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CASE REPORT
Rare diseases of the heart

Hypertrophic cardiomyopathy – symptomatic atrial fibrillation in a patient at high risk of sudden cardiac death (RCD code: V-2A.2)

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Abstract

We present the case of a young patient with significant left ventricular hypertrophy as a common representation of the hypertrophic cardiomyopathy (HCM) phenotype. The clinical presentation and diagnostic route of the disease (despite negative genotype), which can be found in everyday cardiology practice, are shown. Despite the presence of guidelines on this topic, each clinical case is demanding, especially during qualification for invasive procedures. Limited data about the periprocedural risk of catheter ablation and success rate in HCM makes physician decisions for this type of patient challenging. The importance of informed consent and how the patient's decisions affect further progress are also shown. JRCD 2018; 4 (1): 18–21

Key words: rare disease, hypertrophic cardiomyopathy, atrial fibrillation, subcutaneous implantable cardioverter defibrillator, transcatheter ablation

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary disease of the left ventricle muscle that has increased in thickness, irrespective of hemodynamic loading conditions. According to the latest definition, this term covers a wide spectrum of both genetic and acquired disorders [1]. In most cases, HCM is related to autosomal dominant mutations in up to 60% of cases, among which there are mainly with beta-myosin heavy chain (MYH-7) and myosin binding protein (MYBPC3) genes disorders. The prevalence of this disease across North America, Europe, and Asia is estimated to be approximately 0.03–0.05 per 100,000 people [2]. In the early phase, most patients are asymptomatic, but later, they may develop dyspnea, chest pain, palpitations, or syncope. The most common cause of cardiac arrest is spontaneous ventricular fibrillation, and thus an implantable cardioverter-defibrillator is effective. Because of the lack of causative treatment, the therapy focuses on reduction of symptoms, which are caused mainly by left ventricular outflow tract obstruction and by both ventricular and supraventricular arrhythmic episodes. The patient requires regular follow-up including an estimation of their 5-year sudden cardiac death risk to determine if prevention using an implantable cardioverter defibrillator (ICD) is required. Taking care of patients with HCM may be demanding because of their young age at first diagnosis, many drug side effects, and implantable device therapy complications, especially with the long estimated lifespan of the general population.

Case presentation

A 37-year-old male aviation engineer with suspected HCM and no other comorbidities was admitted to our clinic because of recurrent palpitations accompanied by dyspnea. About 2 weeks before admission, he was hospitalized at another clinic because of unexplained syncope during everyday activity. HCM was initially suspected a few years earlier based on electrocardiography (ECG) abnormalities and routine echocardiography examination before extensive sport activity that was planned by the patient. The echocardiography revealed left atrium enlargement (49 mm

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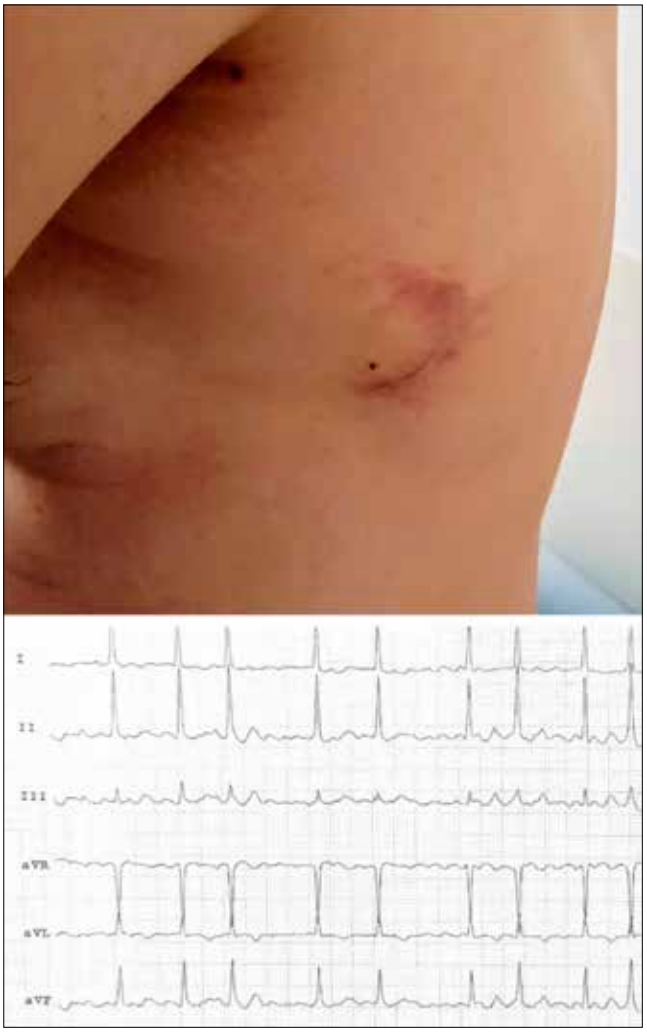

