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Immunoadsorption in a 40 year old man with dilated cardiomyopathy and underlying active myocarditis

Sirs: Patients with dilated cardiomyopathy often present elevated levels of potentially harmful autoantibodies directed against various cardiac antigens, including mitochondrial proteins (e.g., adenine nucleotide translocator), sarcolemmal proteins (e.g., actin, laminin, myosin, troponin), and membrane proteins (e.g., cell surface adrenergic or muscarinergic receptors) [5]. Stimulating anti beta1-adrenergic receptor antibodies are thought to induce and/or worsen dilated cardiomyopathy [4], assumingly also via the induction of cardiomyocyte apoptosis [6]. Recently, it has been shown that patients with progressive dilated cardiomyopathy, who are positive for functional anti beta1-adrenergic receptor antibodies, have an about three-fold increased cardiovascular mortality risk [12] and, thus, may probably benefit from immunoadsorption therapy, particularly, if the levels of IgG3 can be reduced substantially [2, 3, 8].

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Case report

A 40 years old Afro–American male presented in our hospital with severe dyspnea at slightest physical activity (NYHA III) and a body weight gain of 7 kg within the last 2 weeks. Physical examination showed an elevated jugular venous pulse, hepatomegaly and peripheral edema. Upon cardiac auscultation a third heart sound was present, percussion of the chest wall and X-ray examination of the thorax revealed pleural effusion, predominantly on the right side. Electrocardiography (ECG) showed a regular sinus rhythm with an unspecific intraventricular conduction delay. Holter-ECG displayed several episodes of non-sustained ventricular tachycardia. Routine laboratory parameters showed an elevation of CK (395 U/l), CK-MB (6.3%), Troponin I (0.13 μg/l) and B-type natriuretic peptide (2,904 pg/ml). Neither white blood cell count nor CRP were abnormal. Echocardiography displayed enlargement of the left ventricle and both atria, whereas the right ventricle was only marginally enlarged. A moderate insufficiency of the mitral and tricuspidal valve, and severely impaired left ventricular (LV) systolic function (LVEF 16%) could also be detected.

Magnetic resonance imaging (MRI) of the heart revealed severe cardiac dilatation and a left ventricular ejection fraction of ~16%. The right ventricle was of normal size, but systolic function appeared to be impaired as well. Coronary heart disease was excluded by angiography. Biopsies were taken from the inferior septum of the right ventricle and analyzed. Histolog-

ical sections revealed loss of single myocytes and a mild focal interstitial edema and fibrosis (Fig. 1a) associated with an enhanced infiltration of MHC class II expressing macrophages (Fig. 1b). Myocardial infection with cardiotropic viruses or bacteria, including enteroviruses, Parvovirus B19, human herpesvirus 6, Epstein Barr virus, adenoviruses and Borrelia burgdorferi were not detected by nested (RT)-PCR. Taken together these results displayed a dilated cardiomyopathy with an underlying active myocarditis, according to the criteria previously described by Mahrholdt et al. [7]. A standard heart failure therapy was started immediately including a betablocker (Carvedilol 12,5 mg per day), an ACE inhibitor (Ramipril 10 mg per day), an aldosteron antagonist (Eplerenon 25 mg per day), and diuretics (Hydrochlorothiazid 25 mg and Torasemid 100 mg per day). Because of the severely reduced LV function and documented non-sustained ventricular tachycardias an internal cardioverter defibrillator was implanted.

Three months later, despite standard medical therapy and a slight increase in left ventricular ejection fraction (from 16% to 20%), the patient pre-

