pressure was 90/60 mmHg, and her heart rate was 78 bpm. Her cardiovascular examination revealed the following: ictus cordis on the sixth intercostal space, 4 cm from the left midclavicular line; protodiastolic gallop (S3); systolic murmur 3+/6+ on the mitral region; and paradoxical split of the second cardiac sound (S2). On the electrocardiogram, sinus rhythm with third-degree left bundle-branch block was observed.
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The echocardiogram showed left ventricular dilation with an ejection fraction of 25%. The patient underwent gallium-67 myocardial scintigraphy, which showed an image pattern of myocardial inflammation. An endomyocardial biopsy was performed, and its result was compatible with active lymphocytic myocarditis of moderate degree (Dallas criteria). The patient’s laboratory alterations were creatinine level of 2.2 mg/dL and hemoglobin of 12 g/dL.

Despite the optimized treatment with furosemide, carvedilol, spironolactone, and digoxin, the patient remained in NYHA functional class III/IV. Corticoid therapy and azathioprine were initiated, although the patient was using allopurinol for treating her previous hyperuricemia (uric acid = 11g%). The patient developed pancytopenic hematopoietic hypoplasia, and azathioprine was suspended. She remained symptomatic in functional class IV, with an uric acid level of 11g% and hyperuricemia (uric acid = 11g%).

The use of intravenous immunoglobulin at high doses, and the patient evolved with anuria and acute renal failure, when hemodialysis sessions were indicated for 2 weeks. At the end of that period, her renal function returned, and her urea and creatinine values returned to baseline. The patient's clinical condition progressively improved, with stabilization of her cardiological findings and functional class I/II. So far, she has had no clinical problems.

Discussion

The use of intravenous immunoglobulin to treat primary and secondary deficiencies in antibodies began 25 years ago. Later it was used for the first time for an autoimmune disease, idiopathic thrombocytopenic purpura. Since then, this type of therapy has been used in different immunoinflammatory disorders, such as systemic lupus erythematosus, juvenile rheumatoid arthritis, and Guillain-Barré. The mechanisms of action and the side effects have not yet been totally elucidated, and the real efficacy in controlled clinical trials is yet to be revealed.

In 1994, Caforió et al. reported an improvement in cardiac function and survival in children with myocarditis with the use of intravenous immunoglobulin.

The physiological role of the antibodies and of the immune system itself in our body requires clarification, so that the real action of intravenous gamma globulins can be understood. However, among the effects reported in vivo and in vitro, overall regulation of the immune response is observed: the complement cascade has smaller parameters of activation. There is still the reduction in the serum concentrations of inflammatory markers, such as IL-6 and TNF-α, which are produced by some cell types, such as macrophages and T lymphocytes CD4. Lower degrees of activation, differentiation, and clonal expansion of lymphocytic populations, both B and T, are seen.

Several populations of immune cells, such as macrophages, B lymphocytes, and mast cells, have receptors for the constant fraction of immunoglobulins linked to inhibitory domains of the immune response, ie, transmembrane proteins, whose activation triggers the action of intracytoplasmic proteins that inhibit factors of activation, such as NF-κB. Those activation factors cause the synthesis of inflammatory mediators, from specific genome programs, suggesting that those populations could be hindered by the constant fractions of intravenous immunoglobulins.

The effects of the intravenous immunoglobulins on the complex idiotypic network of antibodies should be considered, because they can recognize the specific regions of other antibodies, constituting a complex network of connectivity and interregulation among the immunoglobulins. Such phenomenon has also been observed in the receptors of T-TCR cells, however, it has been less characterized. Solid evidence has indicated that those physiologically auto-reactive antibodies can act by regulating each other, which may occur in immunemediated diseases, such as autoimmune myocarditis, uncontrollable expansions of sectors of that system in constant equilibrium, oligoclonal expansions. Oligoclonal expansions of lymphocytes occur every time a certain antigen should be eliminated, and they lead to a reorganization of the network, which leads to the elimination of those activated clones. In such situations, in which the myocardium is injured, an imbalance of the system occurs, resulting in maintenance of oligoclonality. Intravenous immunoglobulins are believed to reestablish the equilibrium of the idiotypic network, hindering oligoclonal expansions, and stopping the aggression against the target organ.

The effects of gamma globulin on the process of cardiac remodeling should also be highlighted; patients treated with it have smaller indices of chamber dilation, and greater and more stable left ventricular ejection fraction.

Side reactions to intravenous immunoglobulin have been reported in less than 5% of patients. Of the side effects, aseptic meningoencephalitis, peripheral neuritis, cutaneous rash, and cephaléa stand out.

Acute renal failure is a rare complication with approximately 150 cases reported in the literature and has been associated with diabetes, preexisting renal disease, advanced age, and administration of intravenous immunoglobulin in saccharose-based solutions. Adverse thrombotic events have also been reported, such as acute myocardial infarction and stroke. Our patient was advanced in age and had previous renal dysfunction. The pathophysiology of that adverse effect should still be more thoroughly investigated. The immunocomplexes are believed to build up in the glomerular lumen, leading to acute glomerulonephritis, which is self-limited and resolves spontaneously in a few weeks.

Our patient also had pancytopenia, which may be explained by the characteristic of the active metabolite of azathioprine (6-mercaptopurin) to be cleared, among other pathways, by xanthine oxidase, the most important enzyme inhibited by allopurinol, which potentiates its toxic effects due to the decreased clearance.

Intravenous immunoglobulins are tools of an emerging technology in current medicine: immunoregulation. The immune system has abandoned the status of mere champion of the body against infectious microbes and has assumed a position in the organic integration system, with complex mechanisms, essentially present in all diseases. Cardiovascular diseases have been characterized more and more as having an important immune background. To know and to act on this new paradigm is one of the challenges of 21st-century medicine.
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References