Pseudohypobicarbonataemia Unmasking Multiple Myeloma in a Young Female: An Unusual Presentation

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ABSTRACT

The authors present a case of a patient whose blood bicarbonate (HCO_3) levels were extremely low, ranging from 5.4 to 7.9 mEq/L. In clinical chemistry, paraproteins' interference in tests is not unheard of, but is still quite uncommon. Here, we report a case of multiple myeloma in which paraprotein interfered with a bicarbonate test. The serum bicarbonate concentration was measured using both the enzymatic approach of a multiparametric chemistry analyser and a blood gas analyser's specialised electrode assay. A much lower bicarbonate level by the enzymatic approach compared to the normal levels by the gas analyser and the patient's clinical situation were evidence of paraprotein interference with the enzymatic test. Thus, gammapathy must be considered when drawing conclusions from biological data.

Key Words: *Bicarbonate levels, Paraproteins, Multiple myeloma*.

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INTRODUCTION

Blood bicarbonate (HCO_3), pH, and partial pressure of carbon dioxide ($PaCO_2$) levels must be measured to diagnose an acid-base disease. Direct measurement of serum total carbon dioxide (TCO_2) or computation of the Henderson-Hasselbalch equation using arterial whole blood and direct measurement of pH and $PaCO_2$ using a blood gas analyser are the two most frequent ways for estimating HCO_3 levels in blood.[1] As 95% of blood TCO_2 is in the form of HCO_3,[1] this measurement may be used as a proxy for the serum HCO_3 level. Serum TCO_2 may be evaluated in one of the two ways using automated chemistry analysers: An enzymatic/photometric assay or an electrode-based approach.[1] Serum HCO_3 concentrations are measured enzymatically, and the results are analysed visually using a photometric technique. This may be influenced by any factor that alters the photometric measurement of light absorption or the enzymatic reaction steps.[2] Falsely low blood HCO_3 levels owing to interference by increased triglyceride levels have been recorded,[3,4] but only two examples of interference by paraproteins leading to a falsely low serum HCO_3 level have been described.[3] The proliferation of monoclonal plasma cells in the bone marrow in multiple myeloma (MM) causes the overproduction of monoclonal paraproteins, the degradation of bone, and the displacement of other haematopoietic cell lines.[1]

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CASE REPORT

A 30-year Afghan married woman presented to the Emergency Department of the Aga Khan University Hospital, Karachi, Pakistan, with complaint of lower back pain for the past two years, which had worsened for the past 3 months. On systemic review, she also complained of pain in her right shoulder joint, right arm, and neck. She also had decreased appetite and undocumented weight loss.

On examination, her heart rate (HR) was 80 bpm, respiratory rate (RR) was 18 breaths/min, blood pressure (BP) was 130/80 mmHg, temperature was 36.7 °C, SPO_2 was 97% on room air, and weight was 52 kg. She was anaemic with no pedal oedema. The rest of the general physical examination was unremarkable. Her chest was clear. On cardiovascular examination, S1 and S2 were audible. Abdominal and CNS examinations were unremarkable.

Her laboratory work-up showed haemoglobin (Hb) of 5.0 g/dl, mean corpuscular volume (MCV) of 91.8 fL, total leucocyte count (TLC) of 4.7×10^3/cm, platelets 154,000/ml, blood urea nitrogen (BUN) 48, creatinine 2.3 mg/dl, sodium (Na) 131 mmol/L, K 3.2 mmol/L, chlorine (Cl) 93 mmol/L, HCO3 7.9 mEq/L, calcium 15.7 mg/dl, and albumin 2.6 g/dl (corrected calcium for low albumin was 16.82 mg/dl). Her electrocardiogram (ECG) showed shortened ST and QT intervals (Figure 1). She had high-anion-gap metabolic acidosis when corrected for hypoalbuminaemia. Her urine detailed report showed proteins (+2), red blood cell (RBCs) 5/HPF, and white cells 6/HPF. Her arterial blood gases (ABGs) showed pH of 7.57, $PaCO_2$ of 26.4 mmHg, PaO_2 of 112 mmHg, and HCO_3 of 23.7 mEq/L at 1L of supplemental oxygen, which was later stopped as she was maintaining oxygen saturation on room air. There was a significant discrepancy between bicarbonate levels in arterial and venous blood samples.

