Atypical Presentation of Anti-Retroviral Therapy Induced Lactic Acidosis As Acute Right Ventricular Failure And Severe Pulmonary Hypertension

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CASE REPORT

Atypical Presentation Of Anti-Retroviral Therapy Induced Lactic Acidosis as Acute Right Ventricular Failure And Severe Pulmonary Hypertension

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Abstract:

Background:
Lactic acidosis of any etiology is associated with poor prognosis and often fatal. The survival in lactic acidosis depends on the ability to identify and remove the cause and managing organ perfusion. Nucleoside Reverse Transcriptase Inhibitors (NRTIs), which are used widely in the treatment of Human Immune Deficiency Virus (HIV) infection, are known to cause life-threatening Type B lactic acidosis.

Case Presentation:
Severe lactic acidosis can cause organ failure, especially in respiratory and cardiovascular systems. However, the role of acute lactic acidosis in these organ failures is mostly suggested by experimental studies in animals or in vitro, as few clinical studies in humans are available. Acidosis elevates pulmonary vascular resistance, giving rise to pulmonary hypertension and peripheral vasodilation with an associated fall in blood pressure and systemic hypotension. Although lactic acidosis presenting as abdominal pain, vomiting, and pancreatitis have been reported in persons receiving antiretroviral therapy, the presentation as acute right heart failure has rarely been documented in the literature. We report a case of severe metabolic and lactic acidosis in a patient receiving stavudine and lamivudine, with a rare and atypical presentation as acute right heart failure and severe pulmonary hypertension.

Conclusion:
This case emphasizes the need to consider lactic acidosis as a potential cause in patients presenting with acute unexplained right heart failure and severe pulmonary hypertension.

Keywords: Acute RV failure, Type B lactic acidosis, ART induced lactic acidosis, Severe pulmonary hypertension, Nucleoside reverse transcriptase inhibitors, HIV.

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1. INTRODUCTION

Lactic acidosis is defined as serum lactate levels >4 mmol/L and lactate levels >7 to 8 mmol/L are associated with poor prognosis and often fatal [1]. Cohen and Woods broadly classified Lactic acidosis as Type A and Type B based on primary hypoxic or non-hypoxic causes, respectively. Type A lactic acidosis results from hypoxia and poor tissue perfusion due to various causes at a systemic level. Type B lactic acidosis occurs in normoxic and normal perfusion states and is associated with underlying liver disease (decreased clearance of lactate), diabetes mellitus, thiamine deficiency, mitochondrial toxins (e.g., alcohol, salicylates, reverse transcriptase inhibitors, seizures, malignancies, or hereditary enzymatic defects), among other causes [2]. Type B is divided into 3 subtypes based on underlying etiology. Type B1 occurs in association with systemic diseases, such as renal and hepatic failure, diabetes, and malignancy [3]. Type B2 is caused by several classes of drugs and toxins, including biguanides, alcohols, iron, isoniazid, zidovudine, and salicylates [4]. Type B3 is due to inborn errors of metabolism. Type D lactic acidosis is due to excessive production of D-lactic acid from intestinal bacterial proliferation, such as, in patients with short bowel syndrome, ischemic bowel disease, or small bowel obstruction, as it may be noted that mammals produce L-lactic acid, while bacteria produce D-lactic acid [2]. NRTIs described
since the early 1990s are used widely in the treatment of Human Immune Deficiency Virus (HIV) infection and are known to cause [5] life-threatening Type B (Subtype B2) lactic acidosis.

The occurrence of acute severe pulmonary arterial hypertension and cor-pulmonale in patients with idiopathic lactic acidosis was observed and reported by Phillipson [6] in 1965 and Sproule [7] et al. in 1966. In both the reports, the authors concluded that there is a possible association between lactic acidosis and severe pulmonary arterial hypertension, which needs further discussion. However, subsequent research in this field has been sparse, and the exact pathophysiology behind severe pulmonary hypertension and the magnitude of the problem in lactic acidosis remains unknown. The current understanding is that the effects of acid-base changes on the heart, the peripheral vessels, the lungs, and the diffusion of oxygen between air, blood, and tissues, causes a complex interplay in causing elevated pulmonary arterial resistance and systemic vasodilation, giving rise to increased pulmonary arterial pressures with associated fall in systemic blood pressure [8]. These changes in the pulmonary arterial resistance and pressures lead to acute cor-pulmonale, which may culminate in right heart failure closely resembling acute pulmonary thromboembolism.

