Massive Cardiac Thrombosis in a Patient with Sheehan’s Syndrome

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Abstract. Growth hormone deficiency (GHD) is a risk factor for increased cardiovascular disease, and it has been recently demonstrated that abnormalities in coagulation system might contribute to the increased cardiovascular morbidity and mortality. However, there is not enough data related to the major thrombotic events in GH-deficient patients. We describe the case of a 62-year-old woman with Sheehan’s syndrome who developed massive cardiac thrombosis. She was hospitalized with acute pulmonary edema. ECG revealed high ventricular responsive atrial fibrillation (AF) and T-wave inversion on precordial leads. The ejection fraction of left ventricle (LVEF) was measured as 60% by transthoracic echocardiography (TTE) and there was 2nd degree mitral regurgitation with concentric hypertrophic LV walls. Transesophageal echocardiography (TEE) established thrombi both at right atrium and left atrial appendix. Before anticoagulant therapy several hemostatic and fibrinolytic markers were measured. Except increased D-dimer concentration (763.14 μg/L (0–325)) we did not observe any pathological finding in these parameters. After 14 days of discharge, the patient was admitted to the intensive care unit with upper gastrointestinal bleeding. The warfarin and salicilate were stopped for two months. At the end of two months, the patient was again hospitalized with congestive heart failure and there was a high ventricular responsive AF on ECG. TEE was performed and three thrombi were demonstrated at right atrium (RA), left atrium (LA) and left ventricle (LV). There was no active bleeding on upper GIS endoscopy and anticoagulant therapy was restarted. In this particular case massive cardiac thrombi involving three chambers (LA, RA, LV) were more extensive than expected in AF. Moreover, there was a 2nd degree mitral regurgitation in the patient, and based on previous studies mitral regurgitation has been associated with less prevalent LA spontaneous echo contrast and fewer thromboembolic events. Therefore we hypothesized that severe GHD in the present case might be the major contributing factor in massive cardiac thrombosis. In summary, based on previous data there is increased risk of thromboembolic events in GHD although the mechanism is unclear yet. Our case is the first case showing massive cardiac thrombosis in a severe GH-deficient patient with Sheehan’s syndrome. Therefore, patients with GHD should be screened carefully for thrombus in clinical practice, and further studies need to be done to understand the relation between GHD and coagulation system.

Key words: Growth hormone (GH), Growth hormone deficiency (GHD), Cardiac thrombosis, Sheehan’s syndrome, Coagulation system

THE importance of growth hormone deficiency (GHD) in adult life has become more evident over the last decade. GHD is a risk factor for increased cardiovascular morbidity and mortality [1]. The cardiovascular risk factors seen in adult GHD include reduced exercise capacity [2], altered body composition [3], insulin resistance [4], and dyslipidemia characterized by increased LDL and decreased HDL cholesterol levels [5]. It has been recently demonstrated that abnormalities in coagulation system might contribute to the increased cardiovascular morbidity and mortality [6, 7]. However, there is not enough data related to the major thrombotic events in GH-deficient patients.

Sheehan’s syndrome is a clinical condition due to
postpartum necrosis of the anterior pituitary gland after massive bleeding. It is still a serious health problem in developing countries. Postpartum pituitary necrosis, first described by Sheehan in 1937, is characterized by varying degrees of anterior pituitary dysfunction [8]. GH is one of the earliest hormones lost and the clinical features due to GHD are more severe in patients with Sheehan’s syndrome [9]. Even though GHD is a well-known feature of Sheehan’s syndrome, major thrombosis including cardiac thrombus has not been reported.

Here we report a severe GH-deficient patient with Sheehan’s syndrome who developed massive cardiac thrombus.

**Case Report**

A 62-year-old woman was admitted to the hospital because of dyspnea. In 1990 she was given a diagnosis of Sheehan’s syndrome when panhypopituitarism manifested itself after obstetrical labor 20 years earlier. Dynamic tests including TRH stimulation test, LHRH stimulation test, and insulin tolerance test (ITT) were performed in the diagnosis of panhypopituitarism (Table 1). Her clinical course had been generally stable under steroid (prednisolone) and thyroid (levothyroxine) hormone treatments. She had never been replaced by estradiol during her follow-up. She was hypertensive and her blood pressure was under control by enalapril 20 mg/day. The diagnosis of severe GH deficiency was established by insulin tolerance test (ITT) as described previously [10] (Table 1). She was on GH replacement therapy (GHRT) for two years between 1998–2000. Several parameters including some of the cardiovascular risk factors have been analyzed before and after 2 years of GHRT and on admission (Table 2).

In 2003 she was hospitalized with acute pulmonary edema. ECG revealed high ventricular responsive atrial fibrillation (AF) and T-wave inversion on precordial leads.

