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# Pellagra Secondary to Medication and Alcoholism: A Case Report and Review of the Literature

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**Abstract**

Pellagra usually results from niacin deficiency and presents with the classic triad of dermatitis, diarrhea, and dementia. It is most commonly associated with malnutrition and poverty and is extremely rare in industrialized societies. Furthermore, pellagra can be induced by special clinical conditions that interfere with the intake, absorption, and metabolism of niacin. Because of its detrimental effects on health and its favorable prognosis after supplementation of nicotinamide, the importance of early diagnosis and treatment should be emphasized. Herein, we report a case of pellagra in a young alcoholic who underwent combined chemotherapy for tuberculosis. For the first time, a descriptive review of literature from 1957 to 2014 has been conducted to clarify potential etiologies of pellagra: alcoholism (35.24%, 37 articles), various medications (25.71%, 27 articles), inadequate oral intake (16.19%, 17 articles), malabsorption (13.33%, 14 articles), metabolic derangement (7.62%, 8 articles), excessive loss (0.95%, 1 article), and etiology unknown (0.95%, 1 article). (*Nutr Clin Pract*. 2016;31:785-789)

**Keywords**

niacin; pellegra; avitaminosis; dermatitis

Pellagra was first described by Don Gaspar Casal[1] in 1735 and named by Frapolli[2] in 1771. Onset of endemic pellagra was associated with poverty and undernutrition and was often observed in populations subsisting mainly on maize and rarely having fresh meat. As niacin-fortified foods have been popularized, endemic pellagra rarely occurs in industrialized societies. Nowadays, this disease is mostly confined to chronic alcoholics or impoverished populations.[3] However, some special clinical conditions can have a bearing on niacin deficiency and should be timely recognized. We report a case of pellagra induced by antituberculosis therapy in an alcoholic patient who was promptly diagnosed and appropriately treated. Furthermore, a review of literature has been conducted to clarify potential etiologies of pellagra.

## Case Presentation

A 29-year-old man was admitted to our hospital with complaints of skin lesions for 3 months and persistent diarrhea for 1 month. He was diagnosed with pulmonary tuberculosis 1 year ago and underwent antituberculosis therapy for 10 months (oral administration of isoniazid, 0.3 g/d; pyrazinamide, 1.5 g/d; rifampicin, 0.45 g/d; and ethambutol, 0.75 g/d). Skin lesions gradually developed, with symmetric involvement of bilateral extensor surfaces on forearms and feet and dorsal surfaces on hands. Cheilitis, glossitis, and oral ulcers were also present. Symptoms continued despite cessation of antituberculous agents. Persistent diarrhea, with watery stool 4–5 times per day, occurred 1 month before hospitalization. Occult blood was recurrently detected in his stool. Transient delirium and intermittent acroanesthesia were also present. The patient complained of poor appetite and ate only small amounts of food (with intake <1000 kcal/d), which led to 10 kg of weight loss in the recent 1 month.

The patient was a heavy alcoholic, consuming 100–150 g of alcohol daily for 3 years. Sometimes, he even skipped meals and replaced food with binge drinking.

On examination, he was emaciated and wasted, with a body mass index of 15.57 kg/m$^2$. Skin lesions of hyperkeratotic plaques, blisters, erythematous erosion, and hyperpigmented ulcers, all with sharp demarcation, were distributed symmet-

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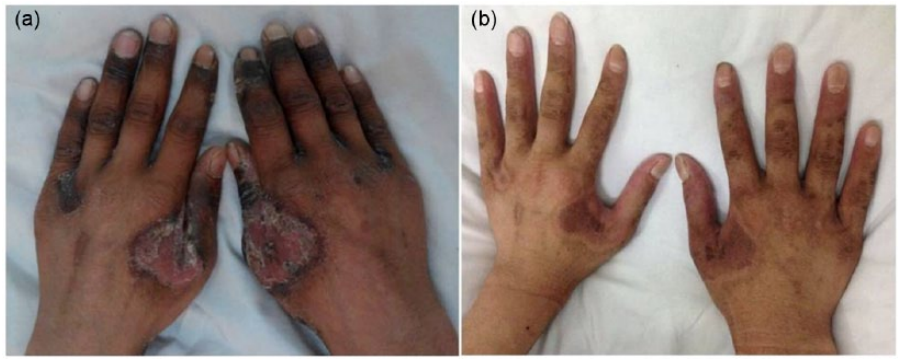


