Recurrent Fulminant Myocarditis Revealing a Pheochromocytoma

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Abstract

Introduction: Pheochromocytoma is a rare etiology of fulminant myocarditis. It is however a curable tumor in which surgical ablation spares patients from dreadful cardiac complications.

Case report: We report the case of a 61-year-old patient, with a pheochromocytoma, documented by pathologic examination and revealed by recurrent fulminant myocarditis.

Conclusion: It is advisable to search for pheochromocytoma in case of a non-explained and a fortiori recurrent myocarditis. Given its curability, potentially fatal complications could possibly be avoided after surgical treatment.

Keywords: Pheochromocytoma; Myocarditis; Cardiogenic shock

Abbreviations: AB: Anti-Bodies ; CPK: Creatine Phosphokinase; CRP: C Reactive Protein; ECG: Electrocardiogram; LV: Left Ventricle; LVEF: Left Ventricle Ejection Fraction; MIBG: Methyl-Iodo-Benzyl-Guaindine; MR: Mitral Regurgitation; MRI: Magnetic Resonance Imaging; PCR: Polymerase-Chain-Reaction; TTE: Trans-Thoracic Echocardiography

Introduction

Acute myocarditis is commonly induced by various infections, toxins, drug reactions and autoimmune diseases. Pheochromocytoma is a rare but curable etiology. The diagnosis of pheochromocytoma, called the "great imitator", is definitely one of the most challenging diagnoses as it can mimic a wide range of presentations. Making this diagnosis can in fact avoid potentially fatal complications. We report the case of a 61-year-old woman in whom the recurrence of fulminant myocarditis revealed a pheochromocytoma.

Case Report

A 61-year-old woman was referred to our center on April 2009 for acute chest pain suggestive of angina. Her previous medical history was significant for type 2 diabetes and systemic hypertension evolving since 2007. She reported flu-like syndrome 15 days before the onset of current symptoms. Electrocardiogram (ECG) at presentation revealed 2 mm ST-segment depression in inferior, apical and lateral leads and premature ventricular beats (Figure 1). Troponin and Creatin-Phospho-Kinase Levels (CPK) were increased and amounted respectively to 23 ng/ml and 495 UI/l. C-reactive protein (CRP) level was inferior to 5 mg/l. Coronary angiography performed at the seventh hour of onset of symptoms showed normal and patent coronary arteries. We did not perform left ventriculography because of high left ventricular end-diastolic pressure (20 mmHg). One hour later, our patient presented rapid deterioration of both hemodynamic and respiratory status justifying her referral to intensive care unit. Cardiogenic shock was confirmed by hemodynamic study performed in the resuscitation department by PiCCO’ monitoring. She received Dobutamine and Furosemide and underwent non-invasive ventilation. Trans-thoracic echocardiography (TTE) performed on the first day (under Dobutamine 10 µg/kg/min) has shown impaired left ventricular systolic function (left ventricular ejection fraction (LVEF)=45%), diffuse hypokinesia, and a moderate functional mitral regurgitation (MR). Clinical course was favorable; Furosemide and Dobutamine were respectively withdrawn on the second and fifth day of hospital stay. Fulminant myocarditis was strongly suspected even if cardiac magnetic resonance imaging, performed later at the ninth day, didn't draw evidence supporting this diagnosis. Control ECG was normal. Control echocardiography (at thirteenth day of hospital stay) showed restitution ad integrum of cardiac function with estimated LVEF at 65%. The patient was discharged with oral Captopril and Atenolol.

On April 2012, she was readmitted with a similar clinical presentation with acute chest pain mimicking acute coronary syndrome and rapid worsening of hemodynamic status, shock and pulmonary edema. We noted on the ECG 2 mm ST-segment depression in apico-lateral leads. Troponin, CPK and CRP levels amounted respectively to 16 ng/ml, 197 UI/l and 4.9 mg/l respectively to 23 ng/ml and 495 UI/l.

Echocardiography performed on the first day of hospitalization showed left ventricular systolic dysfunction (LVEF=45%), diffuse hypokinesia and moderate mitral regurgitation. The patient was referred to the Department of Endocrinology for possible diagnosis of pheochromocytoma.

On June 2013, she was referred to our center for second opinion. She was admitted with hypertension, headaches and palpitations. She reported a similar clinical presentation with acute chest pain. The patient was referred for insertion of a permanent pacemaker for bradycardia. On May 2014, she was readmitted for severe headache, palpitations and syncope. She underwent exploratory laparotomy and revealed a pheochromocytoma. The tumor was removed surgically without complications. The patient was discharged with normal blood pressure and stable clinical and hemodynamic status.

Discussion

Fulminant myocarditis is a rare but curable etiology. It is however a life-threatening disease if left untreated. The diagnosis of pheochromocytoma, termed the "great imitator", is definitely one of the most challenging diagnoses as it can mimic a wide range of presentations. Making this diagnosis can in fact avoid potentially fatal complications. We report the case of a 61-year-old woman in whom the recurrence of fulminant myocarditis revealed a pheochromocytoma.