Severe lactic acidosis of any etiology carries a very poor prognosis, and the reported mortality rate is as high as 76 to 81% [2, 9]. The survival in lactic acidosis depends on the ability to identify and remove the cause, adequate peripheral perfusion, and prompt restoration of pH towards normal [10].

We report a case of successfully treated ART-induced lactic acidosis atypically presenting as acute right heart failure due to severe Pulmonary Hypertension (PH).

2. CASE DETAILS

38-year-old male on anti-retroviral therapy for five years with no comorbidities or habits, presented with sudden onset, progressive exertional breathlessness (NYHA Class III), and giddiness for two days. He was diagnosed to be HIV infected for ten years with a history of treated pulmonary tuberculosis. There was no other significant history in recent times.

On presentation, his vital parameters were pulse 128 bpm, regular, BP 100/60 mmHg, elevated jugular venous pulse (12cm H₂O), respiratory rate of 33 cycles/minute, and peripheral capillary oxygen saturation (SpO₂) of 85% on room air. Further general physical examination revealed mild facial puffiness and bilateral pitting pedal edema. Systemic examination of the cardiovascular system revealed tachycardia, Right Ventricular (RV) S₃, and a systolic murmur in the tricuspid area on auscultation. Respiratory and other systems were unremarkable. Based on history and physical examination, a provisional diagnosis of acute pulmonary thromboembolism was made.

2.1. Investigations

Electrocardiogram (ECG) showed sinus tachycardia, rsr’ pattern in V₁, S wave in the lead I, asymmetric T inversion in II, III, aVF, and V₄-V₆ (Fig. 1). Chest X-ray revealed cardiomegaly, right atrial enlargement, with no remarkable lung pathology (Fig. 2a). A two-dimensional echocardiogram (2D ECHO) showed dilated right heart chambers with moderate tricuspid regurgitation and severe pulmonary hypertension (RVSP-70mmHg). RV function was reduced with normal Left Ventricular (LV) function (Fig. 3a-3d). D-dimer and creatine Kinase were grossly elevated with a marginal rise in cardiac troponins. CT pulmonary angiogram showing dilated right heart chambers with no evidence of pulmonary thromboembolism and few calcified mediastinal lymph nodes. Renal, liver, and thyroid function tests, serum electrolytes, complete blood count, parathormone, serum calcium, magnesium, random blood sugar, and coagulation profile were unremarkable. Arterial blood gas analysis was as shown in Table 1. The immune panel showed decreased absolute lymphocyte count, adequate CD3, CD4, and helper T cell count. Lung secretions were negative for pneumocystis carinii infection. Bilateral lower limb venous doppler and ultrasound abdomen were normal.

2.2. Management

Antiretroviral therapy was completely withdrawn as ART-induced lactic acidosis was suspected. The patient was treated with noninvasive ventilation, noradrenaline, calculated doses of bicarbonate infusion for acidosis, inhaled milrinone, and other symptomatic medications. However, a few hours into hospitalization, because of progressive respiratory failure patient was mechanically ventilated. Vasopressin and dopamine infusions were added for refractory hypotension. After 24 hours of treatment, the patient became hemodynamically stable, and venous lactate level decreased by 33% (to 57 mg/dl). The patient was weaned off from ventilator support and extubated on day two. ECG showed the resolution of initial changes (Fig. 1b), and CXR showed regression of cardiomegaly and right atrial enlargement (RAE) as shown in Fig. (2b). The patient was continued on inhaled oxygen, milrinone nebulization during his hospital stay and discharged on day six.

Table 1. Showing arterial blood gas analysis at presentation and after 24 hours of treatment. The last row in the table shows venous blood lactate levels.