**Figure 1.** (a) Well-defined, hyperpigmented, hyperkeratotic, and symmetric skin lesions on dorsum of both hands. (b) Erosions improved after nicotinamide replacement.

**Table 1.** Laboratory Results in a Patient With Pellagra.

| Items | Results | Reference Range |
|---|---|---|
| White blood cells, $\times 10^9$/L | 13.83 | 4.0–10.0 |
| Platelet, $\times 10^9$/L | 521 | 100–300 |
| Hemoglobin, g/L | 96 | 120–160 |
| Mean corpuscular volume, fL | 77.8 | 82–97 |
| Mean corpuscular hemoglobin concentration, g/L | 308 | 320–360 |
| Mean corpuscular hemoglobin, pg | 27.0 | 27–32 |
| Albumin, g/L | 27 | 35–51 |
| Erythrocyte sedimentation rate, mm/h | 89 | 0–20 |

rically on bilateral forearms, feet, and dorsal surfaces of hands (Figure 1a). The physical examination was otherwise unremarkable.

Laboratory examinations, including complete blood count and basic metabolic panel, yielded nearly normal results except for mild anemia and hypoalbuminemia. The erythrocyte sedimentation rate was notably increased (Table 1). The chest computed tomography scan showed irregular patchy opacities and nodules in the upper lobe of the left lung, which was consistent with active pulmonary tuberculosis. Results from examinations of stool for fungi, ova, parasites, and other pathogens were negative. Colonoscopy revealed multiple shallow ulcers with irregular borders, involving descending colon, transverse colon, and cecum. The head magnetic resonance imaging found no abnormalities, while electromyography confirmed peripheral nerve injury. Owing to limited laboratory conditions, serum nicotinic acid concentration could not be measured. However, based on his clinical manifestation—especially on the history of prolonged alcoholism and isoniazid/pyrazinamide administration—pellagra was suspected.

Oral supplementation of nicotinamide (600 mg/d; 150 mg every 6 hours) was initiated, with concomitant administration of vitamin $B_1$ (10 mg/d), vitamin $B_{12}$ (0.5 mg/d), vitamin $B_6$ (20 mg/d), and B-complex vitamins (3 pills per day containing vitamin $B_1$, 9 mg; vitamin $B_2$, 4.5 mg; vitamin $B_6$, 0.6 mg; and niacin, 30 mg). The patient was advised to abstain from alcohol, and dietary instruction was provided to ensure sufficient dietary niacin (eggs, poultry, fish, red meat, legumes, and seeds). The patient was in regular follow-up every 2 weeks by dietitians to guarantee his adherence with the lifestyle suggestions. Furthermore, antituberculous treatment was continued, with isoniazid and pyrazinamide switched to levofloxacin (0.4 g/d) and streptomycin (0.75 g/d). Vitamin B supplementation was given during the whole antituberculosis treatment.

Diarrhea, glossitis, and oral ulcers resolved within 2 weeks. Skin erosions subsided in 1 month (Figure 1b), with partial remission of acroanesthesia. A colonoscopy was performed 2 months later and confirmed resolution of all the enteral ulcers.

