Case report

Pellagra in the USA: unusual manifestations of a rare entity

Ana Rivadeneira, Patricia Moyer, Justin D Saliccioli

Department of Medicine, Mount Auburn Hospital, Cambridge, Massachusetts, USA

Correspondence to

Dr Justin D Saliccioli,
justin.saliccioli@gmail.com

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SUMMARY

The case involves a 62-year-old female native of the USA with a history of bipolar disorder and chronic obstructive pulmonary disease who presented with intractable diarrhoea. Prior to the index admission, she was admitted to the intensive care unit and required pericardiocentesis for an idiopathic pericardial effusion with tamponade physiology. Following discharge, she suffered intractable diarrhoea and represented for medical evaluation. She had a painful, swollen tongue as well as persistent hypoglycaemia and required glucose infusions. She had adrenal function testing which revealed adrenal insufficiency. Vitamin testing revealed normal B₁₂ and folate levels but undetectable levels of thiamine, riboflavin and niacin. Her symptoms and signs resolved entirely with appropriate vitamin supplementation. Niacin (vitamin B₃) is essential for multiple metabolic pathways, and severe deficiency may cause clinical syndrome of pellagra which is most commonly associated with diarrhoea, delirium and dermatitis. Additional physiological derangements may include adrenal insufficiency, insulin hypersensitivity and pericarditis.

BACKGROUND

Pellagra is rare in developed nations such as the USA and is commonly associated with diarrhoea, delirium and dermatitis. This case of pellagra highlights multiple metabolic and physiological derangements in states of severe vitamin deficiency including adrenal insufficiency and pleuropericardial effusions.

CASE PRESENTATION

A 62-year-old woman native to the USA presented to the emergency department with diarrhoea. The patient reported 2 months of persistent non-bloody diarrhoea occurring approximately 8 or 10 times per day. During hospitalisation 2 months prior to the index presentation, *Clostridium difficile* antigen testing was indeterminate, and reflex PCR testing was positive. However, there were no systemic signs of infection at that time, and eradication therapy was deferred. Following discharge to rehabilitation facility, the patient had persistent diarrhoea in the absence of other systemic signs of infection and was started on a 10-day course of oral vancomycin for *C. difficile* eradication. There was reduced oral intake due to loss of appetite as well as significant mouth, lip and tongue pain. There were

no other systemic symptoms and she denied fever, chills or sweats.

The medical history included depression, bipolar disorder, seizure disorder, chronic obstructive pulmonary disease, hypothyroidism, hyperlipidaemia and gastro-oesophageal reflux disease. Her medications at the index presentation included aspirin, simvastatin, omeprazole, levothyroxine, sertraline, sodium valproate, colchicine and trazodone. She is married with two children. There is a 40 pack-year smoking history and uses medical marijuana. There is no alcohol or illicit substance abuse. She had never travelled outside northeastern USA. Family history is notable for inflammatory bowel disease.

In the year leading to presentation, the patient had lost approximately 36 kg body weight but remained obese at the time of index presentation. Approximately 2 months prior to index presentation, the patient was admitted to psychiatric unit under section 12 and diagnosed with possible delirium related to depression with possible sodium valproate toxicity. The patient developed sharp pleuritic chest pain, hypercarbic respiratory failure, hypotension and tachycardia. She required emergent intubation and mechanical ventilation as well as vasopressor support. CT of the chest with contrast was negative for pulmonary embolism and aortic dissection but revealed moderate pericardial fluid ([figure 1](#)). Transthoracic echocardiogram revealed pericardial effusion with tamponade physiology, and she was transferred to the intensive care unit for management of spontaneous pericardial tamponade. She underwent pericardiocentesis, and pericardial fluid was negative for infection with normal cell cytology. Given the change in her clinical status, *C. difficile* testing was sent which revealed indeterminate toxin with positive antigen testing. There was no evidence of systemic inflammation at the time with normal inflammatory markers, and *C. difficile* eradication therapy was not initiated. She was discharged to a rehabilitation facility with a diagnosis of idiopathic pericarditis and was started naproxen 600 mg three times per day for 1 week as well as colchicine 1.2 mg on the first treatment day followed by 0.6 mg/day for 1 week which was then increased to 0.6 mg two times per day for an anticipated 3-month treatment course. At the rehabilitation facility, she had persistent diarrhoea without symptoms of infection which persisted for greater than 2 weeks, and she was started on empiric oral vancomycin.

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Figure 1 Transverse section of CT of the chest which reveals moderate-sized pericardial effusion.