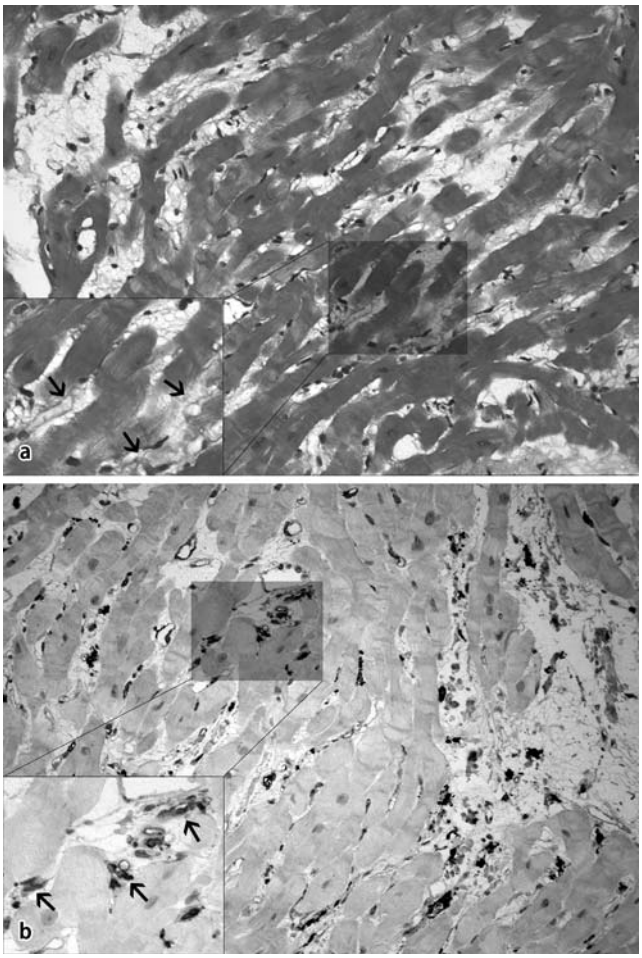

Fig. 1 **a**, **b** Histological sections showing loss of single myocytes, interstitial edema and fibrosis as well as infiltration of MHC class II expressing macrophages (*arrows*) (**a** Masson trichrom staining; **b** immunohistochemical staining for MHC class II expression,). The infiltration of the myocardium with macrophages led to the diagnosis of an active myocarditis. Cardiotropic viruses were not detected in the heart, thus the enhanced infiltration of macrophages might reflect cardiac remodeling processes as a consequence of ongoing cardiomyocyte apoptosis due to a high activity of anti β1-adrenergic receptor antibody in this patient