## Discussion

Primary pellagra is a metabolic disorder caused by deficiency of cellular niacin. Currently, primary pellagra caused by undernutrition is unusual. Except for underfeeding, some other morbidities or clinical conditions may affect niacin absorption or metabolism. We conducted a literature search on pellagra from the databases of PubMed, EMBASE, and Ovid database between 1957–2014 (Figure 2). The search

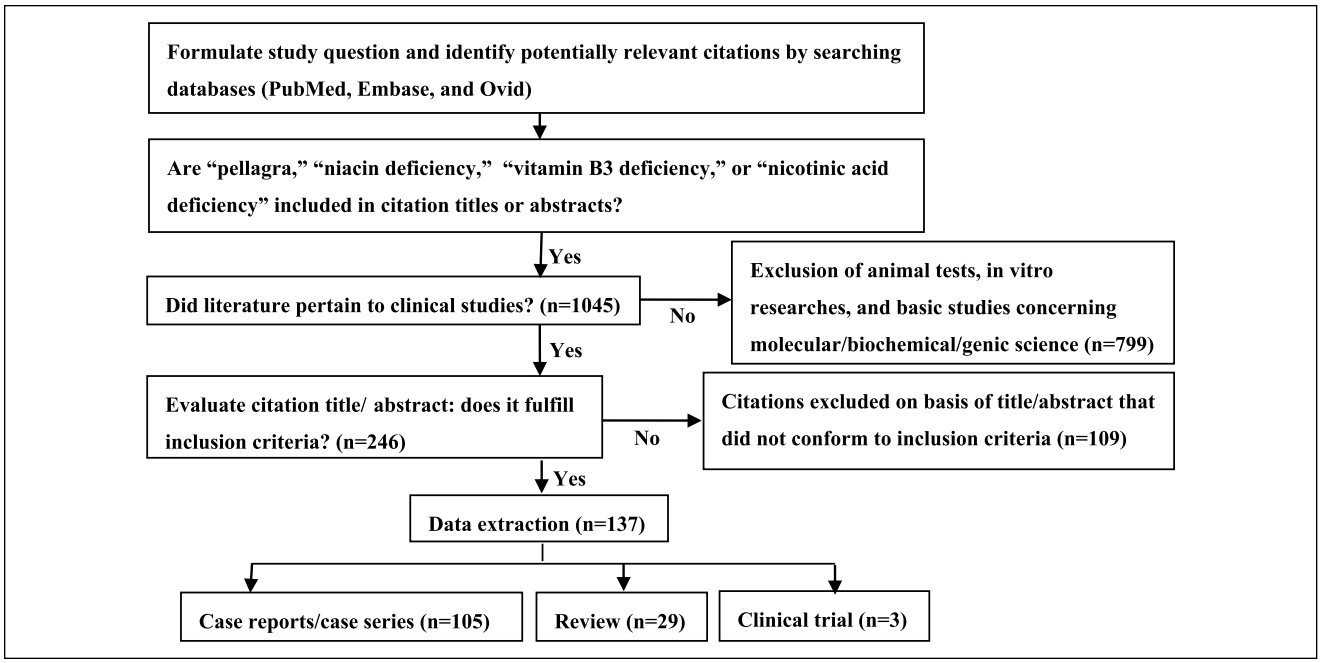


**Figure 2.** Search methodology stages and processing of literature.

terms included *pellagra, niacin deficiency, vitamin $B_3$ deficiency*, and *nicotinic acid deficiency*. A total of 137 clinical studies on pellagra were retrieved, with 76.64% of evidences based mainly on isolated case reports or limited case series (105 publications).

A review of these case studies (105 reports) indicated various etiologies of pellagra. Publications on alcoholism-associated pellagra accounted for the largest proportion (35.24%, 37 articles), followed by case reports on pellagra induced by various medications (25.71%, 27 articles), inadequate oral intake (16.19%, 17 articles), malabsorption (13.33%, 14 articles), metabolic derangement (7.62%, 8 articles), excessive loss (0.95%, 1 article), and unknown etiology (0.95%, 1 article; Table 2). These precipitating factors can influence the intake, absorption, processing, and metabolism of niacin in different ways, contributing to development of pellagra.

