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Metformin induced acute pancreatitis

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Acute pancreatitis frequently presents with abdomen pain but may presents with various skin manifestations as rash and rarely, pancreatic panniculitis. Metformin, one of the most effective and valuable oral hypoglycemic agents in the biguanide class was linked to acute pancreatitis in few cases. Here, we report a case of metformin induce acute pancreatitis in young healthy man with normal renal function.

Introduction

The incidence of acute pancreatitis is increasing around the world,[1] where it is associated with morbidity and even the risk of mortality.[2,3]

It may presents with various skin manifestations as rash and rarely, with erythematous tender subcutaneous nodules, known as pancreatic panniculitis.[4] Alcohol and gallstones are the most important causes,[5-7] while routinely prescribed drugs have been linked to the causation of acute pancreatitis.[8,9]

Metformin, one of the most widely prescribed oral hypoglycemic agents, was linked to pancreatitis, secondary to overdose or in case of impaired renal function. Here, we report a case of metformin induce acute pancreatitis in young healthy man with normal renal function.

Case Report

Nineteen year-old-man, known case of Type 2 Diabetes mellitus for 4 y on 1 g metformin twice daily since diagnosis of his diabetes. He was in his usual state of health till he presented to the emergency department reporting nausea, vomiting and epigastric pain for 3 d.

On physical examination, his height was 170 cm and body weight 99 kg; body mass index (BMI) 34.3 kg/m^2, looked mildly dehydrated. Vitals signs were stable. Systemic examination was unremarkable, apart from mild epigastric tenderness.

Laboratory investigations showed HbA1c 7.7%, Creatinine 58 μmol/L, Amylase 462 units/l (normal range < 100), Lipase 1378 units/l (0–60), white blood cells 16.8/mm^3 (4–11) 80% of which was neutrophils, CRP 258 mg/l (0–5), Mg 0.76 mmol/l (0.7–1.05), Ca 2.17 mmol/l (2.2–2.6), AST 18 units/l (< 39), ALT 34 units/l (< 41), TG 0.95 mmol/l (< 2.3), Lactate 1.4 mmol/l (0.5–1.6). Abdominal Ultrasound and ERCP were done for the patient, results showed no gallstones and clear biliary tract, respectively. CT confirmed the diagnosis of acute pancreatitis, with no identifiable cause.

The patient was admitted to ICU for close monitoring and further investigation. Normalization of Amylase and Lipase was reached after Metformin cessation, and Supportive treatment in the form of IV insulin and IV fluids. Other potential causes of pancreatitis were excluded. Patient was discharged home in stable condition after 2 weeks.

Few days later, after re-exposure to Metformin, he presented with recurrence of his previous symptoms, and elevation of Amylase and Lipase was documented.

As a result, Metformin was suspended with improvement of his symptoms and biochemical profile.

Discussion

Metformin is one of the most effective and valuable oral hypoglycemic agents in the biguanide class. It has been selected as the drug of choice in management of majority of patients with type 2 diabetes mellitus, as it works by several mechanisms; decreasing hepatic gluconeogenesis, increasing glucose transport into glucose utilizing cells,[10] decreasing appetite and caloric intake and reducing intestinal glucose absorption.[11]

As any other medication, Metformin is associated with undesirable side effects and it has been reported in few cases to cause lactic acidosis and pancreatitis.

Acute pancreatitis is attributed to many etiological factors; one of them is medication, where a large number of single case reports on drug-induced pancreatitis were published.[12] Diuretics, antimicrobial agents, HIV therapy and neuropsychiatric agents as well as Metformin are known medication to induce pancreatitis.[13] The underlying pathogenesis in drug induced pancreatitis in some medications as codeine was due to spasm of sphincter of Oddi,[14] in others as azathioprine, immune-mediated mechanism or a hypersensitivity to the drug is the postulated pathogenesis.[15] In Metformin, the exact mechanism is not known, but toxicity is probably secondary to acinar cell injury leading to intercellular leakage of digestive enzymes from ductules.[16]

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Fortunately, drug-induced pancreatitis is an acute edematous pancreatitis of a benign course and good prognosis, but fatal outcome may ensue if proper management is not initiated.[13]

Among the published case reports of metformin induced pancreatitis, one was attributed to metformin overdose,[17] other was caused by metformin accumulation, resulting from combination of drug overdose and acute renal failure triggered by vomiting in patient with concealed renal insufficiency.[18]

Additionally, two case reports were found to be associated with drug induced (angiotensin converting enzyme inhibitor, angiotensin receptor blocker, non-steroidal anti-inflammatory drug as Ibuprofen and celecoxib and diuretics) renal failure, which reduced excretion of therapeutic dose of metformin causing toxicity, leading to sever lactic acidosis and pancreatitis.[16,19]

Lastly, in a case report of patient presented with hyperglycemia after an ingested dose between 64–85 g of metformin in a suicide attempt, the potential mechanism of hyperglycemia is not clear and nothing among metformin's known mechanisms would logically explain the progressive and severe hyperglycemia, pancreatitis remains a potential mechanism, as the patient's clinical presentation with reportts vomiting and abdominal pain is consistent with pancreatitis.[20]

In our case, several signs can guide to and support the diagnosis of metformin induced pancreatitis; first is the clinical presentation of abdominal pain, nausea, vomiting and dehydration. Second, high levels of Lipase and Amylase, which correlate positively with CT findings.

The lack of other known causes of acute pancreatitis such as gall stones, alcohol abuse, hypercalcaemia, hypertriglyceridaemia, and trauma, added more evidence to the diagnosis.

Apart from the therapeutic dose of metformin (2 g daily), our patient has never consumed any other medications known to cause pancreatitis.

Finally, resolution of his symptoms upon metformin cessation and relapse upon re-exposure would strongly suggest that metformin is deemed responsible of our patient's clinical presentation. Available evidence suggests that acute pancreatitis in our patient was probably precipitated by therapeutic dose of metformin with normal renal function, with unknown exact mechanism.

Conclusion

In summary, our case demonstrates the possibility of metformin to induce pancreatitis in a healthy patient without preexisting renal disease. Accordingly, every diabetic patient on metformin should be counseled about symptoms of acute pancreatitis and the urgency to discontinue metformin and visit the emergency department to receive the appropriate treatment. And for us as physicians, metformin should be kept in back of our minds as a cause that would contribute to acute pancreatitis even in a healthy patient.

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