

Metformin: A Differential Diagnosis for Weight Loss, Altered Bowel Habits and B12 Deficiency Anemia in an Elderly Diabetic

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INTRODUCTION

Weight loss, altered bowel habits and anemia, especially in the elderly are symptoms which warrant further investigation. The main concern would be of an underlying gastrointestinal malignancy. Patients will usually be subjected to a battery of tests, including a colonoscopy examination. Here we present a case whereby Metformin, a common anti-diabetic drug caused the above symptoms and B12 deficiency anemia.

CASE REPORT

A 74 year old Chinese gentleman was referred to us for altered bowel habits for the past one year. He would have loose stools up to 5-6 times per day which occurred soon after a meal. He did not pass any blood or mucus and his stools were not bulky, oily nor difficult to flush away. He found this problem very distressing as he led an active lifestyle and enjoyed travelling.

He did not experience any abdominal pain but lost around 12 kg during this time. He weighed 53 kg, with a BMI of 21.1 kg/m² when he first consulted us. His appetite remained good; in fact, he claimed he was eating much more than he used to. He did not have other symptoms to suggest thyrotoxicosis and did not have fever, night sweats or chronic cough. He did not have any reduced effort tolerance, shortness of breath or dizziness.

The patient was diagnosed with hypertension and type 2 diabetes mellitus 20 years ago. His sugar control was exceptional with HbA1c of 6.3 % and was free of chronic complications from both diabetes and hypertension. He did not have any family history of malignancy and does not drink alcohol or smoke. He has been on stable doses of Gliclazide 120 mg bd, Metformin 1 g bd, Aspirin 150 mg OD, Vitamin B complex 1 tablet OD and Perindopril 4 mg OD for the past two years.

On examination, he was noted to be pale with no jaundice. Blood pressure was 160/80 mmHg and pulse rate 92 beats per minute. His tongue was smooth with loss of papillae. Respiratory and cardiovascular systems were normal. No organomegaly was palpable per abdomen and he had no peripheral lymphadenopathy.

Blood investigations revealed macrocytic anemia with hemoglobin of 8.2 g/dl, MCV 108.8 fl and MCH 37.8 pg. His white cell and platelet counts were normal. Serum B12 levels were low, 69 pmol/l (156-690) but folate was within the normal range. Iron studies were also normal. His thyroid function test, renal profile and liver function test were normal with a serum albumin of 46 g/l. Further investigations included a chest radiograph, OGDs, capsule endoscopy and colonoscopy, all of which did not reveal any pathology. CT abdomen was also normal.

The patient was given IM vitamin B12 replacement, initially 1 mg alternate day for 3 days, then 1 mg weekly for 3 weeks followed by monthly for 3 months. Patient's immediate release Metformin was substituted with Metformin XR (sustained release) of an equivalent dose. This was followed by only a slight improvement in the frequency of his loose stools.

About two weeks after his initial consultation, the patient was admitted for symptomatic hypoglycemia. His family members found him unresponsive and drowsy. His capillary blood sugar was 2.6 mmol/l at that time. He made rapid recovery with glucose infusion and cessation of his oral hypoglycemic agents. Malabsorption due to Metformin as well as being on rather high doses of the sulfonylurea Gliclazide probably caused the hypoglycemic episode. After the hypoglycemia had resolved, the patient was started on Gliclazide MR 30 mg dly.

The patient's symptoms dramatically improved and he passed motion only once per day. His stools were also now well formed. During subsequent follow-up, the patient remained well; he gained about 10 kg over the following year. His hemoglobin also increased to 12.4 g/dl with normalization of his MCV, MCH and B12 levels.

Unfortunately, his sugar control worsened and his HbA1c increased to 8.8% despite being on maximum doses of Gliclazide MR. As the patient was not keen for insulin injections, Sitagliptin 100 mg dly and subsequently Acarbose 50 mg bd was added. We were able to bring his HbA1c down to 7.5%.

This article was accepted: 5 February 2013

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DISCUSSION

Type 2 Diabetes Mellitus is a common chronic disorder. Previously thought to be a disease of the affluent, its prevalence is now rising worldwide. Since findings of the United Kingdom Prospective Diabetes Study (UKPDS) came out in the late 1990's, the management of type 2 diabetes mellitus has been evolving constantly with a focus on prevention of chronic micro and macro-vascular complications. The recent American Diabetes Association (ADA) position statement recommended that Metformin be used as the first-line treatment option for type 2 Diabetes Mellitus apart from therapeutic lifestyle changes¹.

Metformin hydrochloride is a biguanide which lowers both fasting and post-prandial glucose in type 2 diabetics. It acts mainly by improving insulin sensitivity and decreasing hepatic glucose production. Common adverse effects include diarrhea (9.6%-53.2%), nausea (6.7%-25.5%), flatulence (12.1%) and indigestion (7.1%); the incidence being generally lower with the extended release formulation². The exact mechanism of how Metformin causes diarrhea is not known. Possible mechanisms include malabsorption and increase in intestinal motility. A rarely reported but usually included side effect in most product inserts is B12 deficiency and malabsorption.

De Jager, *et al* reported in a study that after an average of 4.3 years of Metformin, the absolute risk for vitamin B12 deficiency was 7.2% higher with Metformin as compared to placebo (95% CI, 2.3 - 12.1; P = 0 .004), with 19% decrease in B12 concentration³. The mechanism for Metformin induced B12 deficiency has been postulated to be due to Metformin affecting the calcium dependant B12-intrinsic factor complex uptake by ileal cell membrane receptors⁴.

In the above mentioned case, the patient's symptoms resolved after stopping Metformin, with improvement in his hemoglobin concentration. No alternative explanation for his symptoms was found. Although no recommendation exists for regular screening of patients on Metformin for B12 deficiency, there may be a role for checking a patient's serum B12 levels or MCV/MCH in those who present with gastrointestinal symptoms, weight loss, anemia or peripheral neuropathy.

CONCLUSION

Metformin is recommended as the first line treatment for type 2 diabetes mellitus apart from therapeutic life-style changes. Gastrointestinal side effects are common with Metformin. It can also cause malabsorption and B12 deficiency. A high index of suspicion is needed to avoid unnecessary investigations in a diabetic who is on Metformin who presents with macrocytic anemia, weight loss and altered bowel habits.

ACKNOWLEDGEMENT

The author would like to thank the Director-General of Health, Malaysia for his permission to publish this case report.

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