Figure 1. Upper panel: ICD pocket healing after 12 weeks. Lower panel: Patient's ECG on admission with atrial fibrillation

in parasternal long axis view), asymmetric intraventricular septum thickening, with a maximum diameter of 19 mm. Because of the unclear clinical presentation and his negative family history of HCM or sudden cardiac death, diagnostic tests were extended to genetics (Sanger method), which did not detect any known, scientifically proven causative mutations. On admission, ECG results showed atrial fibrillation with a high rate of ventricular response (Figure 1, lower panel). On echocardiography left atrium enlargement was observed, including significant intra-ventricular septum thickening (19 mm in end-diastole) with a normal ejection fraction. The left ventricle outflow tract (LVOT) gradient was 22 mmHg, with an increase to 71 mmHg after Valsalva provocation, and to 84 mmHg after standing. There were no abnormalities in laboratory blood tests. In our patient, the test results did not detect scientifically proven mutations for HCM, storage diseases, or amyloidosis type V (ACTC1, ACTN2, CSRP3, GAA, GLA, JPH2, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PRKAG2, TNNI3, TNNT2, TPM1, or TTR), which could mean that the patient's disease was caused by a mutation that was not yet associated with the phenotype. During the patient's hospital stay, spontaneous return of the sinus rhythm was observed, with many episodes of

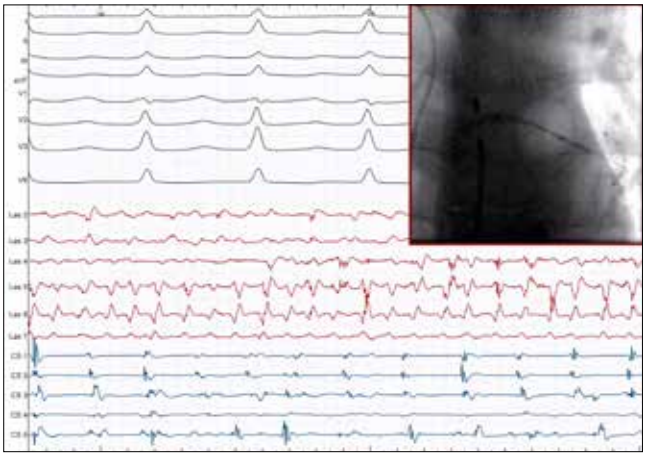

Figure 2. Surface ECG and simultaneous endocardial tracings from the pulmonary vein (Las 2-Las 7) and coronary sinus (CS1- CS 5) showing rapid activity (approximately 600 bpm) in the right inferior pulmonary vein, much faster than the activity inside the coronary sinus. Inset: cryoballoon wedged in the antrum of the left inferior pulmonary vein