At index presentation, the patient's temperature was 36.7°C, heart rate 75 beats/min, blood pressure 121/77 mm Hg with oxygen saturation 98% while breathing ambient air. She was comfortable appearing without acute distress. There were no obvious rashes or skin discolouration. Eyes were symmetric with normal pupillary responses. There was no nystagmus or disorder of eye movements. There was angular cheilitis and a large painful beefy tongue (figure 2A). Cardiopulmonary examination was normal. There was no abdominal tenderness and no palpable masses with normal bowel sounds. The neurological examination was otherwise normal.

INVESTIGATIONS

The white cell count was $5.0 \times 10^9/L$, haemoglobin level 124 g/L, mean cell volume 91.5 fL and platelet count $192 \times 10^9/L$. The basic metabolic panel revealed sodium 139, potassium 4.8 with serum glucose 42 mg/dL (3.4 mmol/L). Liver function testing and lipase within normal limits. Thyroid stimulating hormone (TSH) was 1.99 (reference: 0.465–4.68 $\mu IU/mL$). Valproate level 34 $\mu g/mL$ (reference: 50–100 $\mu g/mL$). Stool studies for culture, ova and parasites and stool leucocytes were within normal limits. Anti-tissue transglutaminase and anti-gliadin studies were normal.

Figure 2 (A) Photograph showing an enlarged, beefy tongue at presentation to hospital. Associated symptoms also included intractable diarrhoea. (B) Photograph showing resolution of tongue following supplementation with vitamins.

Repeat serum glucose testing by capillary blood glucose test and serum levels were 28 mg/dL and 30 mg/dL, respectively. Random serum cortisol was 0.8 $\mu g/dL$ (reference: 4.46–22.7 $\mu g/dL$) and subsequent synthetic adrenocorticotrophic hormone (ACTH) stimulation test revealed an inadequate rise in cortisol from 2.37 to 8.0 $\mu g/dL$ at 60 min. Follicle-stimulating hormone levels were 4.54 mIU/mL. ACTH level was 12 pg/mL (reference: 6–50 pg/mL).

Markers of nutritional status at the time of presentation revealed thiamine 7 nmol/L (reference: 8–30 nmol/L), vitamin D 25 hydroxy 33.6 ng/mL (reference: 30–100 ng/mL), iron 54 $\mu g/dL$ (reference: 35–143 $\mu g/dL$), folic acid 13.60 ng/mL (reference: >2.76 ng/mL), vitamin B₁₂ 888 pg/mL (reference: 239–931 pg/mL), vitamin B₆ 6.0 ng/mL (reference: 2.1–21.7 ng/mL), zinc 83 $\mu g/dL$ (reference: 60–130 $\mu g/dL$) and niacin <20 ng/mL (reference >20 ng/mL).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included infectious causes (eg, *C. difficile*), inflammatory (eg, inflammatory bowel disease, amyloidosis), toxic causes (eg, colchicine therapy) and metabolic causes (eg, vitamin B₁₂, insulin hypersecretion or micronutrient deficiency). With respect to infectious causes, the patient was non-toxic appearing at presentation and no evidence of systemic inflammation on blood testing. Additionally, she had completed a full course of oral vancomycin for eradication. Stool culture, *C. difficile* toxin, ova and parasite, and yersinia were normal. Given her weight loss over the preceding months, inflammatory bowel disease is possible. However, stool was non-bloody, without faecal leucocytes and normal celiac screening antibodies. While colchicine has been associated with diarrhoea, this medication was initiated following symptom onset and less likely related temporally. Metabolic causes such as vitamin deficiency were examined at presentation with serum levels of vitamins B₁, B₃, B₆, B₁₂, folic acid and vitamin D.

TREATMENT

The patient was haemodynamically stable and without hypoglycaemic awareness. Blood testing was performed prior to treatment for micronutrient deficiency. Her colchicine was stopped at presentation, and other medications were continued. She received thiamine intravenously, as well as vitamin B₁₂, folate and multivitamins. She required infusion of dextrose 5% and 0.45% saline for a duration of 4 days. She required in two occasions 25 mg intravenous dextrose (dextrose 50%). Following identification of adrenal insufficiency, she was treated with prednisone 5 mg/day.

OUTCOME AND FOLLOW-UP

The patient's symptoms of diarrhoea, hypoglycaemia and painful, swollen tongue improved following supplementation with appropriate vitamins (figure 2B). Repeat micronutrient testing in the outpatient setting revealed thiamine 121 (8–30 nmol/L), nicotinimide 27 ng/mL (reference: >20 ng/mL) and niacin 26 ng/mL (reference: >20 ng/mL). She underwent MRI of the brain which revealed empty sella.

