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Mixed malarial-hypertriglyceridemia induced acute pancreatitis complicated by diabetic ketoacidosis: A case report

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Abstract

Acute Pancreatitis (AP) due to mixed malarial infection and Hypertryglyceredmia (HTG) complicated by Diabetic Ketoacidosis (DKA) is a very rare clinical scenario with viscous cycle resulting in high mortality and morbidity along with a great diagnostic and treatment challenge for the treating physician. Most of the novel therapies for Hypertglycerdmia induced Pancreatitis (HTGP) are not available in low-income countries, which force us to look for alternative locally available treatment modalities.

We present a case of a 47-year-old male uncontrolled type 2 Diabetic Mellitus (DM) patient from Ethiopia, who presented to the emergency department with one week fever, abdominal pain and associated symptoms. Laboratory tests studies revealed serum lipase 250 IU/L, serum triglyceride level 1021 mg/dl and mixed malarial infection (plasmodium vivax and plasmodium falcifarum). The patient was diagnosed with mixed malarial-hypertriglyceridemia induced AP complicated with DKA and treated with fluid resuscitation, pain management, insulin infusion and artusenate. The patient had an uneventful medical intensive care unit follow-up and he was discharged with full recovery. The case report highlights the importance of early recognition of malarial- hypertriglyceridemia induced AP in uncontrolled DM patients who are from malaria endemic country. It also highlights the role of insulin infusion and artusenate therapy in preventing disease progression and improving outcome in low-income countries.

Keywords: Acute pancreatitis; Hypertyglyceridemia; Malaria; Diabetic ketoacidosis; Insulin infusion; Ethiopia.

Abbreviations: AP: Acute Pancreatitis; DM: Diabetes Mellitus; DKA: Diabetic ketoacidosis; HTG: Hyperthyglycerdmia; HTGP: Hypertyglycerdmic Pancreatitis; TG: Triglyceride.

Introduction

Acute Pancreatitis (AP) is a life-threatening condition and diagnose according to the Atlanta criteria, 2 of the following 3 criteria need to be present for the diagnosis: (a) abdominal pain compatible with AP, (b) serum amylase and/or lipase ≥3 times the upper normal limit, and (c) abdominal cross-sectional imaging findings suggestive of AP [1].

The most common causes of AP are gallstone disease (45%), alcohol consumption (20%), and hypertriglyceridemia (3%-10%), particularly when the serum Triglyceride (TG) levels rise beyond 1000 mg/dL. However, AP can occur in mild or moderate hypertryglyceredmia [1,2]. In addition, tropical infectious etiologies including malaria are recently being recognized as a cause of AP, though the diagnosis of these conditions as a cause of AP requires excluding other common factors [3].

Only a small proportion of patients with HTG develop AP [4]. HTGP generally occurs in patients with HTG and one or more secondary factors, including inadequately controlled DM, alcoholism, pregnancy, medications and genetic abnormalities [4,5]. Uncontrolled type 2 DM patient develop hypertriglyceredmia due hyperinsulinemia and insulin resistance, which enhances triglyceride production and decreases plasma triglyceride clearance [6]. In addition, DKA can cause both hypertyglyceredmia and AP, however the concurrent occurrence of DKA with HTGP is a rare clinical scenario with unique diagnostic and management challenge for the treating physician [7]. Furthermore, a meta-analysis and systemic review also showed that patients with malarial infection had hypertrglyceredemia compared to control groups and it was associated with the severity of malarial infection [8].

The pathophysiology of HTGP complicated by DKA isn't clear and it's assumed a result of complex interplay between multiple factors with varying contribution in individual patient. A recent study involving a cohort of 48 patients diagnosed with AP, DKA, and HTG revealed that DKA in AP is mainly triggered by high levels of HTG, which exacerbated HTG levels creating a vicious cycle [9]. The accumulation of triglycerides in the pancreas leads to inflammation resulting in tissue and vascular injury with ischemia, which can result in the development of AP [10,11].

Recent studies demonstrate trend towards severe pancreatitis in patients with HTGP when compared with non HTGP. However, there was no relationship between the severity of TG level and mortality [12]. In addition, patients with HTGP complicated by DKA had higher levels of HTG and more prolonged hospital stays and complications compared to those without DKA [9]. However, early recognition and prompt management are associated with improved outcomes [13]. After recovery, the serum triglyceride levels appear to correlate with the risk of recurrence and it increase by 4% for every 100 mg/dl increase in serum triglyceride concentration [14,15].

The management of HTGP includes; standard AP treatments along with treatments targeted to acutely decrease the serum TG level below 500 mg/dl. To attain these goals insulin, heparin, Plasmapharesis (PEX) have been used [16]. Though, PEX have high efficacy in lowering serum TG level to its target within three hours, it's inaccessible, expensive, have significant adverse effect and lacks strong evidence for improving morbidity and mortality [17]. Once the patient stabilized and can tolerate oral feeding they can be started on fibrate, niacin, omega 3 fatty acid or statin [18,19].

