

Successful treatment of acute myocarditis with right and left ventricular assist devices complicated by heparin-induced thrombocytopenia

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Myocarditis is defined as an inflammatory disease of the heart muscle, diagnosed by established histological, immunological, and immunohistochemical criteria (1). It is commonly developed by virus, but also can be a result of bacterial infection or various toxins (2–4). The exact incidence is unknown, however, in number of routine autopsies, 1–9% of all patients had signs of myocardial inflammation. In young adults, almost 20% of all cases of sudden death are due to myocarditis (5). In symptomatic patients, myocarditis often presents as acute heart failure, although it can mimic acute myocardial infarction or a tachyarrhythmia (6). The use of Intravenous Immunoglobulin in the treatment of acute myocarditis is controversial (7, 8). High dose of steroids have been used in certain types of myocarditis, although the treatment regimen is not defined (9–11). In severe cases patients develop cardiogenic shock and require mechanical circulatory support or heart transplantation (4). Here we present a case of acute myocarditis managed with left and right ventricular assist devices and good outcome despite of postoperatively developed heparin induced thrombocytopenia.

Key words: myocarditis, ventricular assist device, heparin-induced thrombocytopenia.

Úspěšná léčba akutní myokarditidy pomocí mechanické podpory pravé a levé komory srdeční komplikovaná heparinem indukovanou trombocytopenií

Myokarditida je definována jako zánětlivé onemocnění srdečního svalu, diagnostikované pomocí zavedených histologických, imunologických a imunohistochemických kritérií (1). Je běžně způsobována virem, ale mohou ji rovněž způsobovat bakteriální infekce nebo různé toxiny (2–4). Její přesná incidence není známá, nicméně u celé řady rutinně prováděných pitev mělo příznaky zánětu myokardu 1 až 9% všech pacientů. U mladých dospělých zodpovídá myokarditida za téměř 20% všech případů náhlého úmrtí (5). U symptomatických pacientů se myokarditida často projevuje jako akutní srdeční selhání, i když může napodobovat akutní infarkt myokardu nebo tachyarytmii (6). Užití intravenózně podávaného imunoglobulinu v léčbě akutní myokarditidy je diskutabilní (7, 8). Ačkoliv léčebný režim není definován, byly u určitých typů myokarditidy použity vysoké dávky steroidů (9–11). V závažných případech se u pacientů objevuje kardiogenní šok a je nutná mechanická podpora cirkulace nebo transplantace srdce (4). Uvádíme případ akutní myokarditidy řešený mechanickou podporou levé a pravé komory srdeční s dobrým výsledkem navzdory pooperačně vzniklé heparinem indukované trombocytopenii.

Klíčová slova: myokarditida, mechanická srdeční podpora, heparinem indukovaná trombocytopenie.

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Case report

A 32-year-old woman, obese (body mass index was 36.7), with history of diabetes mellitus, visited her primary care physician complaining of two days lasting chest pain, radiating to the left arm, shortness of breath, nausea and perspiration. She was admitted to the cardiac ICU with suspected myocardial infarction. On physical examination, her blood pressure and heart rate were 110/75 mmHg and 100 beats/min. A total blood count and biochemistry analysis were following: white blood cell count – $5.8 \times 10^9/l$, C-reactive protein – 10.7 mg/l, brain natriuretic peptide (BNP) – 1052.6 ng/l, troponin I – 16.0 µg/l. Electrocardiogram of

Figure 1. ECG, showing ST-segment elevation in leads I, aVL, V2–V4

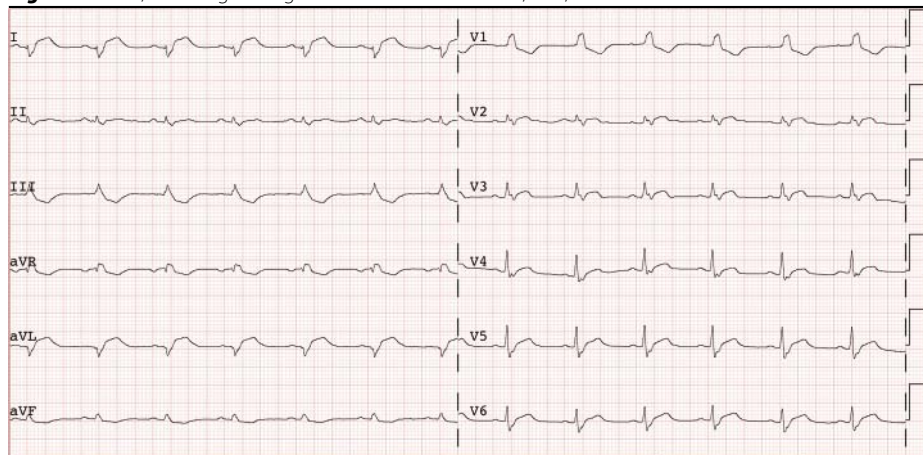


Figure 2. Chest X-ray, showing left lower lobe pulmonary infiltration (pneumonia)