DISCUSSION

Pellagra is uncommon in industrialised nations, and there are few recent reports of this clinical entity.¹ Niacin deficiency may result from chronic alcohol consumption, chronic liver disease or gastrointestinal malabsorption, anorexia nervosa or poor dietary intake. In the present case, niacin deficiency is likely to

be multifactorial. There was an antecedent history of anorexia with significant weight loss. Further, the adrenal insufficiency identified in this case also raises mechanistic explanations for niacin deficiency and pellagra presentation.

Niacin is an essential micronutrient and plays a central role in regulating multiple metabolic pathways including, but not limited to, energy metabolism (eg, Krebs cycle), DNA repair (including ultraviolet-related damage), free-fatty acid release and lipid profile, as well as steroid synthesis. The main source of niacin is dietary and typically 11 or 12 mg/day is required to maintain normal cellular and biochemical function in adults.² In the absence of adequate dietary intake, the liver is able to synthesise endogenous niacin from tryptophan via Trp 2,3-dioxygenase (TDO).³ The adrenal insufficiency observed in this patient impaired glucocorticoid induction of TDO, thereby limiting TDO synthesis of niacin from Trp. Further, the metabolism of tryptophan to nicotinic acid requires other B vitamins, including thiamine (vitamin B₁), riboflavin (vitamin B₂) and pyridoxine (vitamin B₆), via the hepatic kynurenine pathway, and deficiency in one or more of these vitamins may reveal the peculiar manifestations of each but also aggravate niacin deficiency through impaired tryptophan metabolism.³

Insulin hypersensitivity has been described previously in states of severe niacin deficiency.⁴ Rosenthal and Lees reported Addisonian crisis secondary to severe niacin deficiency which is thought to be due to 'failure in the main two organs implicated (with others) in the regulation of carbohydrate metabolism, the adrenal glands and the liver'.⁵ Previous reports have demonstrated pericardial effusion as a presentation of adrenal insufficiency,^{6,7} and other cardiac manifestations of adrenal insufficiency have been described in isolated cases.^{8,9}

The clinical presentation of pellagra classically includes gastrointestinal, dermatological and neurocognitive alterations. In addition to these classical features of niacin deficiency, the current case highlights that severe nutritional deficiency may also result in life-threatening multiorgan dysfunction. The constellation of symptoms and findings in this case are diverse but may

be explained by severe micronutrient deficiency and to the best of our knowledge, no previous report has demonstrated the association between niacin deficiency, adrenal insufficiency and pericardial effusion. The patient's poor dietary habit for nearly 1 year leading to her presentation with profound weight loss during this time raised the concern for nutrient deficiency. The dermatologic manifestation of pellagra usually affects sun-exposed areas and was likely not immediately apparent in this case as the patient had been bed bound for many months due to underlying psychiatric illness without significant sunlight exposure.

Learning points

- ▶ Niacin is an essential micronutrient and deficiency of which may result in multiple physiological and metabolic derangements.
- ▶ The syndrome of pellagra is most often associated with diarrhoea, delirium and photosensitive skin rash. Adrenal insufficiency, insulin hypersensitivity and pleuropericardial effusions have also been reported.
- ▶ Although rare in developed regions of the world, micronutrient deficiency should also be considered for complex presentations without a clear aetiology.
- ▶ Significant nutritional deficiency accompanied by persistent diarrhoea and profound adrenal insufficiency may have contributed to the niacin deficiency observed in this case, although previous reports have suggested adrenal insufficiency secondary to niacin deficiency.

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ORCID iD

Justin D Saliccioli <http://orcid.org/0000-0001-8092-0883>

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Patient's perspective

There is a lot of the experience that I am unable to remember. My thinking was not entirely clear at the time, but I remember being very worried about my tongue. In general, I do worry a fair bit about my health and my family often tells me that I worry too much. At the time, I felt like I was going to choke and was really worried about sleeping as it could block off my breathing. I could not imagine what could be wrong, but I had been in the intensive care unit, and my initial thought was that the pain and swelling of my tongue related to the tube that I needed while on the ventilator.

My symptoms did improve with the vitamins, but the improvement took a few weeks and maybe as long as a month for my mouth to feel better. My blood sugars were still very low when I left hospital and have improved with the prednisone that I am taking every day. I never have symptoms of low blood sugar, but I have a blood sugar monitor and use this regularly.

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