Insulin infusion therapy is cheap, accessible and there are many case reports and series demonstrating TG lowering effect, though there are no comparison studies evaluating insulin versus conservative therapy [20,21]. The assumed mechanism is it activates Lipoprotein Lipase (LPL) activity which in turn accelerates chylomicron degradation thus lowering TGs levels [22]. In addition, it will also rest pancreatic tissue and may improve immunoparalysis via upregulating the expression of human leukocyte antigen on monocytes and decreasing cell apoptosis [23]. Insulin lowers TGs levels by 50-75% over 2-3 days and its effective even in non-diabetic patients, lower APACHE II score and shorten duration of hospitalization [22,23]. Though heparin considered as effective therapy for HTGP, due to concern of rebound hypertriglyceridemia and risk of hemorrhage into the pancreas during acute attack on continuous heparin infusion, it should preferably be avoided [16].

To the author's knowledge, this is the first case report to present the development of AP following mixed severe p.vivax and p.falciparum acute malarial infection and hypertryglycerdmia complicated by DKA and there has been no publication regarding the use of insulin infusion monotherapy from the African continent for HTGP management, particularly when it's complicated by acute malarial infection. This case report specifically hopes to show that easily accessible, effective, and safe therapy for mixed malarial-HTGP complicated by DKA is available, and can be used in the low-income countries.

Case presentation

A 47 years old male patient from Ethiopia, who was known type 2 diabetic for the past seven years on metformin 500 mg BID and glibenclamide 5 mg po BID with no regular follow up. He presents with seven days history of sever epigastric burning pain radiating to back associated with frequent vomiting of ingested matter and excessive fatigue. In addition, he had also similar duration of history of fever, chills, and polyarthralgia. Otherwise, he was not on lipid lowering agents, didn't took any medications other than mentioned above, no previous history of pancreatitis, no alcohol intake history and his previous lipid panel wasn't known.

Clinical examination at initial presentation showed blood pressure of 100/70 mmHg, pulse rate of 110 beat per minute, respiratory rate of 28 breath per minute, axillary temperature of 36.7°C and SPO_2 of 96% on room air. His weight was 72 kg with BMI of 28.1 kg/m^2 and he had prostration with icteric sclera, dry buccal mucosa and tongue, and epigastric tenderness with normoactive bowel sound. There was no xanthoma, xanthelasma, eruptive xanthoma or palpable lymph node over neck and axilla.

Laboratory tests at admission showed elevated white blood cell count (12.2×10^3/uL), hematocrit (35.9%), low platelet (35×10^3/uL), sever HTG (1021 mg/dl), elevated transaminase and alkaline phosphates with indirect hyperbilurubinemia with normal coagulation profile and renal function test. He had also mild hyponatremia (127 mmol/l) and hypocalcemia (3.6 mg/dl). His HbA1c was 9.5 and his RBS was 430 mg/dl. His periph-

Table 1: Biochemical parameter of a patient with mixed malarial-hypertriglyceridemia induced acute pancreatitis: A case report.

Variables	At admission	After 48 hrs	After 72 hrs
Serum lipase (IU/L)	250	47	43
White blood cell (Cells/mm^3)	12200	9600	5900
Hematocrit (%)	35.9	22.8	24.6
Platelet (Cells/mm^3)	35	49	66
Serum triglyceride (mg/dl)	1021	692	483
LDL-cholestrol (mg/dl)	94		
HDL-cholestrol (mg/dl)	20		
Total cholesterol (mg/dl)	114		
AST (IU/L)	104	296	154
ALT (IU/L)	56	53	62
ALP (IU/L)	496	568	633
Total bilurubin (mg/dl)	6.95		1.5
Direct bilurubin (mg/dl)	0.5		0.3
PT (s)	12		
PTT(s)	35		
INR	1.0		
Serum Creatinin (mg/dl)	0.9		
BUN (mg/dl)	14		
LDH (IU/L)	310		
CRP (mg/dl)	60		
Peripheral morphology	Mixed p.vivax + & p.faciparum + 4	+2	free
Serum sodium (mmol/l)	127	129	
Serum potassium (mmol/l)	4.0	3.2	
Serum ionized calcium (mg/dl)	3.6	4.0	
Serum total calcium (mg/dl)	7.7	8.3	
RBS (mg/dl)	430		
HbA1c (%)	9.5		
Urine keton	+4	+2	free
TSH (mUI/ml)	1.65		

ALT: Alanin Transferase; AST: Aspartate Transferase; ALP: Alkaline Phosphatase; BUN: Blood Urea Nitrogen; CRP: C- Reactive Protein; LDH: Lactate Dehydrogenase; PT: Prothrombin Time; PTT: Partial Prothrombin Time.

eral morphology showed mixed malarial infection (p.vivax & p.falcifarum) with ketonuria (+4). In addition, his serum lipase was 250 iu/L, C-Reactive Protein (CRP) 60 mg/dl and Lactate Dehydrogenase (LDH) of 310 iu/L. His abdominal ultrasound was also normal.