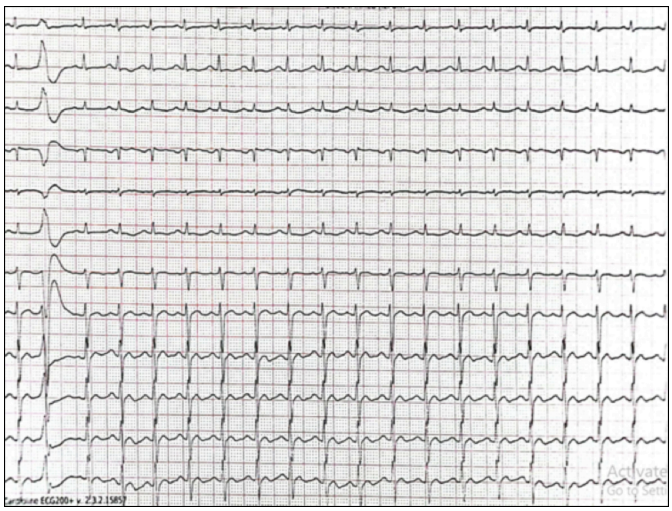

Figure 1: ECG showing shortened ST and QT intervals.

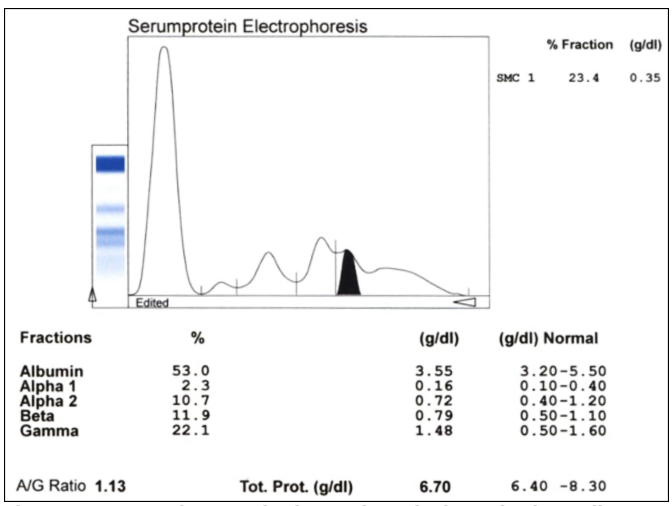

Figure 2: Serum urine protein electrophoresis showed a sharp, discrete, well-defined M-spike in the gamma region.

During her hospital stay, she was managed with intravenous fluids, sodium bicarbonate, and analgesics. She was transfused with packed cell volumes and was producing good urine output. Her venous HCO_3 levels remained low, varying from 6 to 9.3 mEq/L, and arterial HCO_3 levels remained normal, varying from 22.6 to 24 mEq/L. Visual inspection was used to rule out systematic test-tube underfilling as a possible reason for the erroneously low bicarbonate levels. The difference between venous bicarbonate level and gas panel-derived plasma bicarbonate values remained in a sample of arterial blood drawn without the use of a tourniquet; hence, the tourniquet-related artefact was ruled out.

Her further work-up showed serum parathyroid hormone (PTH) of 10.7 pg/ml and vitamin D3 level of 28 ng/ml. Her fasting lipid profile, blood sugar, and lactate levels were within normal range. Skeletal survey showed multiple lytic lesions. Serum and urine protein electrophoresis showed a sharp, discrete, well-defined M-spike in the gamma region (Figure 2). Her serum immunofixation findings were consistent with IgA lambda monoclonal gammopathy, and the free light chain assay showed raised-lambda chain and low kappa/lambda ratio. Bone marrow biopsy findings were consistent with MM. She was started on lenalidomide, bortezomib, and steroids. Her acute kidney injury and hypercalcaemia resolved. She was haemodynamically stable and was discharged. She was kept on the above treatment and was later followed as an outpatient, with an improvement in her venous bicarbonate level to 17.5 mEq/L.

