Journal of Community Hospital Internal Medicine Perspectives

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CASE REPORT

Zinc-deficiency acrodermatitis in a patient with chronic alcoholism and gastric bypass: a case report

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Acquired adult-onset zinc deficiency is occasionally reported in patients with malnutrition states, such as alcoholism, or malabsorptive states, such as post-bariatric surgery. The defining symptoms of hypozincemia include a classic triad of necrolytic dermatitis, diffuse alopecia, and diarrhea. We report a case of zinc deficiency in a 39-year-old man with history of gastric bypass surgery and alcoholism. For this patient, severe hypozincemia confirmed acrodermatitis, and zinc supplementation was met with gradual improvement.

Keywords: *acquired*; *zinc defiency*; *bariatric surgery*; *alcoholism*; *malnutrition*

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Received: 19 April 2014; Revised: 9 June 2014; Accepted: 16 June 2014; Published: 31 July 2014

Acquired adult-onset zinc deficiency may stem from poor intake, diminished uptake, or enhanced excretion. Clinically and histologically this entity belongs to the family of necrolytic erythema that include necrolytic migratory erythema, necrolytic acral erythema, and pellagra (1). The defining symptom is a papulosquamous erupting rash with well-demarcated borders, which characteristically crusts, scales, and eventually erodes. These patches of inflamed skin may begin in orificial and intertriginous regions before migrating outwards. A diffuse alopecia and watery, non-bloody diarrhea completes a classical triad. Other symptoms may include poor appetite, weight loss, immune dysfunction, and delayed wound healing.

In developed countries with stable socioeconomic societies, two notable causes of acquired zinc deficiency are malnutrition from alcoholism and malabsorption from gastric bypass surgeries (2, 3). Their combined incidence is not unusual, according to a report by King et al., which states there is an increased incidence of alcohol abuse in gastric bypass patients 2 years postoperatively (4). Furthermore, studies have quantified the extent of zinc deficiency in both conditions. A study assessing the effect of Roux-en-Y gastric bypass on zinc status found diminished plasma zinc levels as early as 6 months postoperatively compared to preoperative zinc levels (5). In addition, approximately 30–50% of alcoholics are found to have low zinc status because ethanol consumption decreases intestinal absorption of zinc and increases urinary zinc excretion (6). Although not conclusively established in literature, one would expect a combination of malnutrition and malabsorption to be additive if not synergistic toward hypozincemia.

The reported case is of a 39-year-old man with history of chronic alcoholism and gastric bypass procedure admitted for a syncopal episode. During initial evaluation, he was noted to have dry, peeling skin rash in acral and orificial regions that progressed into desquamating lesions over several days. We believe this case to be a delayed onset of acrodermatitis in a patient with two significant risk factors. Furthermore, we seek to clarify the underlying mechanism for progressive symptomatology despite nutrition replacement.

Case report

A 39-year-old male with medical history of gastric bypass surgery and chronic alcoholism was admitted for a syncopal episode. Previously, the patient underwent Roux-en-Y gastric bypass in 2008 after failed lifestyle modifications in effort to reduce body weight. Additionally, in the last two and half years, the patient had abused alcohol in the amount of one pint daily, 3 days per week. In the interim, he suffered multiple syncopal episodes with the most recent occurring 2 weeks previously. That admission was attributed to alcohol withdrawal seizures after an uneventful hospital course and unremarkable workup.

The patient was at a grocery store on the day of admission when he had one episode of unwitnessed 'passing out' with urinary incontinence. This presentation

Citation: Journal of Community Hospital Internal Medicine Perspectives 2014, **4**: 24707 - http://dx.doi.org/10.3402/jchimp.v4.24707

was similar to his previous admission 2 weeks earlier with added complaints of four episodes of non-bloody watery diarrhea and dry skin on his lower extremities. Vital signs were stable except orthostasis. Physical examination revealed conjunctival pallor and scleral icterus. There was mild epigastric tenderness and left hip tenderness. Skin examination showed multiple patches of dry, peeling skin on both feet (Image 1). Neurological and cardiopulmonary examinations were unremarkable. Significant laboratory values included Hb 8.7 g/dL (normal 13.5–17.5 g/dL), and liver functions consistent with alcoholism (AST 139 U/L [8–20 U/L], ALT 52 U/L [8–20 U/L], alkaline phosphate 196 U/L [20–70 U/L], and total bilirubin 2.9 mg/dL [0.1–1.0 mg/dL]). INR was 1.3 with significant electrolyte abnormalities of hypomagnesemia (0.9 mg/dL [1.6–2.3 mg/dL]) and hypophosphatemia (2.2 mg/dL [2.5–4.5 mg/dL]). Urine toxicology was positive for opiates and ethanol level was <3 mg/dL. Head CT showed diffuse atrophy, and the electrocardiogram showed normal sinus rhythm. An echocardiogram revealed ejection fraction of 45%. Abdominal radiographs revealed hepatomegaly and surgical sutures of the previous gastric bypass surgery. Abdominal ultrasound showed fatty liver changes with normal appearing pancreas. The patient was placed on chlordiazepoxide and given thiamine along with multivitamins. The alpha agonist midodrine was given for orthostasis.