Conclusion

Fulminant myocarditis is a rare but curable etiology of myocarditis. Given its curability, potentially fatal complications could possibly be avoided after surgical treatment.
to 1.15 ng/ml, 350 UI/l and 6.2 mg/l. On TTE, LVEF was estimated at 30% and diffuse hypokinesis and grade 1 MR were noted. Likewise, recurrent myocarditis was suspected and clinical course was also good after a medical management similar to that of previous hospitalization. LVEF improved to 58% at the ninth day of hospitalization. Oral treatment was compound of Bisoprolol and Captopril. Magnetic resonance imaging (MRI), performed at day sixteen, was normal. Etiological investigations for cardiotropic viruses (Coxackie A/B, Lyme's disease, measles, rubella, herpes zoster virus, hepatitis B and C infections and HIV infection), thyroid function and immunologic disorders (anti-nuclear anti-bodies (AB), anti-DNA AB, rheumatoid factor, anti-ANCA AB and anti-thyroperoxydase AB) were negative. Careful questioning revealed not only a history of pheochromocytoma triad symptoms (paroxysmal headache, palpitations and sweating) but also several consultations in the emergency department between 2009 and 2012 for hypertensive crisis in which treatment frequently led to severe hypotension and pre-syncpe. During hospital stay, orthostatic hypotension and hypokalemia were documented. Pheochromocytoma was finally confirmed by imaging examinations; abdominal computed tomography scan revealed 4 × 3 cm contrast enhancing left adrenal nodule without area of calcifications or necrosis (Figure 2). Although methoxylated derivatives assays (admittedly performed once) were negative, the diagnosis of secreting pheochromocytoma was almost certain given the clinical data (urinary Normetanephrin Metanephrin and 3-Methoxytyramin concentrations amounted respectively for 450, 79 and 130 nmol/mmol creatinin). Methyl-iodo-benzyl-guanidine (MIBG) scintigraphy overruled extra-adrenal localizations (Figure 3). Multiple endocrine neoplasia was also ruled out owing to biological findings (normal phosphocalcic, parathormone and thyroid levels). The patient was referred in July 2012 to a department of urologic surgery and underwent left adrenalectomy with a favorable issue. At 1 and 6-month follow-up, the patient was asymptomatic and had normal physical examination and normal ECG and echocardiography.

Discussion

Viral or catecholamine-induced fulminant myocarditis?

The context of flu-like syndrome and the absence of any alternative diagnoses supported the etiological hypothesis of viral myocarditis in 2009. Since viral infections were responsible for almost cases of recurrent myocarditis [1,2], this hypothesis was also initially privileged to explain the recurrent fulminant myocarditis three years later. However, given the normality of biological investigations (mentioned above and certainly not-exhaustive) on one hand, and the discovery of valuable anamnestic data evocative of pheochromocytoma on the other hand, catecholamine-induced fulminant myocarditis was then strongly suspected.

Regarding pathophysiology, viral and pheochromocytoma related myocarditis are fundamentally different although both of them lead to the same end result: myocardial injury. While viral myocarditis evolves in three stages consisting of viral invasion, auto-immune process and potentially late myocardial remodeling, pheochromocytoma-related cardiomyopathy is rather due to toxic effect of increased catecholamine release.

This latter mechanism was described since 1966 based upon autopsy findings in 26 deceased patients having pheochromocytoma. Pathology data consisted of focal degeneration of myocardial fibers, inflammatory infiltrates and band myocardial necrosis. In order to explain the pathogenic effect of excessive levels of catecholamine, three hypotheses have been proposed:

- Ischemia induced by epicardial coronary artery spasm, however it has seldom been documented and regional ST segment elevation on ECG and kinetic abnormalities are rather rare (usually many myocardial territories are affected at the same time) [3].
- Microvasculature spasm [4].
- And direct myocardial toxicity of catecholamine mediated by increased release of free radicals and increased myocardial inflow of calcium leading to myocyte dysfunction [5].

Pheochromocytoma-related fulminant myocarditis is also called stress-induced myocardiopathy which is caused by brutal and massive release of high amounts of catecholamine probably responsible for a kind of myocardial "sideration". Only few cases of pheochromocytoma-related myocarditis have been reported (Tables 1 and 2) [3,6-13].
This entity is extremely rare so that “real” incidence cannot be accurately determined. Among 119 adrenalectomies performed by Vandwalle et al. [13], between 1998 and 2009, 19 cases were in relation to pheochromocytoma among which three presented with cardiogenic shock and fulminant myocarditis. The scarcity of this disease may be due to the rarity of the tumor itself. However, the absence of specific signs of pheochromocytoma-related cardiomyopathy may lead to frequent misdiagnosis and then to underestimation of its real incidence. However, features associating loud cardio-respiratory symptomatology, labile systemic hypertension and acute abdominal pain are highly suggestive of pheochromocytoma. In case of pseudo surgical abdominal pain, complications like tumor necrosis and intratumor hemorrhage have to be carefully eliminated.

Methoxylated derivatives assays were highly positive in all cases mentioned in Table 1 except for those who died in the first days of hospital stay.

Table 1: Reported cases of pheochromocytoma-related cardiomyopathy.

