Successful intravenous immunoglobulin therapy in a case of acute fulminant myocarditis

Akut fulminan seyirli miyokarditli bir olguda başarılı intravenöz immünglobulin tedavisi

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Summary – Fulminant myocarditis is an inflammatory process that occurs in the myocardium and causes acute-onset heart failure. Its prognosis is poor unless patients are promptly and aggressively supported. Although an autoimmune mechanism has been postulated for myocarditis, immunomodulatory treatment strategies are still under investigation. We report on a 30-year-old woman with acute myocarditis, whose condition rapidly deteriorated despite standard medical therapy. High-dose intravenous immunoglobulin therapy (70 g/day for 2 days) was given and the patient showed dramatic improvement on the second day. Left ventricular ejection fraction increased from 32% to 40% and to 50% at 24 and 48 hours of treatment, respectively. She was discharged on the tenth day with normal ejection fraction. She was free of cardiac events during a two-year follow-up. High-dose intravenous immunoglobulin may be potentially useful in selected patients, especially if given early in acute fulminant myocarditis.

Özet – Fulminan miyokardit, miyokardı tutan ve ani başlangıçlı akut kalp yetersizliğine neden olan enflamatuvar bir hastalıktır. Hastalar hızlı ve agresif tedavi edilmezlerse prognoz kötüdür. Miyokardit gelişiminde otoimmün mekanizmaların rolü olduğu düşünülse de, miyokarditte immündüzenleyici tedaviler halen araştırma konusudur. Bu yazıda, standart medikal tedaviye rağmen klinik durumu hızla bozulma gösteren, akut miyokarditli 30 yaşında bir kadın hasta sunuldu. Hastaya yüksek doz intravenöz immünglobulin tedavisi (2 günde 70 gr/gün) uygulandı ve tedavinin ikinci gününde klinik tablosunda belirgin iyileşme görüldü. Sol ventrikül ejeksiyon fraksiyonu %32'den tedavinin 24. saatinde %40'a, 48. saatinde %50'ye yükseldi. Hasta 10. günde normal ejeksiyon fraksiyonu ile taburcu edildi ve iki yıllık takip süresince yeni kardiyak olay gelişmedi. Yüksek doz intravenöz immünglobulin tedavisi seçilmiş hastalarda, özellikle akut fulminan miyokarditin erken döneminde yararlı olabilir.

Myocarditis is clinically and pathologically defined as inflammation of the myocardium and is one of the most common causes of dilated cardiomyopathy.[1] Its clinical presentation ranges from nonspecific systemic symptoms (fever, myalgia, palpitations, or exertional dyspnea) to fulminant hemodynamic collapse, cardiogenic shock, and sudden death due to malignant arrhythmias.[1] Immunosuppressive therapy has been widely investigated in acute myo-

carditis. However, mortality benefit has not been proved with randomized trials yet.[2] We report on a young female patient with acute fulminant myocarditis, who recovered rapidly after high-dose intravenous immunoglobulin therapy.

CASE REPORT

A previously healthy 30-year-old female patient was admitted to our emergency service with fatigue, vomiting, and sharp chest pain following a flu-like syndrome. Physical examination revealed marked jugu-

Abbreviations:

EF   Ejection fraction
IVIG Intravenous immunoglobulin
MRI   Magnetic resonance imaging