DISCUSSION

Approximately 95% of all MM cases are diagnosed in individuals over the age of 50 years. Less than 2% of all cases are diagnosed in people under 40 years. It is rare for MM to occur in people under 30 years of age, and this population is poorly understood.[1] Interference in biochemical tests is mostly caused by haemolysis, jaundice, and circulating lipids, all of which can already be detected by most machines. Nevertheless, other less common interferences have been discovered, such as those in MM.[5] These paraproteins may be found in extremely high concentrations in the serum or urine of these individuals, and their presence can interfere with the detection of some parameters by precipitation or direct contact with the reagents, or even by disrupting chemical processes.[5] Bilirubin,[6] phosphates,[7] high-density lipoprotein cholesterol,[8] lactate dehydrogenase,[9] and most recently, bicarbonates,[6,7] and troponin I have all been documented as being affected by interference from paraproteins.

This patient had hypo-albuminaemia (2.6 g/dl), and a decrease in negatively charged albumin (anion) lowers the anion gap and requires correction using a formula. This correction is important because hypo-albuminaemia may conceal an elevated anion gap metabolic acidosis. However, the corrected anion gap in this patient was found to be high. An increase in a positively charged plasma protein (cation) lowers the anion gap; therefore, a low anion gap also prompts consideration of a monoclonal gammopathy; however, on the contrary, the present patient had high anion gap metabolic acidosis. According to one study, 31% of IgA monoclonal gammopathies had higher serum anion gap. IgA is an anionic protein that has a favourable correlation with serum anion gap, which is a similar finding as observed in this case.

Either a direct measurement using the enzymatic approach or a spectrophotometric reading is available for determining the blood bicarbonate levels in our laboratory. This system relies on the principle of converting total bicarbonates in the sample to oxaloacetate, subsequently transformed to malate. The reduction in absorbance at 410 nm, inversely proportional to TCO_2, is then quantified as its oxidation to NAD+. This approach has a linear range down to 10 mEq/L based on the Henderson-Hasselbalch equation.

The HCO_3 content in the blood is determined using a calculation based on the findings of the potentiometric technique (particular electrodes) measurements of pH and $PaCO_2$ by devices such as the GEM 4000. The incongruity between the biological data obtained using the two techniques (assay by particular electrodes and enzymatic procedure) is indicative of interference. Factors such as sample lactescence[10] or serum precipita-

tion during sample dilution[3] are identified in the literature that might skew the results of a bicarbonate test. Another possible explanation is that the paraproteins have direct contact with the reagent; eliminating the proteins by precipitation or ultrafiltration would get rid of this interference.[6] Various methods can be used, including enzymatic assay on the *Advia® 1800* and Cobas® *6000* (clinical chemistry system), assay by calculation from the pH and $PaCO_2$ measured by specific electrodes (GEM 4000 analyser), and enzymatic assay after serum ultrafiltration on a Microcon® filter as suggested by Nauti *et al*.[6]

This experiment reveals protein interference, evident by transparent serum, no jumbling upon dilution, and slowed enzymatic reaction with paraproteins. Hence, paraprotein interferences with biochemical tests are reagent-specific and only seen in 2-4% of samples with very high paraprotein concentrations.[6]

In conclusion, paraproteins may impede HCO_3 measurements in the blood. However, it is possible to eliminate the interference by precipitating or filtering out the proteins responsible for the disparity. Clinical interpretation of data should proceed with care when high-concentration hyperproteinaemia (>100 g/L) is present in a patient.

PATIENT'S CONSENT:
Written informed consent was obtained from the patient.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
AH: Contribution to the conception and design of the work, drafting, and revision of the manuscript critically for important intellectual content, and agreement to be accountable for all aspects of the work.
HUT: Drafting of the work and revision of the manuscript critically for important intellectual content.
Both authors approved the final version of the manuscript to be published.

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