At this time, the clear history of gastric bypass surgery compounded by alcoholism in conjunction with an extensive and unremarkable initial workup lead to the conclusion that the constellation of signs and symptoms were related to a single etiological process.

He was transfused two units of packed blood cells due to a repeat Hb of 6.7 g/dL. A previous esophagogastroduodenoscopy a month prior showed distal esophagitis and hiatal hernia. These relatively benign findings, combined with an unremarkable abdominal CT scan just prior to transfusion, prompted the combined decision of the primary team and the gastroenterology consult to defer further esophagogastroduodenoscopy studies. On day 5, the patient had altered mental status for which a head CT and CSF analysis were done, and were normal. Later that day, the cutaneous lesions worsened to include both hands, extensor surfaces of the arms, and around the mouth. Previously dry skin was noted to be tender and desquamating (Images 2–5). Diarrheal episodes had increased to five times daily. In light of leukocytosis 16 K/UL (4.0–10.8 K/UL), infectious disease consult was placed. Among important differentials considered were cellulitis, Stevens-Johnson syndrome, and staphylococcal scaled skin syndrome. Stevens-Johnson syndrome, a possible adverse effect of midodrine, was quickly ruled out clinically due to lack of progression of lesions or mucosal involvement. Empirical vancomycin was begun for presumptive cellulitis after an initial set of blood cultures grew methicillin sensitive *Staphylococcus aureus* in one of two bottles. Stool cultures were negative despite progressing diarrhea and leukocytosis. Repeat echocardiogram (EF 75%) did not reveal vegetations. Additional investigations for the skin rash revealed negative tissue transglutaminase and ANCA. Nutritional indices recommended by a nutritionist included folate 47.2 ng/mL (2.8–14.0 ng/mL), B12 1,699 pg/mL (211–911 pg/mL), zinc 0.27 μg/mL (0.66–1.10 μg/mL), and copper 65 μg/dL (70–175 μg/dL). Niacin level was 2.66 μg/mL (0.50–8.45 μg/mL). Skin biopsy revealed mild psoriasiform hyperplasia with broad parakeratosis. The epidermis lacked a granular layer and demonstrated spongiosis. The finding of zinc deficiency along with a negative repeat blood culture prompted discontinuation of vancomycin on day 4 of treatment by infectious disease, with the original positive blood culture being attributed to contamination. The focus of etiology shifted from an infectious process to either a drug reaction or nutritional deficiency with zinc deficiency the working diagnosis. Zinc supplementation (220 mg/daily) was started along with corticosteroids before transfer to a tertiary care center for definite diagnosis of the skin biopsy.

On admission to the tertiary center, a rash was noted to have progressed and the patient was still severely orthostatic, requiring continued use of midodrine. Oral steroids were started but discontinued after a dermatology consult

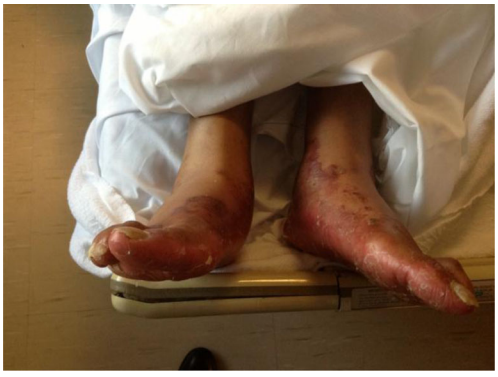

Image 1. Multiple patches of dry, peeling skin bilaterally.

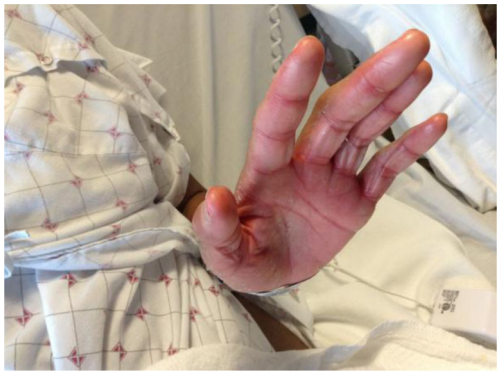

Image 2. Peeling skin on left hand, day 17.