lar venous distension, tender hepatomegaly, and an S$_3$ gallop rhythm. Blood pressure was 90/60 mmHg and heart rate was 110/min. The electrocardiogram showed sinus tachycardia. Laboratory findings on admission revealed elevated cardiac and liver enzymes, and increased N-terminal proBNP and C-reactive protein levels (Table 1). There was neither hypoxia nor hypocapnia in arterial blood gas. There was not any significant increase in autoantibody levels (anti-nRNP/Sm, anti-Sm, anti-SS-A native, anti-Ro-52, anti-SS-B, anti-Scl-70, anti-PM-Scl, anti-Jo-1, anti-centromere B, anti-PCNA, anti-dsDNA, anti-nucleosomes, anti-histones, AMA-M2, anti-ribosomal P-protein, rheumatoid factor). Coagulation markers were within normal range. Echocardiography showed impaired systolic function of both ventricles, mild to moderate mitral regurgitation, and minimal pericardial effusion. Cardiac magnetic resonance imaging also showed small pericardial effusion with global left ventricular dysfunction and an ejection fraction of 32%. There was no perfusion defect in early perfusion MRI (Fig. 1), which ruled out acute ischemic heart failure. Based on history, clinical findings, laboratory parameters, echocardiography, and cardiac MRI findings, she was diagnosed with acute heart failure, most probably due to acute myocarditis. Endomyocardial biopsy was not performed considering its procedural complications, limited sensitivity and specificity, and the patient's reluctance. Viral serology was not investigated as laboratory results would take long time and would not affect the treatment strategies.

Standard heart failure therapy was started including ramipril 2.5 mg/day, metoprolol 25 mg/day, spironolactone 25 mg/day, and furosemide 80 mg/day. Supplementary coenzyme Q10, carnitine, and pyridoxine were also given at high doses even though

they were not found to be effective in large randomized clinical trials. The patient's condition showed a rapid deterioration during the third day of treatment, requiring intravenous inotropic agents. High-dose IVIG (Octagam, osmolality 310-380 mOsmol/kg, Na ≤30 mmol/l, pH 5.1-6.0) was given as 70 g per day for two days with a total dose of 140 g. On the following day, the patient began to improve dramatically. Left ventricular EF increased to 40% and 50% at the 24th and 48th hours, respectively. Serial echocardiography also showed improvement in mitral regurgitation. Serial changes in the levels of inflammation markers, NT-proBNP, and cardiac enzymes are shown in Table 1.

The patient was discharged on the tenth day with a normal EF (Fig. 2). Intravenous immunoglobulin did not cause any adverse effects including renal failure or thrombotic events. Two years later, the patient was still in good health without any subsequent cardiac events.

DISCUSSION

Supportive care is the first-line treatment in acute myocarditis. Standard treatment consists of diuretics and aldosterone antagonists, vasodilators, angiotensin-converting enzyme inhibitors, beta-adrenergic blocking agents, and inotropic agents when necessary. A minority of patients with acute or fulminant myocarditis will require an intensive level of hemodynamic support and aggressive pharmacological intervention, including vasopressors and positive inotropic agents. A variety of immunomodulatory therapies have been proposed for the autoimmune phase of myocarditis, including immunosuppression, manipulation of cytokines, and anti-T-cell-receptor vaccines. Several clini-
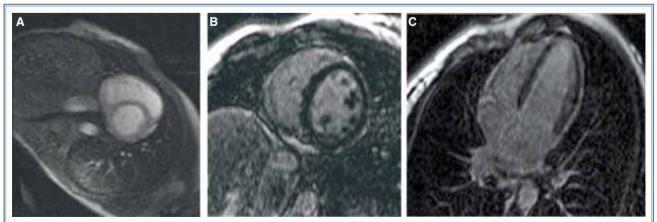

Figure 1. **(A)** No perfusion defect is seen on early perfusion MRI sections. **(B)** Short-axis and **(C)** four-chamber delayed enhancement MRI sections show no finding of delayed enhancement in the subendocardial layers.