<table>
<thead>
<tr>
<th>Arterial Blood Gas Analysis</th>
<th>At Presentation</th>
<th>After 24 hours of Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>6.90</td>
<td>7.45</td>
</tr>
<tr>
<td>pCO₂ in mmHg</td>
<td>13.1</td>
<td>34.9</td>
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<tr>
<td>pO₂ in mmHg</td>
<td>123</td>
<td>98.2</td>
</tr>
<tr>
<td>sO₂ in %</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Bicarbonate (HCO₃) in mmol/L</td>
<td>3.0</td>
<td>24.9</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Arterial Blood Gas Analysis</th>
<th>At Presentation</th>
<th>After 24 hours of Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate in mmol/L</td>
<td>25</td>
<td>05.9</td>
</tr>
<tr>
<td>Venous Blood lactate in mg/dl, Normal range 4.5-20</td>
<td>84</td>
<td>57</td>
</tr>
</tbody>
</table>

Fig. (1). (a) ECG on presentation showing sinus rhythm, rsr’ in V1, s waves in lead I, T inversion in II III aVF, V4-V6, (b) ECG on Day 3 showing sinus rhythm, resolution of rsr’ in V1 ‘s’ waves in lead I.

Fig. (2). (a) CXR on presentation showing cardiomegaly, with features of Right Atrial Enlargement (RAE), (b) After recovery on day 6, CXR shows regression of cardiomegaly with no evidence of RAE (Right Atrial Enlargement).
At one-week follow-up ECG and 2D ECHO were normal, RVSP 32mmHg (Fig. 4). Serum lactate level normalized by 6 weeks (to 17mg/dl). As the patient’s genotypic resistance testing showed resistance to Abacavir, Zidovudine-based (Zidovudine, Lamivudine, and Atazanavir) regimen was started. As Zidovudine can rarely cause lactic acidosis, the patient is on close monitoring.

3. DISCUSSION

Lactic acidosis is the most common cause of metabolic acidosis in hospitalized patients [11]. Severe metabolic acidosis causes organ failure, especially in respiratory and cardiovascular systems, secondary to increased ventilatory demand, arterial vasodilation, decrease in cardiac inotropy, reduction in cardiac output, and sometimes ventricular arrhythmias [12]. The role of acute metabolic acidosis in these organ failures is mostly suggested by experimental studies in animals or in vitro, as few clinical studies in humans are available.

Acidosis affects pulmonary vascular pressures in two ways. One, acidosis tends to increase pulmonary vascular resistance and raise pulmonary artery pressure [13]. Two, acidosis redistributes blood from peripheral venous beds into the lung, thereby elevating pressures in the left atrium, pulmonary veins, capillaries, and pulmonary arteries as a compensatory mechanism [14]. On systemic circulation, reduction of perivascular pH in acidemia decreases the responsiveness to vasoconstrictors and results in vasodilation and associated fall in blood pressure [15].

NRTIs used in the treatment of patients with HIV-infection is associated with chronic hyperlactatemia and acute lactic acidosis, named as severe Nucleoside-Associated Lactic Acidosis (NALA) as a serious side effect. Mitochondrial toxicity due to inhibition of mitochondrial DNA γ-polymerase and impaired synthesis of mitochondrial enzymes that generate Adenosine Triphosphate (ATP) is said to be the cause of lactic acidosis [16]. Other attributed mechanisms are a shift toward anaerobic metabolism, increased apoptosis, and decreased lactate clearance secondary to hepatic dysfunction [17]. The pathophysiology of NRTI-induced acidosis might be even more complex, and genetic risk factors could also play a role [18]. The mortality rate in Highly Active Antiretroviral Therapy (HAART) induced lactic acidosis is reported to be as high as 50%. Following discontinuation of NRTIs, lactate levels usually normalize within 4-20 weeks [17, 18].
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The patient in this report was receiving two NRTIs: Stavudine and Lamivudine, both are known to cause severe lactic acidosis, which was associated with pulmonary vascular abnormalities causing severe pulmonary hypertension and consequent RV failure. Withdrawal of the offending NRTIs and correction of acidosis with supportive therapy prevented the potential fatality.

CONCLUSION

ART drugs are known to cause severe lactic acidosis, which has high fatality. Reports of lactic acidosis presenting as acute right heart failure with severe PH are rare. As survival depends on the ability to identify and remove the cause for lactic acid overproduction, this case emphasizes the need to keep lactic acidosis as a differential diagnosis in all cases of unexplained RV failure and prompt withdrawal of offending drug/factor.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient.

STANDARDS OF REPORTING

CARE guidelines were followed.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

REFERENCES


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