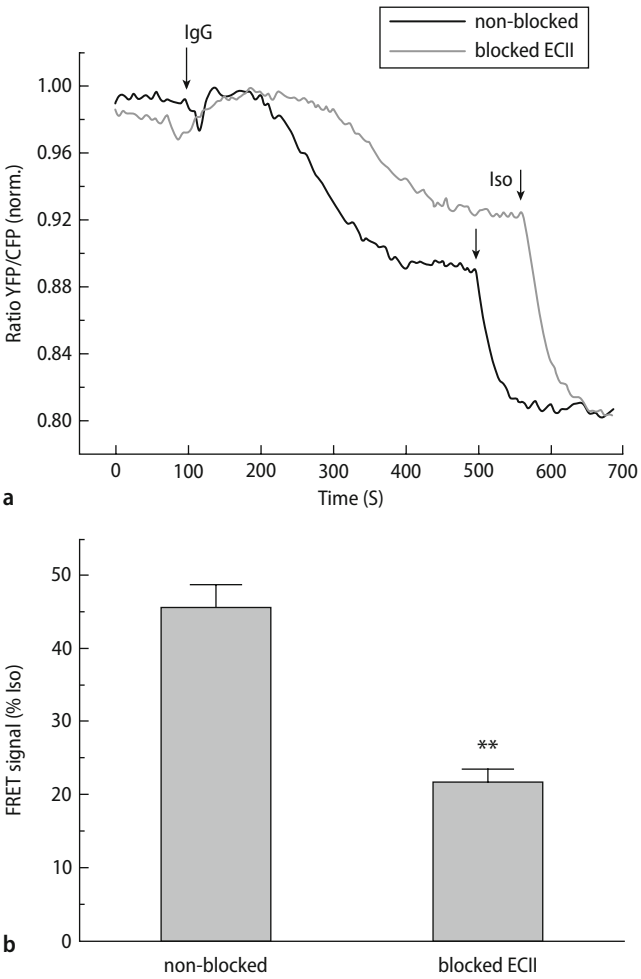

Fig. 2 **a** Detection of functional β1-adrenergic receptor autoantibodies by FRET. Human HEK293 cells transiently expressing a novel highly sensitive fluorescent cAMP-sensor (Epac1-camps), allow for the on line monitoring of cellular cAMP changes by fluorescence-resonance-energy-transfer (FRET). Representative FRET-traces of four independent experiments demonstrating the increase in cAMP induced by binding of the patient's immunoglobulin G fraction (*black*, indicating receptor activation) and its blockade by preincubation with peptides corresponding to the second extracellular receptor loop (*red*, ECII-blocked). FRET was monitored by measuring fluorescent emissions of cyan (CFP) and yellow fluorescent proteins (YFP) in the Epac1—camps sensor. Antibody-induced decrease of the normalized YFP/CFP Ratio (shown on the *y*-axis) reflects an increase in intracellular cAMP. B: High activator IgG (45.8% ± 3.2% of the maximal signal obtained with 5 μg of the full agonist (-)isoproterenol) from our patient could be blocked significantly with ECII-peptides (ANOVA, $P < 0.001$) achieving a partial about 50% inhibition of the antibody-induced FRET signal

sented with progressive clinical deterioriation. Consequently, heart transplantation was considered. However, by virtue of religious reasons the patient denied this treatment option. In our aim to extend treatment modalities, a screening for cardio-noxious antibodies was performed, and revealed the presence of functional anti-beta1-autoantibodies with high FRET-activity (corresponding to a high adrenoceptor-stimulating capacity, see Fig. 2) [9]. In consent with the patient immunoadsorption therapy employing a protein A column followed by immunoglobulin-substitution was performed as described previously by Staudt et al. [11]. IgG3 titers were measured before and after immunoadsorption. Left ventricular function was followed non-invasively by echocardiography. Immunoadsorption reduced the level of IgG3 from an initial level of 120–29 mg/dl. Left ventricular ejection fraction increased from 20% after 3 months of medical treatment to 25% after immunoadsorption therapy. This improvement of LV function was assessed 4 weeks after immunoadsorption therapy had been completed. In addition, the patient reported an improvement of clinical symptoms. However, despite continued state-of-the-art pharmacotherapy, in our patient the rapid and progressive deterioration of cardiac function could finally not be stopped. He died 8 months after first medical treatment, and 5 months after immunoadsorption therapy had been completed from acute decompensated congestive heart failure.

Discussion

Immunoadsorption therapy is thought to reduce cardio-noxious antibodies, such as cardiostimulatory anti beta1-adrenergic receptor antibodies. Preliminary and mostly un-controlled clinical studies indicate a beneficial effect of immunoadsorption therapy on left ventricular performance in patients with dilated cardiomyopathy. Especially patients positive for autoantibodies directed against the beta1-adrenergic receptor might profit from such a procedure [1, 2, 10]. In addition, these preliminary studies show that under continued adequate heart failure medication in this selected patient subgroup left ventricular ejection fraction may even be improved by 10%–15% for longer time intervals (of up to 3 years) [2]. Also our patient seemed to profit from immunoadsorption therapy. Left ventricular ejection fraction increased by 4% under consequent conventional heart failure medication, and by another 5% after immunoadsorption therapy. However, since in our case the progressive character of the disease led to an early death, we cannot draw any general conclusions on the possible influence of immunoadsorption on survival in dilated cardiomyopathy. The detected improvement of LV function in our patient might even not have been induced by immunoadsorption therapy, but caused by the medical treatment only. Or it might have occurred spontaneously, as it can be seen in many patients suffering from acute dilated cardiomyopathy. Decreased survival rates have recently been demonstrated in patients with dilated cardiomyopathy positive for stimulating beta1-adrenoceptor antibodies [12]. To address the role of potentially cardio-noxious antibodies more in detail and, of course, to determine the potentially beneficial effects of immunoadsorption on survival, a randomized double-blinded clinical trial is currently under way.

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