Table 1. Serial changes in laboratory findings of the patient during hospitalization

	Day 1	Day 3*	Day 5*	Day 6	Day 7	Day 8	Day 10
Creatinine (mg/dl)	1.02	1.86	1.64	1.32	1.30	1.28	1.10
Na (mmol/l)	136	130	131	134	134	135	136
AST (U/l)	129	456	313	285	189	76	32
ALT (U/l)	155	498	368	302	159	72	52
CK-MB (U/l)	45	64	23	–	–	–	8
Troponin I (ng/ml)	1.8	1.1	0.32	–	–	–	0.12
NT-proBNP (pg/ml)	>3000	>3000	–	1250	–	–	456
CRP (mg/l)	89	107	45	24	15	11	3.5
Ejection fraction (%)	32	–	–	40	50	–	71

*Day 3 and Day 5 denote the time for the initiation and end of intravenous immunoglobulin therapy, respectively.

cal trials based on the concept of autoimmunity have been conducted in humans, in which steroids, azathioprine, cyclosporine, and OKT3 have been used as immunosuppressive agents.[1]

Immunosuppressive agents has been widely investigated in myocarditis, and to date, no randomized trial has shown mortality benefit.[2] In 1993, Parrillo et al.[3] conducted the first immunosuppressive trial in patients presenting with unexplained dilated cardiomyopathy and evidence for immune activation. They randomized the patients to either steroids or placebo. They reported a temporary improvement in ventricular function in reactive patients treated with prednisone, but there was no sustained benefit at 6 or 9 months because the reactive control group also showed comparable spontaneous improvement in function. The Myocarditis Treatment Trial randomized 111 patients with biopsy-verified myocarditis to receive conventional therapy or an immunosuppressive regimen of

prednisone combined with either azathioprine or cyclosporine.[4] There was a similar degree of recovery of ventricular function in both arms of the study, and there was no difference in mortality, which was 20% overall at 1 year and 56% at 4.3 years of follow-up. These two controlled trials suggest that immunosuppression should not be prescribed for the routine treatment of viral myocarditis.

Experimental studies have shown that IVIG is an effective therapy for viral myocarditis by antiviral and anti-inflammatory effects. Besides, it is considered to be a safe treatment considering the numerous side effects of immunosuppressive therapy with corticosteroid and other agents. McNamara et al.[5] showed improvement in EF in patients with new-onset dilated cardiomyopathy treated with high-dose IVIG. Similarly, Kishimoto et al.[6] showed that high dose of IVIG improved EF in patients with myocarditis and acute dilated cardiomyopathy through the
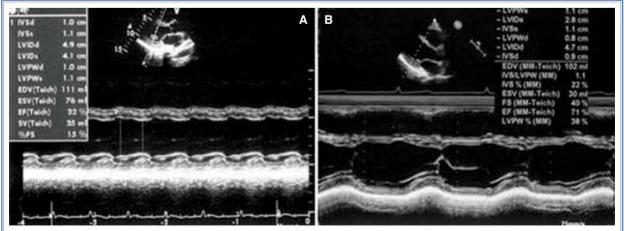

Figure 2. M-mode echocardiography recordings. **(A)** On the first day of admission ejection fraction is 32%, **(B)** which then increased to 71% after high-dose IVIG treatment.

reduction of cytokines and associated improvement in oxidative stress. Intravenous immunoglobulin therapy has also been used in children with acute myocarditis. Drucker et al.[7] treated 21 children presenting with presumed acute myocarditis with IVIG, 2 g/kg, over 24 hours and reported that high-dose IVIG for treatment of acute myocarditis was associated with improved recovery of left ventricular function and a tendency to better survival during the first year after presentation.

Although observational studies have reported success with the use of a variety of immunosuppressive agents, there are conflicting results about the success of these therapies in randomized studies. In a double-blind, randomized, controlled trial of IVIG in 62 patients with recent-onset heart failure and unexplained dilated cardiomyopathy, no differences were observed in all-cause mortality or improvement in EF at 6 or 12 months, and both groups demonstrated substantial increases in EF during the study period.[8] In contrast, Gullestad et al.[9] studied the efficacy of IVIG in a randomized trial of 40 patients with chronic dilated cardiomyopathy and found that IVIG therapy was associated with marked increases in serum anti-inflammatory markers, which correlated with significant improvement in EF at 6 months. These changes were not observed in the control group.

