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Case report

Rosiglitazone-induced anasarca without heart failure: capillary leakage?

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ABSTRACT

Severity of thiazolidinedione (Rosiglitazone)-induced fluid retention is linked almost exclusively to cardiac decompensation. We here report a 68-year old female with type 2 diabetes mellitus, in whom a life-threatening (anasarca type) acute pulmonary edema, induced by rosiglitazone plus insulin therapy, occurred without any evidence of left ventricular systolic or diastolic dysfunction. It seems that thiazolidinedione-induced severe edema does not have to be the result of acute congestive heart failure. These agents have been shown to increase vascular permeability in experimental models. Thus, the recommendation of only cardiac monitoring in pulmonary edema, associated with thiazolidinediones, should be reconsidered.

Key words: Anasarca, Diabetes mellitus, Heart failure, Insulin, Pulmonary edema, Rosiglitazone, Thiazolidinediones

INTRODUCTION

Fluid retention and plasma volume expansion are well known adverse effects of thiazolidinedione therapy.[1] Peripheral edema occurs in 2-5% of patients on thiazolidinedione (TZD) monotherapy, and 5-15% when TZD is combined with insulin.[1,2]

During the premarketing clinical trials of rosiglitazone and pioglitazones, the cases with moderate and/or severe congestive heart failure (New York Heart Association Class-III and Class-IV) were excluded; hence these drugs are not recommended for patients with moderate or severe symptomatic heart failure.[2] On the other hand, sufficient evidence does not exist regarding the cardiac safety of these drugs in asymptomatic heart failure or in cases without prior history of congestive heart failure.

The European Agency for the Evaluation of Medicinal Products considers insulin therapy as a contraindication to the use of thiazolidinediones.[1] However, the recent consensus statement by the American Heart Association and the American Diabetes Association does not prohibit the use of thiazolidinediones in combination with insulin and considers anasarca in such situations to result from an aggravation of pre-existing congestive heart failure.[2]

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We herein present a 68-year old female patient with type 2 diabetes mellitus who developed anasarca following addition of rosiglitazone to on-going insulin therapy despite preserved systolic and/or diastolic cardiac function.

PATIENT'S DESCRIPTION

A 68-year old woman was admitted to the emergency department with shortness of breath, orthopnea and paroxysmal nocturnal dyspnea. The symptoms initially mild, had started 3 weeks previously.

The patient had a 24-year history of type 2 diabetes mellitus (T2DM), diabetic background-retinopathy, microalbuminuria, diabetic neuropathy, previous thrombo-embolic cerebrovascular accident without any sequelae and had been on conventional insulin therapy for the past 16 years. She also had a 19-year history of hypertension. She had no history of either arrythmia or an established and/or symptomatic heart failure up to her present emergency admission. Her daily insulin requirement had gradually increased throughout follow-ups. Despite compliance with nutritional therapy, her fasting blood glucose levels remained above 10 mmol/L and her HbA_{1c} level was at 8.8%. Five months before her recent admission to the emergency department, she was 1.55 m in height and 78 kg in weight, with a body mass index of 32.5 kg/m^2. She was on a diabetic diet of 15 kcal/kg and her conventional insulin regimen consisted of 68 U neutral protamine Hagedorn (NPH) insulin and 12 U regular insulin in the morning and 48 U NPH insulin and 10 U regular insulin in the evening. Her post-prandial blood glucose levels remained between 11.9 and 14.1 mmol/L, prompting the initiation of combination therapy with an insulin-sensitizer. Rosiglitazone 4mg once daily in the morning was initiated, and increased to 4mg twice daily on the 62th day. On the 97th day of rosiglitazone therapy, she presented with shortness of breath and decreased effort capacity. She had no history of smoking. A chest X-ray revealed a peripheral opacity on the right lung and a computerized tomography of the thorax revealed a consolidation in the superior lobe of the right lung, a few millimeters of parenchymal nodules and a slight widening of the main pulmonary artery. She was given clarythromycin 500mg twice daily on the clinical diagnosis of community-acquired atypical pneumonia for 14 days. The microbiological confirmation was unavailable due to lack of sputum. On her visit on the 103rd day of rosiglitazone-start, insulin dosage was decreased to 52U NPH and 8U regular insulin in the morning and 40U NPH and 6U regular insulin in the evening. She complained of nocturnal hypoglycemia symptoms and the rosiglitazone dose was decreased to 4mg once daily. However, 30 days later (on the 133rd day of rosiglitazone start), she was admitted to the emergency department with recurrent respiratory symptoms as described above. Upon admission, on-going medications were as follows: insulin, rosiglitazone, salisylate and atorvastatine.

On this admission, the body temperature was 36.4 ^{o}C and the pulse was rhythmic at a rate of 77 bpm. Respiratory rate was 26/min and blood pressure was 140/70mmHg. Central cyanosis was present. Chest auscultation revealed bilateral crackles up to the middle lung fields. She also had bilateral peripheral pitting edema.

A complete blood count revealed a hemoglobin level of 10.8 g/dl and white blood cell and platelet counts of 8900/mm^3 and 295000/mm^3, respectively. The blood glucose was 4.5 mmol/L, with normal liver enzymes and kidney function tests, and there was no macroalbuminuria. A chest X-ray showed bilateral reticular non-homogenous perihilar infiltrates and signs of bilateral pleural effusion. Initial ECG and cardiac enzymes were normal. On arterial blood gas analysis pH was 7.369, with PCO_2 of 58 mmHg and 89% O_2 saturation. An echocardiogram revealed an ejection fraction of 64% and preserved diastolic functions with 1^0 mitral regurgitation at the time of anasarca diagnosis, which was comparable to an echocardiogram carried out 3 years previously with an ejection fraction of 68%.