recurring atrial fibrillation detected using telemetry, with symptoms classified up to IIb on the modified European Heart Rhythm Association symptom classification (EHRA) scale (mEHRA). Pharmacological treatment was modified, with betaxolol being switched to increasing doses of metoprolol succinate,up to 200 mg/day. A reduction in atrial fibrillation episodes was observed. Serial echocardiography examinations revealed a decrease in the provoked LVOT gradient to 36 mmHg. A 24-hour Holter monitor did not reveal any non-sustained ventricular tachycardia episodes. Magnetic resonance imaging (MRI) results showed asymmetric left ventricular thickening, mainly in the basal and medial intraventricular septum segments, with late gadolinium enhancement, which supported the HCM diagnosis. Apixaban was ordered for prevention because of the high risk of thromboembolic complications in patients with atrial fibrillation and co-existing HCM with left atrium enlargement. After collecting all the required data, the risk of sudden cardiac death (SCD) at 5 years was estimated to be 6.3% based on the calculator provided with the ESC guidelines, and ICD implantation should be considered. The patient did not agree to the procedure, mainly because of the fear of periprocedural complications, and an increased risk that the device and lead would malfunction in the future. On the tenth day, he was discharged from the hospital. During routine outpatient care, the patient reported reduction of arrhythmic episodes with EHRA IIa symptoms, but the risk of SCD was still above 6%. Based on the entire clinical course and patient preferences, implantation of a totally subcutaneous cardioverter defibrillator (S-ICD) was proposed. The procedure was performed under general anesthesia, and an EMBLEM MRI S-ICD with associated subcutaneous lead was successfully implanted. During the procedure, induced ventricular fibrillation was correctly recognized and terminated using the device. The device was programmed in accordance with the manufacturer's recommendations; the conditional shock zone was set at 200 bpm and the unconditional shock limit was 220 bpm. Further ambulatory

follow-up showed proper device pocket healing (Figure 1, upper panel), and no sensing issues. However, after 1 year, the patient reported symptom progression to EHRA class III, and he agreed to the proposed interventional treatment for atrial fibrillation. The S-ICD device memory indicated that he spent over 50% of time in atrial fibrillation. Pulmonary vein isolation was performed using the 28-mm cryoballoon technique. Transseptal puncture was uneventful and all four pulmonary veins were isolated; both inferior veins showed rapid activity (Figure 2). Our patient remained in ambulatory care, with substantial relief of his symptoms. During 12 weeks of follow up, there were no atrial fibrillation episode recurrences, based on the implantable device's memory. Anticoagulation therapy with apixaban was continued, with no bleeding episodes to date.

Discussion

HCM is defined as a primary myocardium dysfunction, which is presented by increased left ventricular wall thickness, which cannot be explained by abnormal loading conditions. The cut-off value for single segment diameter is 15 mm in adults [1]. A diagnosis based solely on this parameter can be difficult to make in the early phase of the disease or among end-stage patients when left ventricle wall thinning is observed. Thus, it is important to extend diagnostics to include a family history of HCM or unexplained cardiac death, and ECG abnormalities. In some cases, genetic testing may be helpful, but it is not necessary to make a diagnosis. For our patient, the tests did not detect scientifically proven mutations, which could mean that the patient's disease was caused by a mutation that has not yet been associated with the phenotype [3]. If a final diagnosis of HCM is made, screening of the patient's family is recommended. During the evaluation, basic blood tests including high-sensitivity troponin and N-terminal pro B-type natriuretic *peptide* may be helpful to estimate the cardiac risk, based on the results of recent studies [4,5]. Echocardiography plays an important role in making a diagnosis and it provides information about hemodynamics. Left ventricular outflow tract obstruction (LVOTO) or systolic anterior movement (SAM) of the mitral valve leaflet are strongly correlated with symptoms, and thus, in our clinic, echocardiography is performed each time a patient reports symptom exacerbation. The routine examination consists of measuring the LVOT resting gradient after Valsalva provocation and in some cases after exercise. Collected data are used to estimate the 5-year sudden cardiac death risk in patients with HCM after every ultrasound examination. This gives the physician information about the current risk, which in some cases can be reduced, and indicates the best time for ICD implantation.