<table>
<thead>
<tr>
<th>References</th>
<th>Sex/Age</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
<th>Autopsy/pathology findings</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sardesai [6]</td>
<td>F 44</td>
<td>Pulmonary edema</td>
<td>Right AP healthy coronary arteries</td>
<td>Death in about 12 h</td>
<td></td>
</tr>
<tr>
<td>Baratella [7]</td>
<td>F 25</td>
<td>Syncope and pre-syncope</td>
<td>Left AP</td>
<td>Restitution ad integrum of cardiac function three months after adrenalectomy</td>
<td></td>
</tr>
<tr>
<td>Mootha [8]</td>
<td>F 34</td>
<td>Thoracic oppression</td>
<td>Right AP</td>
<td>Restitution ad integrum of cardiac function three months after adrenalectomy</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Reported cases of pheochromocytoma-related cardiomyopathy.

<table>
<thead>
<tr>
<th>References</th>
<th>Sex/Age</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
<th>Autopsy/pathology findings</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouchikhe [9]</td>
<td>M 23</td>
<td>Cardiogenic shock</td>
<td>Left adrenalectomy and partial right adrenalectomy</td>
<td>Hospital discharge at day 101</td>
<td></td>
</tr>
<tr>
<td>Vahdat [10]</td>
<td>M 54</td>
<td>Acute respiratory failure</td>
<td>Left AP</td>
<td>Restitution ad integrum at day 11 of hospital stay</td>
<td></td>
</tr>
<tr>
<td>Sanchez [3] Recalde</td>
<td>F 41</td>
<td>Headaches, Nausea and vomiting, Acute respiratory failure</td>
<td>Right AP</td>
<td>LVEF =55% 14 days after adrenalectomy</td>
<td></td>
</tr>
<tr>
<td>Tetelin [11]</td>
<td>F 29</td>
<td>Heart failure</td>
<td>Right adrenalectomy</td>
<td>Normal cardiac function at three months of discharge</td>
<td></td>
</tr>
<tr>
<td>Deltreuil [12]</td>
<td>M 66</td>
<td>Abdominal pain</td>
<td>Left adrenalectomy</td>
<td>Normal physical examination - discharge 10 days after adrenalectomy</td>
<td></td>
</tr>
<tr>
<td>Vandwalle [13]</td>
<td>F 37</td>
<td>Abdominal pain</td>
<td>Right AP</td>
<td>Restitution ad integrum of cardiac function -hospital discharge 8 days after adrenalectomy</td>
<td></td>
</tr>
<tr>
<td>Vandwalle [13]</td>
<td>M 41</td>
<td>Hypertensive crisis</td>
<td>Healthy coronary arteries</td>
<td>Hospital discharge 14 days after adrenalectomy -normalization of cardiac, liver and renal functions</td>
<td></td>
</tr>
</tbody>
</table>

AP: Adrenal Pheochromocytoma; ECG: Electrocardiogram; F: Female; LEVF: Left Ejection Ventricular Fraction; M: Male; NP: Not Given
24 hours), thereby affirming the secreting nature of the tumor. In fact, it was confirmed that this testing provides a most interesting diagnostic tool. Its specificity and sensitivity are around 90% and 99% respectively. Moreover, methoxylated derivatives production is independent of the intermittency or intensity of tumor secretion making these assays thoroughly reliable with an excellent predictive value. Despite those testing were negative in our patient, the diagnostic of secreting pheochromocytoma was almost certain. In our case, they were considered as false negative which may represent a rare but not impossible situation.

An association between viral myocarditis and pheochromocytoma-related cardiomyopathy remains possible, as viral serological tests were not exhaustive. To make the difference, endomyocardial biopsy would be of a great help as it allows pathology study coupled to immunohistochemistry test (searching viral genomes by polymerase-chain-reaction).

Are MRI findings in case of fulminant myocarditis different from those usually observed in case of acute myocarditis?

Cardiac MRI is one the most interesting non-invasive tools available for the diagnostic workup of myocarditis. Ought to its unique potential for tissue characterization, Cardiac MRI can evaluate three markers of tissue injury; intracellular and interstitial edema, hyperemia and capillary leakage, and necrosis and fibrosis. The diagnostic accuracy reaches 78% based on Lake Louise criteria [14] when two imaging MRI criteria or more are present; it drops to 68% when only late Gadolinium enhancement is present.

On two occasions, no signs on cardiac MRI that could support myocarditis were retrieved. This is consistent with MRI findings in fulminant myocarditis, which are quite different of those in classical acute myocarditis. According to a recent study regarding MRI results in case of fulminant myocarditis caused by H1N1 virus infection, edema (in T2-weighted images) was the sole anomaly [15]. Similar findings were noted in many other cases of fulminant myocarditis regardless of etiology (herpes zoster virus, phenytoin-induced lupus) [16-17]. The importance of myocardial edema might explain the quick installation of cardiac failure. In the same vein, restitution ad integrum could possibly be explained by the absence of late or early post-gadolinium enhancement.

Conclusion

Pheochromocytoma should be looked for in case of a non-explained and a fortiori recurrent myocarditis. Given its curability, potentially fatal complications could possibly be avoided after surgical treatment.

References