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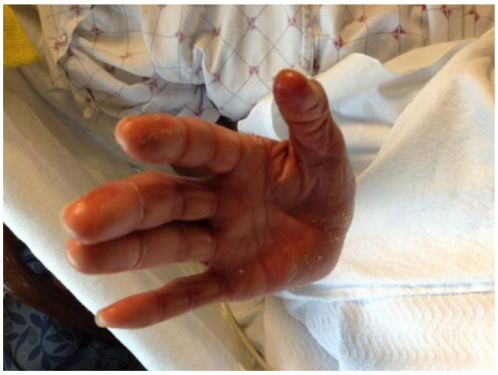

Image 3. Peeling skin on right hand, day 17.

attributed the lesions to nutrient deficiency, while also considering Stevens-Johnsons syndrome, pellagra, and glucagonoma syndrome in the differential diagnoses. An upper GI small bowel series showed a mild gastrojejunal stricture measuring 1 cm. With poor oral intake, total parenteral nutrition was initiated but discontinued after development of *Candida parapsilosis* fungemia. The patient's previously poor appetite improved with encouragement and low-dose mirtazapine. The rash showed continuous improvement with maintained dosages of zinc (220 mg/daily) with gradual clearance of desquamative lesions upon discharge. The patient was encouraged to continue vigorous oral and nutritional supplementation and to follow up in 2 weeks.

Discussion

The role of zinc as an essential nutrient in human metabolism has been well known for decades. Zinc has been demonstrated as an integral constituent of the catalytic site of hundreds of metalloproteinases, most notably alkaline phosphatase and carbonic anhydrase. Additionally, zinc finger proteins, a special motif of various steroid hormone receptors, play a special role in structural differentiation of multiple organs including the skin. The decreased enzymatic activity precipitated by zinc deficiency manifests as a broad range of clinical signs and symptoms.

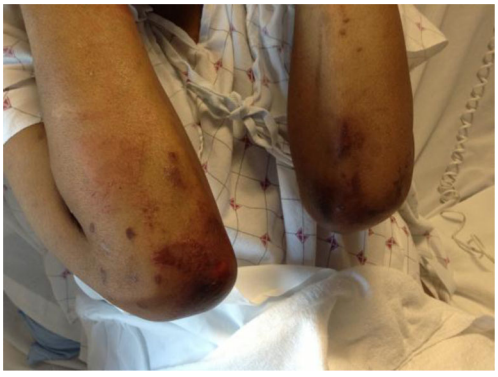

Image 4. Extensor desquamation, day 17.

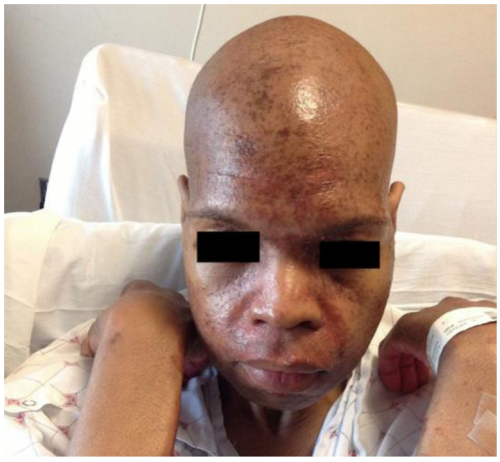

Image 5. Perioral dermatitis, day 18.

Zinc deficiency has been implicated in delayed puberty, impaired cognition, diarrhea, alopecia, dermatitis, immune dysfunction, and delayed wound healing (7).

The transport protein ZiP4 mediates the absorption of zinc in the jejunum. The inherited autosomal recessive deficiency of this transporter is termed acrodermatitis enteropathica. This clinical entity was first described as a rash with diarrhea in 1936 by Brandt, and first reported by Danbolt (8). Later studies revealed low zinc levels correlated with symptoms by demonstrating improvement when zinc was replaced (9). A similar clinical entity occurring commonly in later years of life is termed acquired acrodermatitis or acquired zinc deficiency. The patient in the case report suffered acquired zinc deficiency due to two significant risk factors: alcoholism and gastric bypass surgery. Other conditions linked with zinc deficiency include anorexia nervosa, total parenteral nutrition, pancreatic disorders, malignancies, and renal disorders (10).

As mentioned, one important risk factor for zinc deficiency is previous gastric bypass surgery. Gastric bypass surgery is the most common form of bariatric surgery, with Roux-en-Y bypass the most popular, having doubled in number between 2003 and 2009. The procedure entails a portion of the stomach being made into a small 30-mL pouch that is then attached to a distal segment of intestine. This anastomosis avoids the entirety of the duodenum and the majority of the jejunum that comprise major locations for micronutrient absorption. Perioperative complications are generally quite low while numerous post-operative complications exist (11).