The main goal of pharmacological therapy is reduction of the LVOT gradient, prevention of cardiac arrhythmia, and management of heart failure. Non-vasodilating beta-blockers are the first-line treatment, but a lack of comparative data regarding heart rate and the LVOT gradient reduction makes the therapeutic decision difficult [6,7]. Based on our institution's experience, switching from betaxolol to metoprolol provides better heart rate control, reduces arrhythmic episodes, and, in this particular case, significantly reduces both the symptoms and the LVOT gradient.

Currently, there is no causative treatment for HCM, but a new molecule designed to reduce left ventricular contractility, called mavacamten (formerly MYK-461), has entered phase 3 clinical studies. In HCM mutant mice, it prevented hypertrophy and reduced myocyte disarray and interstitial fibrosis compared with placebo [8].

Despite the significant reduction of the LVOT gradient using pharmacological therapy, the estimated 5-year SCD risk was still above 6%, mainly because of syncope in the patient's medical history, which strongly suggests this result. The patient's lack of consent for TV-ICD implantation was partially based on the available data on late complications in a young patient's subgroup, and these patients will require several device replacements including defibrillation lead removal. The 8-year risk of high-voltage lead failure reaches 40% and increases by 20% per year at 10 years after implantation [9,10]. Based on the estimated lifetime of the Polish male population, the patient would have to undergo at least three device replacements because of battery limitations, with the probable necessity of high-risk transvenous extraction of non-functional leads, which is recommended by the consensus statement issued by the Heart Rhythm Society [11]. However, the patient loses the possibility of reducing the LVOT gradient by dual-chamber pacing with atrioventricular delay optimization, as was reported to be effective in some studies [12]. Recently, the opportunity to provide permanent ventricular arrhythmia protection can be obtained using S-ICD. S-ICD is a device that is placed into an intramuscular pocket that is made between serrated muscles, and it is connected with a complementary subcutaneous lead that is placed parallel to the sternum. The device is able to provide high-energy therapy up to 80 J, with maximum of five shocks per episode. The battery longevity is estimated to be approximately 7 years. The main limitations are passing the screening test for the quality of an electrical signal from the chest and lack of pacing ability for both bradycardia and anti-tachycardia pacing; the device is only capable of providing post-shock pacing using 50 bpm for a maximum time of 30 seconds [13]. However, this patient did not have indications for bradycardia pacing and passed the screening test. Our only concern was paroxysmal atrial fibrillation with a high ventricular response, which could lead to inadequate interventions of the device, compared to TV-ICD that likely has better signal quality based on an intracardiac electrogram. During a 1-year observation period after the procedure, there were no interventions, although the arrhythmia burden reached 50% of the total rhythm. The second step was to qualify the patient for catheter ablation of atrial fibrillation. The decision was difficult, especially with limited data available regarding HCM patients, and it was based on a serious exacerbation of symptoms reported by the patient, moderately abnormal left atrium volume (39 mL/m^2), and good local experience with cryoballoon ablation [14]. Patients with HCM and recurrent AF may benefit from interventional catheter-based radiofrequency ablation, but randomized controlled trials are limited [15]. However, the reported success rate of 50–60% seems to be acceptable [16]. The optimal ablation strategy and energy force (radiofrequency ablation (RFCA) vs. cryoablation) in HCM patients has been investigated in some recent studies, which showed that RFCA ablation may be more effective than cryoablation [17], but the success rate during almost 3-years of

follow-up remains below 30% [18]. We believe that this case report will add to the current data on this subject.

Conclusions

In our case, we pointed out the major issues that need attention when caring for patients with HCM. Systematic follow-up, with a detailed medical history regarding changes in symptoms, is crucial for proper decision-making. Regular echocardiography and Holter monitoring is necessary for SCD risk stratification using an HCM risk calculator. We strongly encourage stratification of this risk at each visit, which will help to introduce timely and adequate therapy. Finally, new pharmacological causative therapy may be available in the near future, but for now, S-ICD implantation and catheter ablation of AF may be suitable for some patients.

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