Cardiogenic pulmonary edema treatment was initiated with intravenous furosemide and rosiglitazone was discontinued. Nasal oxygen was administered.

By the end of her 17-day hospitalization with daily diuretic treatment and water restriction she had lost 4 kilograms. There was a marked improvement in her effort capacity with complete resolution of her orthopnea and paroxysmal nocturnal dyspnea as well as for her hypoxia. Hemoglobin level was increased up to 13.1 g/dl.

Metformin 850 mg twice daily was added to the insulin regimen upon complete remission of her hypervolemia. The presence of congestive heart failure is a well-known contraindication to metformin therapy, but because the patient had no cardiac dysfunction, metformin was administered as an adjunctive therapy.

One month after discharge from the hospital her echocardiogram revealed no abnormality, except for a 1^0 mitral regurgitation. The patient has remained well and has not developed any new cardiac/respiratory sign or symptom for the following 16 months while on insulin plus metformin, salicylate, quinaprile and simvastatin therapy. In order to exclude the possibility of a silent ischemia, a myocardial perfusion scan with 201-Thallium was obtained at the 13th month, which revealed no major perfusion defect.

DISCUSSION

The case we herein present developed anasarca (peripheral plus pulmonary edema) 133 days after starting rosiglitazone in combination with insulin. During the clinical presentation of anasarca, left ventricular systolic functions were still preserved. Additionally, except for a mild mitral regurgitation, there was no abnormality in echocardiogram including diastolic function. Thus, the patient developed anasarca, which does not seem to be of cardiac origin. Her hypervolemia induced by insulin plus rosiglitazone was not surprising, but anasarca including pulmonary edema, despite normal left ventricular function, is not a well-known entity.

Since 1999, including the premarketing clinical trials, several cases presented edema due to congestive heart failure (CHF) while on thiazolidinedione.[1-5] The underlying mechanism of thiazolidinedione-induced CHF seems to be an increased retention of water and sodium, and the resulting edema depends on the status of background cardiac function.[3,6] Hence, other mechanisms not related to cardiac function, such as altered endothelial permeability and peroxisome proliferator-activated receptor-γ-mediated expression of vascular permeability growth factor, could also contribute to the development of edema.[1-3] The latter mechanisms suggest a role for capillary leakage, which is not related to the cardiac function.[7] In support of this, two cases of anasarca (on troglitazone therapy) and two additional cases of only peripheral edema (on rosiglitazone therapy) with normal cardiac function, as well as two cases of anasarca (rosiglitazone and pioglitazone) with only diastolic dysfunction (but not systolic dysfunction) have been reported in the literature.[4,8-10] To the best of our knowledge, this is the first report of life-threatening acute pulmonary edema associated with normal left ventricular function related to rosiglitazone therapy.

Our patient developed an anasarca 36 days after the –microbiologically unproven diagnosis of community– acquired atypical pneumonia. Cheng et al have reported a similar but more severe case involving anasarca and adult respiratory distress syndrome (ARDS) of a subject on insulin plus pioglitazone therapy.[10] All the cultures including respiratory secretions remained negative during their patients' hospitalization.[10] ARDS is characterized by increased permeability of the alveolar-capillary membrane and the accumulation of protein-rich pulmonary edema.[11] It is thus possible to speculate that a previous and/or concurrent inflammatory process in the lung parenchyma during thiazolidinedione therapy could precipitate the pulmonary edema, despite preserved cardiac functions, against a hypervolemic background. Furthermore, the lung-injuring potential of thiazolidinediones in a given subpopulation of type 2 diabetics requires further research.

Insulin itself has also been implicated in causing localized or, rarely, generalized edema.[12] Kalambokis et al recently reviewed the clinical characteristics of insulin edema through reported cases or small-numbered series (Table 1).[12] Because of the resolving and subsequently non-relapsing course of the anasarca, despite on-going insulin therapy, we have

Table 1. Clinical risk factors for insulin edema#

Age	20-40 years
Type of Diabetes	Type 1
Glycemic control	Poor >strict
Nutritional status	Malnutrition
Diabetic duration	New-onset diabetes
Duration of insulin therapy (mean)	9.2 years
In Insulin dosage	High dose >low dose

#Adapted from Kalambokis et al[12]

not proposed the insulin therapy as being the cause of edema in our patient.

As has recently been documented in a meta-analysis, thiazolidinedione-induced edema is not a rare entity.[13] Our case suggests that the pulmonary edema induced by rosiglitazone plus insulin therapy cannot be attributed to cardiac decompensation alone. In fact, a capillary-leakage syndrome-like phenomenon could contribute to thiazolidinedione-associated edema. As the presence and/or possibility of capillary leakage syndrome in our report comprises merely a retrospective comment, pulmonary artery catheterization for the measurement of capillary wedge pressure (PCWP) has not been performed. We nonetheless propose that rosiglitazone should not be combined with insulin, especially in elderly patients with lung injury even with normal cardiac function, and that further monitoring tools –other than echocardiography– are warranted to evaluate such a life-threatening complication. Specifically, in cases of anasarca on thiazolidinedione therapy, PCWP measurements should be obtained to document whether or not the underlying mechanism is capillary leakage.

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