One important complication is nutrient depletion secondary to gut manipulation, which alters sites for natural absorption. To that end, a major component of post-operative management in bariatric patients is vitamin supplementation. A useful guideline published in 2008 by Aills et al. expertly outlined suggested supplement regimens (12). Important causative factors for post-operative

nutrient deficiencies are poor follow-up and noncompliance on the part of patients. A study by Dalcanale et al. found the following deficiencies in 75 patients up to 5 years post Roux-en-Y procedure: magnesium (32%), zinc (40.5%), B12 (61.8%), and vitamin D3 (60.5%). Most of the deficiencies were attributed to patient noncompliance of post-operative vitamin replacement regimens (13) An additional study by Toh et al. demonstrated low levels of ferritin (15%), B12 (11%), RBC folate, and vitamin D (12%) for similar reasons (14). The reported patient suffered appreciable deficiencies in zinc and copper, with normal B12 and folate indices.

Aside from the symptoms of hypozincemia, the patient also suffered possible hypocupremia induced peripheral neuropathy in the form of moderate orthostasis requiring the alpha agonist midodrine after failed fluid challenge. Copper, similar to zinc, is an important cofactor in enzymatic reactions, particularly important in processes pertaining to anti-oxidation. Absorption occurs primarily in gastric and duodenal mucosa with recommended daily allowance of 700 μg (11). Copper deficiency presents with neuropathy, cutaneous lesions, and increased neuromuscular tone. The interaction of copper and zinc at the molecular level of absorption is an important consideration when treating zinc deficiency with zinc supplementation. Zinc upregulates the expression of the important chelator, metallothionein at the level of enterocytes. Copper's increased affinity for this chelator results in it being bound and trapped in the enterocyte while zinc is free to be absorbed into the bloodstream. For bariatric patients requiring zinc supplementation, co-administration of copper supplementation is suggested to avoid cuprate deficiency (15). For the reported patient, the amount of copper in the standard multivitamin was deemed sufficient not to warrant stand-alone dosages.

It is the belief of the authors that zinc deficiency is a common yet significantly underdiagnosed entity. Therefore the diagnosis of zinc deficiency requires a high index of suspicion in bariatric patients due to the large overlap in symptoms amongst nutritional deficiencies. Specifically, the cutaneous manifestations of peeling and later desquamating, ulcerating skin requires considering multiple differential diagnoses. Zinc deficiency falls under the category of necrolytic erythemas that include necrolytic migratory erythema, necrolytic acral erythema, and pellagra. Necrolytic migratory erythema is a blistering, patchy rash that spreads across the abdomen, perineum, and buttocks. It is associated with glucagonoma, a glucagon-producing tumor of the pancreas, which is definitely diagnosed with CT or ultrasonography. Its histopathology is characterized by parakeratosis and epidermal necrosis in a psoriasiform pattern (16). Necrolytic acral erythema shares similar histology but classically the lesions are well circumscribed and dusky with an adherent scale. It is most classically associated with concurrent Hepatitis C infection (17). Pellagra is deficiency of niacin and classically presents as a diarrhea, dermatitis, and dementia in patients. Normal niacin levels, lack of hepatitis C risk factors, and continually normal abdominal imaging were sufficient to rule out these entities. Furthermore, a clear history of post-surgical failure to thrive and hypozincemia with resulting improvement with daily zinc, clinched the diagnosis.

One important feature of the case was the progressive worsening of symptoms despite appropriate multivitamin replacement for chronic alcoholism. One possibility is that multivitamin replacement causes brief, sustained increases in metabolism demand in highly active tissues such as gastrointestinal mucosa and skin. With such upstrokes in metabolism in the background of decreased zinc level, relevant zinc-mediated enzymatic reactions would continue to proceed in suboptimal fashion, acutely worsening symptoms. The basis for this thought is the established thiamine-glucose sequence of replenishment in hypoglycemic patient to guard against iatrogenic induction of Wernicke's encephalopathy and lactic acidosis. Thiamine is an important cofactor in key enzymes of the Krebs cycle following glycolysis. Deficiencies in thiamine force pyruvate to convert to lactate, causing lactic acidosis and altered mental status, organ damage, and possibly death (18). It is standard practice to administer thiamine before glucose to ensure such enzymatic pathways are able to handle substrates appropriately. Could the patient's condition have acutely worsened due to a similar mechanism? This question remains unanswered and additional studies are warranted to help revise established treatment protocols for alcoholism and zinc deficiency.

Conflict of interest and funding

No financial disclosures or conflicts of interest.

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