### Table 1. Basal and peak hormone responses after stimulation tests in the patient for diagnosis of panhypopituitarism due to Sheehan’s syndrome. ITT (cortisol and GH response), LHRH (100 μg iv; FSH and LH response) and TRH (200 μg iv; TSH and prolactin response)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basal</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (μg/dl)</td>
<td>4.83</td>
<td>7.94</td>
</tr>
<tr>
<td>GH (mIU/l)</td>
<td>0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>FSH (mIU/l)</td>
<td>1.84</td>
<td>1.86</td>
</tr>
<tr>
<td>LH (mIU/l)</td>
<td>1.61</td>
<td>1.63</td>
</tr>
<tr>
<td>TSH (μIU/ml)</td>
<td>1.26</td>
<td>2.4</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>6.4</td>
<td>13.3</td>
</tr>
</tbody>
</table>

- Peak cortisol response lower than 20 μg/dl is accepted as cortisol deficiency.
- Peak GH response lower than 6 mIU/l is accepted as severe GH deficiency.
- Peak FSH/LH response lower than two fold increase is accepted as gonadotrophin deficiency.
- Peak TSH response lower than 5 μIU/ml is accepted as TSH deficiency.
- Peak prolactin response lower than 20 ng/ml is accepted as prolactin deficiency.

### Table 2. Parameters evaluated before and after 2 years of GHRT, and on admission

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before GHRT</th>
<th>During GHRT (2 years of GHRT)</th>
<th>On admission*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mmHg)</td>
<td>140/80</td>
<td>130/80</td>
<td>150/100</td>
</tr>
<tr>
<td>BMI</td>
<td>27.2</td>
<td>28</td>
<td>28.5</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>104</td>
<td>98</td>
<td>106</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>1.1</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>84</td>
<td>96</td>
<td>103</td>
</tr>
<tr>
<td>Na</td>
<td>145</td>
<td>146</td>
<td>141</td>
</tr>
<tr>
<td>K</td>
<td>3.9</td>
<td>3.8</td>
<td>4.5</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>15</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.1</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>IGF-I</td>
<td>9</td>
<td>318</td>
<td>20</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>250</td>
<td>210</td>
<td>236</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>185</td>
<td>133</td>
<td>167</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>44</td>
<td>65</td>
<td>51</td>
</tr>
<tr>
<td>ECG</td>
<td>Sinus rhythm</td>
<td>Sinus rhythm</td>
<td>Atrial fibrillation</td>
</tr>
</tbody>
</table>

* 3 years after the cessation of GHRT
leads. Except mild dyslipidemia, biochemical values were normal on admission (Table 2). Under thyroid therapy (100 μg/day) she was euthyroid, and under prednisolone therapy (7.5 mg daily; 5 mg in morning and 2.5 mg in evening) her clinical findings were stable regarding the cortisol deficiency or excess. On admission, hormone profile was as follows: free T₃, 2.37 pg/ml (1.5–3.2); free T₄, 13.89 pg/ml (8.9–17.9); TSH, 0.01 μIU/ml (0.2–4.5); FSH, 0.01 mIU/ml (23–116 at menopausal age); LH, 0.07 mIU/ml (16–54 at menopausal age); and cortisol, 8.30 μg/dl (9–23 in the morning). Additionally hemoglobin, white blood cell count, thrombocyte count, creatinine kinase (CK), CK-MB, LDH and troponin levels were all within normal reference range.

The ejection fraction of left ventricle (LVEF) was measured as 60% by transthoracic echocardiography (TTE) and there was 2nd degree mitral regurgitation with concentric hypertrophic LV walls. LV systolic diameter (LVDs) and diastolic diameter (LVDd) were 3.2 cm (normal range, 2.2–4.0 cm) and 4.5 cm (normal range, 3.8–5.6 cm), respectively. The diameter of left atrium (LA) was 4.3 cm. By TTE there was a thrombus at right atrium (Fig. 1). Transesophageal echocardiography (TEE) established thrombi both at right atrium and left atrial appendix (Fig. 2a, b).

Before anticoagulant therapy several haemostatic and fibrinolytic markers including: prothrombin time, 14.5 seconds (12–16); activated partial thromboplastin time, 26.3 seconds (23–35); International Normalized Ratio (INR), 1.05 (0.9–1.1); fibrinogen concentration, 298.1 mg/dl (146–380); antithrombin-III, 87.48% (75–125); protein C, 153.7 seconds (120–300); and protein S, 97% (60–140) activities, lupus anticoagulant activity, 33.95 seconds (30–38); anticardiolipin antibody IgG and IgM, antiphospholipid antibody IgG and IgM, and D-dimer levels were measured. Except increased D-dimer concentration (763.14 μg/L (0–325)) all the measured parameters were within normal ranges, and anticardiolipin and antiphospholipid antibodies were negative.

Initially the patient was treated with salisilate, beta blocker, unfractioned heparin and diuretics. After her clinical findings and heart rate stabilized coronary angiography was performed, which revealed a noncritical lesion (20–30%) on circumflex artery, and 2nd degree mitral regurgitation was observed at ventriculography. The patient was discharged with salisilate, beta blocker, ACE inhibitor, pituitary hormone replacement (thyroid and steroid replacement) and oral warfarin. INR was 2.02 at discharge. After 14 days of discharge, the patient was admitted to intensive care unit with upper

Fig. 1. Demonstration of a thrombus at right atrium (RA) by using transthoracic echocardiography.