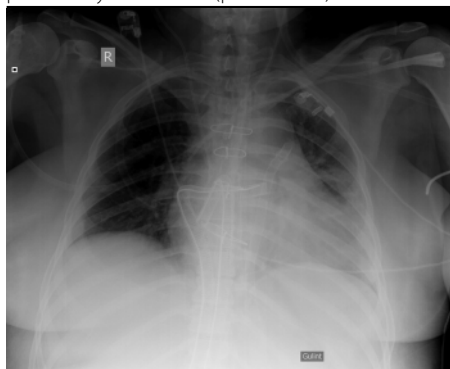


Figure 3. H&E X 200; lymphocytic infiltration (1) with myocytolysis (2)

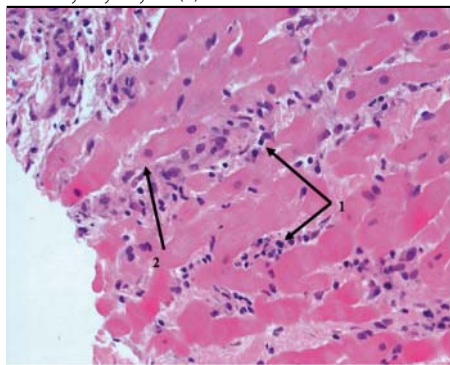
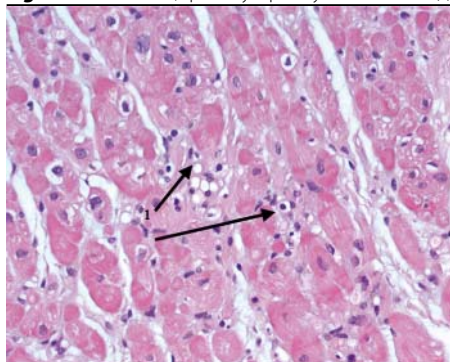


Figure 4. H&E X 200; sparse lymphocytic infiltration (1)



12 leads showed ST-segment elevation in leads I, aVL and V2–4 (Figure 1). Emergency coronary angiography was performed but coronary stenosis was not found. Echocardiography revealed signs of local myocardial damage at the rear wall with left ventricular (LV) ejection fraction of 50%.

Over the next 36 hours atrial fibrillation occurred and the patient became hypotensive. A repeated echocardiogram showed severely reduced LV function without local hypokinesia. Despite the treatment with noradrenaline, dobutamine, furosemide, broad-spectrum antibiotic therapy due to infiltration seen on chest X-ray and suspicion of pneumonia (Figure 2), and intra-aortic balloon pump, she developed liver (AST and ALT were 2639 U/l and 6597 U/l), respiratory (PaO₂/FiO₂ ratio of 120 mmHg) and renal (Creatinine level was 418 µmol/l) failure.

After resuscitation due to ventricular fibrillation the left and right ventricular assist devices (VAD) as rescue therapy were inserted (Levitronix, CentriMag). The procedure was uneventful and device parameters were following: left VAD 5.2 litres/min pump flow with speed of 3 400 rpm, and right VAD 4.5 litres/min with speed of 3 000 rpm.

Postoperative period was complicated by heparin induced thrombocytopenia type II (HIT II) and anticoagulation therapy with fondaparinux under strict control of anti-Xa factor was applied. Patient suffered re-exploration without clear surgical site of bleeding on the first and sixth postoperative day. Hospital-acquired infection (*Acinetobacter baumannii* from bronchial secretions and Vancomycin-resistant *Enterococcus faecium* (VRE) from urine) was treated with antibiotics following antibiotic sensitivity testing with a good response.

Serological testing for *Borrelia* and polymerase chain reaction to detect the genomic sequences of most common viruses (adenovirus, enterovirus, cytomegalovirus, Epstein-Barr, Hepatitis B, HIV, Herpes simplex, Influenza A, B and H1N1) were performed. All tests came back negative. Myocardial biopsy using light microscopy showed diffuse inflammatory infiltration with visible cardiomyocyte necrosis (Figure 3). Immunohistochemical examinations for CD3-T-lymphocytes and CD-68-macrophages were positive for up to 60 cells per 1 mm².

Patient's hemodynamic status had been stabilized under mechanical circulatory support and she was successfully weaned from mechanical ventilator on the 21st day after surgery. Ten days later echocardiogram done with reduced left VAD pump flow to 2 litres/min and right VAD to 1.5 litres/min showed significant improvement in LV ejection fraction and only mild right ventricular dilatation. Explantation of both VAD was performed on the thirty third day after insertion. The following period was uneventful. Patient was extubated within several hours and inotropic support was withdrawn within 24 hours after explantation of devices. She was transferred to the surgical ward with no renal, respiratory or liver insufficiency five days following explantation. The following light microscopy showed inflammatory infiltration but no visible myocyte damage (Figure 4). Immunohistochemistry for CD-3 and CD-68 was still positive.