Hospital course: The patient was admitted to medical intensive care unit with a diagnosis of acute pancreatitis secondary to mixed sever malarial infection and hypertryglyceredmia with uncontrolled type 2 diabetes mellitus with diabetic ketoacidosis, hydrated with seven bags of intravenous normal saline, put on morphine sulphate standing dose, started on insulin infusion therapy with 0.1 Iu/kg/hr for three days, took artusenate 2.4 mg/kg at 0 hr, 12 hr, 24 hr and then daily for five days.

He had an hourly measurement of his blood sugar, with two hourly measurements of his urine ketone. He had required infusions of 500 ml, 5% dextrose in water, mixed with 500 ml of normal saline in one bag, along with intravenous potassium chloride, when his random blood sugar dropped below 250 mg/dl, and his serum potassium dropped below 5.3 meq/L. He had one episode of hypoglycemia at 56 mg/dl during his management, which required 1.25 ml/kg Iv push of 40% dextrose.

The abdominal pain, nausea and fatigue improved in the first day. He was taken out of DKA in 50 hrs, and the serum TG level had dropped below target, within three days of his treatment. The fever subsides in the second day of admission and the paracitemia become clear in the blood film after 2 days of treatment with artusenate. He was discharged one week after admission, with omega 3 fatty acids, atorvastatin, and Neutral protamine Hagedorn insulin. After one month he came for follow up and he is in good health with serum TG level of 378 mg/dl.

Discussion

This case report highlights an unusual presentation of mixed malarial-HTGP with concurrent DKA in a male patient with uncontrolled type 2 DM. Although these conditions have been separately associated with AP, their simultaneous occurrence in a single patient is uncommon [7]. When this triad (i,e. DKA, HTG, AP) occur, it usually causes high plasma TG and severe AP since it usually create a vicious cycle [9].

Our patient had severe mixed p.vivax and p.falcifarum acute infection and there are case reports which reported malarial infection either p.vivax or p.falcifarum can cause hypertrlyglycerdmia, AP, DKA and the presence of this complications associate with the severity of the malarial infection [8,24-26]. Up to date there are only 33 case reports which reported that malarial infection can cause AP regardless of the severity of infection [25]. Vascular changes caused by infected red blood cells, cytoadherence to the endothelium, sequestration, and rosetting leading to ischemia are implicated in the pathogenesis of malarial pancreatitis [27]. Whenever AP is stated as a complication of severe falciparum malaria, a query arises whether it is a mere association or a causal relation [28]. Since a significant proportion of the population from an endemic area may be asymptomatic carriers of the parasite, it is difficult to ascertain if the organ involvement is due to malaria [29]. However, until further experiments establish this fact adequately, we have to suspect AP as a complication of malaria once other causes are ruled out.

In our patient the diagnosis of acute pancreatitis was made according to the Atlanta criteria [1]. In this case, the classic abdominal pain with raised lipase values supported the diagnosis of acute pancreatitis. Hence, the diagnosis was made in the absence of standard abdominal imaging (CT or MRI). In addition, our patient background characteristics is similar to most case series and case reports on HTGP, where it usually occurred in middle age patients (28-55 years), patients with DM, who had presented with epigastric pain, and more than 85% of these patients were male [5,30,31].

The management of HTGP complicated by DKA centered on targeted at reducing TG level along with standard DKA and AP managements. However, insulin resistance can be more severe, necessitating higher insulin doses [32]. Most of the patients described in the literature had attained a serum TG level target of less than 500 mg/dl, at or beyond day three of their treatment using insulin infusion monotherapy (i.e, without heparin) for HTGP [20,22,23]. Similarly, case reports of malaria induced AP have showed improved outcome with artusenate therapy [33,34]. We were able to achieve the same results in our patient with insulin infusion and artusenate along with standard treatment of AP. His serum TG level fell from 1021 mg/dl to 483 mg/dl by day three (Table 1).

Conclusion

Mixed malarial-HTGP complicated by DKA is a rare but life-threatening clinical scenario with vicious cycle requiring urgent diagnosis and treatment. Clinicians should be vigilant about the potential coexistence of malarial-HTGP and DKA in patients with poorly controlled diabetes, particularly in malaria endemic countries such as Ethiopia. Based on our case and review of literature, in low resource areas insulin infusion monotherapy and artusenate along with standard treatments of AP can be used to treat mixed malarial-HTGP complicated by DKA.

Declarations

Author contributions: YYA: planning, literature review and manuscript writing & editing. TE, TM, AKY, YN and TH: Supervision and data validation and quality assurance. All authors have reviewed and agreed on the final manuscript.

Ethical approval: The ethical committee approval was not required give the article type (case report). However, the written consent to publish the clinical data of the patients was given and is available to check by the handling editor if needed.

Data availability: All have been included in the manuscript

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