Fig. 2. Demonstration of thrombi both at right atrium (RA) and left atrial appendix (LAA) by using transesophageal echocardiography.
gastrointestinal bleeding. The warfarin and salicylate were stopped for two months.

At the end of two months, the patient was again hospitalized with congestive heart failure and there was high ventricular responsive AF on ECG. TEE was performed and three thrombi were demonstrated at RA, LA and LV (Fig. 3a, b), and again 2nd degree mitral regurgitation was established. There was no active bleeding on upper GIS endoscopy and anti-coagulant therapy was restarted.

**Discussion**

The most common causes of adult GH deficiency are pituitary tumors and their treatment [11]. Sheehan’s syndrome is still a serious health problem in some developing countries and is characterized by varying degrees of anterior pituitary dysfunction [9]. We have previously reported that 56.2% of patients with Sheehan’s syndrome had panhypopituitarism and 43.8% had selective pituitary insufficiency; all the patients had severe GHD [12, 13]. In our particular case with Sheehan’s syndrome, severe GHD was well established by ITT (Table 1). Before GHRT she had abdominal obesity (high waist circumference), increased total and LDL-cholesterol levels and low HDL-cholesterol levels. She was overweight according to BMI, but it is known that abdominal or central obesity predicts subsequent coronary artery disease better than body BMI [14]. After 2 years of GHRT these parameters related to cardiovascular risk factors were improved. However, three years after the cessation of GHRT (on admission) waist circumference, total and LDL-cholesterol levels were increased, and HDL-cholesterol level was decreased (Table 2). In accordance with previous studies [1, 5] the present findings clearly demonstrated that GHD is related to increased cardiovascular risk factors, and that GHRT may have beneficial effects on these risk factors. Additionally by coronary angiography we have proved the presence of mild coronary artery disease in the patient.

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, accounting for approximately one third of hospitalizations for cardiac rhythm disturbance. The prevalence of AF is estimated as 0.4% of the general population, and it increases with age [15]. AF is often associated with structural heart disease including valvular heart disease, coronary artery disease and hypertension [16]. Prevalence of intra-cardiac thrombus is increased in AF but thrombus associated with AF arises most frequently in the left atrial appendage (LAA), which cannot be regularly examined by TTE [17]. Serial TEE studies of the LA [18] and LAA [19] have demonstrated reduced flow velocities related to loss of organized mechanical contraction during AF. This substrate of decreased flow within the LA/LAA has been associated with spontaneous echo contrast, thrombus formation and embolic events [20]. In our particular case massive cardiac thrombi involving three chambers (LAA, RA, LV) were more extensive than expected in AF. Moreover, there was a 2nd degree mitral regurgitation in the patient, and based on previous studies increased flow within the LA in patients with mitral regurgitation has been associated with less prevalent LA spontaneous echo contrast [21, 22] and fewer thromboembolic events, even in the presence of LA enlargement [23]. Therefore we hy-

![Fig. 3](image-url)

**Fig. 3.** Demonstration of three thrombi at right atrium (RA), left atrium (LA) and left ventricule (LV) by using transesophageal echocardiography.
pothesized that severe GHD in the present case might be the major contributing factor in massive cardiac thrombosis. Although GHD was more likely the reason for the cardiac thrombosis in this particular case, this was not the only major reason. Underlying atrial fibrillation might be the other additional contributing factor.

Alterations of fibrinolytic and coagulation systems might contribute to the increased thromboembolic events in patients with GH deficiency [7]. A small number of studies have shown higher levels of plasminogen activator inhibitor activity (PAI-1), fibrinogen, and tissue plasminogen activator antigen (tPA) in GH-deficient patients compared to controls [7, 24, 25]. This decrease in fibrinolytic activity may contribute to an increased atherothrombotic propensity. However, there is only one study reporting a massive thrombus at inferior vena cava in a GH-deficient patient with Sheehan’s syndrome [26].

In contrast, GH replacement for 2 years in 17 patients induced a reduction in PAI-1 activity and tPA [6]. One year of GH replacement in 15 GH-deficient patients also led to significant reductions in cytoadhesive molecules such as soluble E (sE)-selectin and sP-selectin (the products of activated platelets and endothelial cells, reported to predict progression of peripheral atherosclerosis) [27] and intercellular adhesive molecule 1 (ICAM 1) [28]. These results suggest that GH may have a protective effect on the vascular endothelium. In our case we analyzed several fibrinolytic and hemostatic markers except PAI-1 activity and tPA. All the markers that we measured were normal, but D-dimer level was high which is an indirect marker of the thrombus. Previous data clearly demonstrate that there is an increased risk of thrombosis in GH-deficient patients, but the mechanism of the relation between GH and coagulation system remains to be clarified.

In summary, based on previous data there is increased risk of thromboembolic events in GHD although the mechanism is unclear yet. This case is the first showing a massive cardiac thrombosis in a severe GH-deficient patient with Sheehan’s syndrome. Therefore, patients with GHD should be screened carefully for thrombus in clinical practice, and further studies need to be done to understand the relation between GH and coagulation system.

References

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