Discussion

The natural history of myocarditis varies in its clinical presentations (12). Myocarditis mimicking myocardial infarction typically results

in a full recovery of cardiovascular condition in previously healthy adults (6, 13). Patients may have slightly compromised ventricular function and usually recover within weeks. Otherwise, a smaller group of patients present with severe impairment of left and right ventricular function. Among these 50% develop chronic ventricular dysfunction, and 25% of patients progress to transplantation or death; yet, the remaining 25% will spontaneously improve in their ventricular function (14, 15). The smallest group presents with cardiogenic shock requiring mechanical circulatory support as a bridge-to-recovery or bridge-to-transplantation therapy (4).

Treatment of myocarditis is usually symptomatic and based on clinical presentation, as causative agent is rarely identified. Because of high incidence of LV dysfunction, heart failure therapy is essential for these patients. Standard treatment includes beta-blockers, angiotensin-modulating agents (ACE and ARBs), diuretics and positive inotropes (4). Nonsteroidal anti-inflammatory drugs (NSAIDs) showed benefit only in patients with perimyocarditis as usually these patients suffer from chest pain and rarely have any LV dysfunction (4). There are some trials that report improvement of left ventricular function with the use of high dose intravenous immunoglobulin but results are conflicting (7, 8). A number of studies reported the use of immunosuppressants (cyclosporine and corticosteroids) in myocarditis treatment, but with minimal proven benefit and only in specific types of myocarditis (cardiac sarcoidosis and giant cell myocarditis) (9–11). In our case electron microscopy was not performed since light microscopy and immunohistochemistry already confirmed myocarditis diagnosis. Although virology tests were negative we made an assumption that myocarditis was triggered by virus. There are no established specific treatment options for viral myocarditis. BICC (Beta-Interferon in Chronic Viral Cardiomyopathy) trial showed that antiviral therapy with interferon-beta may significantly reduce viral load in the myocardium but complete elimination of virus was not achieved, although patients NYHA functional class has improved (16).

There is evidence that early use of mechanical circulatory support in combination with proper medical therapy may prevent development of cardiomyopathy in these patients (17–19). In our case the patient suffered both left and right ventricular dysfunction that required left and right VAD insertion. A faster option to VAD could be extracorporeal membra-

ne oxygenation (ECMO), allowing oxygenation support through peripheral access. In our case, because of patient's obesity a decision to sternotomy and VAD insertion was made instead of peripheral ECMO.

Prognosis of myocarditis depends on causing agent and severity of heart damage. Overall mortality rates vary. The Myocarditis Treatment Trial showed a 20% mortality rate at 1.0 year and a 56% mortality rate at 4.3 years (11). These results are similar to the Mayo Clinic's observational data of 5-year survival rates that is nearly 50% (20). There are series of complications related to VAD implantation, including driveline infection (7–47%) (21), major bleeding (up to 50%) (22) and thromboembolism (> 20%) (23). Appropriate anticoagulation therapy, usually with heparin, for these patients is essential. Up to 10% of post-cardiac surgical patients suffer from heparin-induced thrombocytopenia (HIT) (24). Two types can be distinguished, but type II is more severe. Unfortunately, our patient was diagnosed with type II thrombocytopenia (HIT II), an immune-mediated syndrome caused by an antibody to the PF4/heparin complex. It is characterized by decreasing platelet counts beginning 5 to 14 days after heparin exposure and in 50% of cases leads to devastating arterial and venous thrombotic complications such as limb ischemia, deep venous thrombosis, cerebral sinus thrombosis and pulmonary embolism. In patients with implanted VAD it can lead to pump thrombosis. Our patient's platelet count (PLT) dropped from $160 \times 10^9/l$ to $26 \times 10^9/l$ within days. After discontinuation of heparin PLT increased to $54 \times 10^9/l$ on the first and was $94 \times 10^9/l$ on second non-heparin day. Alternative anticoagulants for these patients could be direct thrombin inhibitors (lepirudin, bivalirudin and argatroban) and selective factor Xa inhibitors (fondaparinux and danaparoid) (25). According to the literature, therapeutic ranges of anti-Xa levels vary between 0.5 to 1.5 IU/ml (26, 27). We have chosen a starting dose of 5.0 mg/day anticipating a possible accumulation because of renal insufficiency. The patient experienced a late bleeding episode (at sixth day after insertion of VAD) that required re-ex-

ploration and likely to be associated to the daily dose of fondaparinux (anti-Xa level was 1.5 IU/ml). After this incident we have decided to keep anti-Xa levels between 0.5 and 0.8 IU/ml. Further management with fondaparinux was successful.

Conclusion

We have described the case when a patient suffering from acute myocarditis complicated by HIT II was successfully treated with both left and right VAD and selective factor Xa inhibitors. The initial presentations of acute myocarditis could be lethal but an adequate mechanical support has proved an excellent outcome. Our patient was discharged out of the hospital in good health condition.

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