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Acid-Base Balance-Electrolyte Quiz – Case 73

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A 76-year-old male presented at the Emergency Department due to weakness without reporting any other symptom. His personal history was remarkable for mantle-cell lymphoma (MCL) having been diagnosed 13 years ago with favorable prognostic characteristics; stage IA and low-risk group according to MCL-International Prognostic Index (MIPI) score. Six cycles of the regimen R-CHOP (rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone) had been administered and complete remission (CR) of the disease had been achieved. At his admission, the patient was alert, orientated and hemodynamically stable. Though, cachexia was noticed, while clinical examination revealed a left orbital mass along with cervical and inguinal lymphadenopathy. Complete blood count was significant for severe normochromic, normocytic anemia (hemoglobin: 6.6 mg/dL), while normal white blood cell count along with normal differential and normal platelets count were found. Basic biochemical examinations showed only acute renal insufficiency (creatinine: 3.1 mg/dL). Blood smear did not demonstrate any significant morphological abnormality. Arterial blood gases (ABGs) revealed a severe metabolic acidosis with an increased anion gap; pH=7.24, $PaCO_2$=30 mmHg, PaO_2=100 mmHg, SaO_2=98%, lactic acid=12 mmoL/L, $HCO3^-$=13 mEq/L, not sufficiently explained only by the severe acute renal failure, due to lactic acid elevation. Thus, blood cultures were negative for infection, while other signs of sepsis or causes of tissue hypoperfusion were absent. Whole-body computed tomography (CT) showed left orbital mass along with marginally abnormal cervical and abdominal lymphadenopathy along with renal edema. Histologic examination of the orbital mass and cervical lymph nodes confirmed relapse of the MCL. The patient received 6 cycles of rituximab-bendamustine and achieved a CR with complete resolution of lactic acidosis (LA).

Comments

Metabolic acidosis is caused by the blood accumulation of any acid other than carbonic acid leading to primary decrease in the plasma [HCO_3^-]. Several disorders can lead to metabolic acidosis: Acid administration, acid generation (e.g. lactic acidosis during shock or cardiac arrest), impaired renal acid excretion, or bicarbonate losses from the gastrointestinal tract. From a diagnostic point of view, calculation of the plasma anion gap is extremely useful in differential diagnosis, as the first step is to identify whether the acidosis is due to retention of hydrochloric acid (H^+Cl^-).

For the calculation of the anion gap, the below formula is used:

Anion gap={[Na^+]+[K^+]}–{[HCO_3^-]+[Cl^-]}

The normal anion gap is 10–18 mmoL/L. Causes of metabolic acidosis with a normal anion gap as well as an increased anion gap are depicted in tables 1 and 2, respectively.[1]

In cases of LA, type-A (LA-A) is more common than type-B (LA-B). In the majority of cases, type A reflects tissue depletion of oxygen supply due to hypoperfusion. On the other hand, LA-B, a rare entity, occurs under normoxemic conditions with no evidence of organ hypoperfusion.[2–4]

Malignancy-related LA is a rare oncological emergency that can be fatal, if not promptly identified and treated. It has been associated with both hematological (85%) and solid (15%) tumors. Among hematologic malignancies, lymphoma accounts for 50%

Table 1. Causes of metabolic acidosis with a normal anion gap.

Increased gastrointestinal bicarbonate loss
Diarrhea
Ileostomy
Ureterosigmoidostomy
Increased renal bicarbonate loss
Acetazolamide therapy
Proximal (type 2) renal tubular acidosis
Hyperparathyroidism
Tubular damage, e.g. drugs, heavy metals, paraproteins
Decreased renal hydrogen ion excretion
Distal (type 1) renal tubular acidosis
Type 4 renal tubular acidosis (aldosterone deficiency)
Increased HCl production
Ammonium chloride ingestion
Increased catabolism of lysine, arginine

Table 2. Causes of metabolic acidosis with an increased anion gap.

Renal failure (sulphate, phosphate)
Accumulation of organic acids
Lactic acidosis
Type A–anaerobic metabolism in tissues: Hypotension/cardiac arrest, sepsis
Type B–decreased hepatic lactate metabolism: Insulin deficiency, metformin accumulation, hematological malignancies, rare inherited enzyme defects
Ketoacidosis
Insulin deficiency
Alcohol excess
Starvation
Exogenous acids
Salicylate

cases, predominantly non-Hodgkin's type.[5] LA-B is an extremely rare but potentially life-threatening condition that has been described mostly in hematological malignancies, having been also documented in some cases of solid tumors.[2–4,6]

The pathogenesis of LA in lymphoma is multifactorial, but not well-understood. Rapid replication of tumor cells may lead to increased needs of blood supply which could provoke hypoxia inside the tumor microenvironment. These circumstances cause anaerobic glycolysis, as well as lactate dehydrogonase and lactate overproduction.[14] However, other potential mechanisms may be liver metastasis, overexpression of type II hexokinase (a glycolytic enzyme found in mitochondria), and regulatory effect of insulin-like growth factor.[8] Liver dysfunction due to malignant cells infiltration may gradually reduce hepatic utilization of lactate via gluconeogenesis causing LA.[7–10] Moreover, a distinct mechanism of acidosis in malignancies is the so called "Warburg effect" or "aerobic glycolysis"; malignant cells under aerobic conditions use glucose via upregulation of glucose transporters and overproduction of type II hexokinase, insulin-like growth factors and tumor necrosis factor-alpha (TNF-α).[8,11–13]

More than half of lymphoma cases associated with LA-B is related to advanced-stage high-grade non-Hodgkin's lymphoma, frequently with high-tumor burden, while LA-B in MCL has been rarely reported.[15] LA associated with hematologic malignancies is a rather infrequent, life-threatening condition whose pathogenesis is not well understood. Its presence at diagnosis is considered to have a poor prognostic impact on patient's survival. Rapid initiation of treatment along with remission of disease remains the only successful therapeutic approach to achieve complete resolution of LA.

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