There are several reasons why the results of observational and randomized studies differ. First, histological resolution of myocardial inflammation does not closely correlate with improvement in ventricular function. Second, the high incidence of spontaneous improvement in contractile function may lead to overestimation of the benefit of IVIG and supports the need for a control group whenever treatment success is evaluated. Third, the specific viral agent and the immunologic state of the host may result in different response rates to immunosuppression. Finally, despite the well-established morbidity and mortality rates associated with myocarditis, clinical practice guidelines with regard to its evaluation are lacking. Endomyocardial biopsy remains the gold standard for establishing the diagnosis, despite its considerable limitations such as procedural complications, limited sensitivity and specificity, and variability of pathologic interpretation. Thus, the vast majority of diagnoses are based upon history (especially recent flu-like syndrome), physical examination, 12-lead electrocardiogram, serum cardiac biomarkers, echocardiography, and cardiac MRI, as in our case. On the other hand, the sensitivity and specificity of the Dallas criteria and the more recent World Heart Federation criteria used in histological confirmation are uncertain. In parallel to improvements in diagnostic tools, identification of patients with acute myocarditis who will respond to IVIG therapy will be easier.

Finally, it is important to recognize that patients with fulminant myocarditis who develop abrupt severe hemodynamic compromise may have a much better prognosis than those with mild acute or chronic forms of myocarditis. These patients should be supported aggressively because there is a high likelihood of recovery. Goland et al.[10] reported that high-dose IVIG may be a potentially useful treatment in selected patients if given early in the course of acute fulminant inflammatory dilated cardiomyopathy. Similar to their series, our patient improved dramatically with IVIG therapy with no side effects and without developing cardiac events. Randomized prospective trials are still warranted to prove the real benefit of IVIG in this patient population.

Conflict-of-interest issues regarding the authorship or article: None declared

REFERENCES

1. Magnani JW, Dec GW. Myocarditis: current trends in diagnosis and treatment. Circulation 2006;113:876-90.

2. Liu C, Chen J, Liu K. Immunosuppressive treatment for inflammatory cardiomyopathy: meta-analysis of randomized controlled trials. Int Heart J 2005;46:113-22.

3. Parrillo JE, Cunnion RE, Epstein SE, Parker MM, Suffredini AF, Brenner M, et al. A prospective, randomized, controlled trial of prednisone for dilated cardiomyopathy. N Engl J Med 1989;321:1061-8.

4. Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. N Engl J Med 1995;333:269-75.

5. McNamara DM, Rosenblum WD, Janosko KM, Trost MK, Villaneuva FS, Demetris AJ, et al. Intravenous immune globulin in the therapy of myocarditis and acute cardiomyopathy. Circulation 1997;95:2476-8.

6. Kishimoto C, Shioji K, Kinoshita M, Iwase T, Tamaki S, Fujii M, et al. Treatment of acute inflammatory cardiomyopathy with intravenous immunoglobulin ameliorates left ventricular function associated with suppression of inflammatory cytokines and decreased oxidative stress. Int J Cardiol 2003;91:173-8.

7. Drucker NA, Colan SD, Lewis AB, Beiser AS, Wessel DL, Takahashi M, et al. Gamma-globulin treatment of acute myocarditis in the pediatric population. Circulation 1994;89:252-7.

8. McNamara DM, Holubkov R, Starling RC, Dec GW, Loh E, Torre-Amione G, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. Circulation 2001;103:2254-9.

9. Gullestad L, Aass H, Fjeld JG, Wikeby L, Andreassen AK, Ihlen H, et al. Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. Circulation 2001;103:220-5.

10. Goland S, Czer LS, Siegel RJ, Tabak S, Jordan S, Luthringer D, et al. Intravenous immunoglobulin treatment for acute fulminant inflammatory cardiomyopathy: series of six patients and review of literature. Can J Cardiol 2008;24:571-4.