Niacin and nicotinamide are precursors of nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), which play a significant role as coenzymes or cosubstrates in myriads of vital oxidation-reduction reactions. Thus, deficiency of niacin may interfere with metabolism of carbohydrate, protein, and fatty acid and disturb the generation of high-energy phosphate bonds. These can lead to pellagra, resulting in a classical triad of dermatitis, diarrhea, and dementia.[4]

Insufficient niacin absorption or production in the human body may constitute complicated processes. Normally, niacin and nicotinamide can be absorbed directly from food or after they are generated from digestion of dietary NAD and NADP in the intestinal lumen. Niacin and nicotinamide can be also converted from absorbed tryptophan mainly in liver or kidney. The kynurenine pathway—a metabolic pathway leading to formation of niacin and nicotinamide from tryptophan degradation—depends on the effect of phosphopyridoxal-containing enzymes (kynurenine aminotransferase and kynureninase). Thus, pyridoxine deficiency may induce a niacin deficiency.[5] Riboflavin deficiency also disturbs tryptophan metabolism by inhibiting kynurenine hydroxylase and possibly kynureninase along the kynurenine pathway[5] (Figure 3). In short, cellular niacin deficiency results from inadequate intake of food containing niacin, nicotinamide, NAD, NADP, or tryptophan or from a conversion disorder of tryptophan to niacin.

Some medications can interrupt production of niacin from tryptophan. Effects of isoniazid[6-16] and pyrazinamide[17] on niacin conversion was depicted in previous case reports. Isoniazid is the structural analog of niacin and may competitively suppress endogenous niacin production. Inhibited production of pyridoxine by isoniazid can also interfere with biosynthesis of niacin. Pyrazinamide, by playing a role similar to isoniazid, may also precipitate niacin deficiency.[7,17,18]

Severe alcoholism can likewise exert a negative effect on niacin production.[19-24] Chronic alcoholism may cause inadequate intake of protein (tryptophan) and vitamin B, inhibition of Trp 2,3-dioxygenase activity by an NAD(P)H-mediated allosteric mechanism, and repression of kynurenine aminotransferase and kynureninase activities by acetaldehyde through binding of their pyridoxal 5'-phosphate cofactor and thereby lead to disturbance of the kynurenine pathway.[5]

**Table 2.** Case Reports and Series (105 Publications) Categorized According to the Different Etiologies of Pellagra.

| Etiologic Causes | Publications, n |
|---|---|
| Alcoholism | 37 |
| Deficiency of intake | |
| Dietary deficiency | 11 |
| Anorexia nervosa | 5 |
| Total parenteral nutrition | 1 |
| Malabsorptive states | |
| Crohn's disease | 5 |
| Ulcerative colitis | 1 |
| Celiac disease | 1 |
| Esophageal carcinoma | 1 |
| Intestinal impairment induced by bacterial colonization | 1 |
| Pediatric malabsorption syndrome | 1 |
| Amyloidosis secondary to multiple myeloma | 1 |
| Gastrointestinal surgery associated complication | 3 |
| Gastrectomy | 1 |
| Roux-en-Y bariatric surgery | 1 |
| Jejunoileal bypass | 1 |
| Excessive loss: hemodialysis | 1 |
| Metabolic derangement | |
| Hartnup disease | 4 |
| Carcinoid tumor/carcinoid syndrome | 2 |
| Genetic defect in tryptophan metabolism (hydroxylation of kynurenine) | 2 |
| Drug-induced pellagra | |
| Isoniazid | 16 |
| Pyrazinamide | 1 |
| Ethionamide | 1 |
| Azathioprine | 2 |
| 5-Fluorouracil | 1 |
| Chemotherapy (docetaxel, estramustine, dexamethasone) | 1 |
| Sodium valproate | 2 |
| Other anticonvulsant agents (phenytoin, ethosuximide) | 1 |
| Glibenclamide | 1 |
| Analgetics | 1 |
| Etiology unknown | 1 |

Diagnosis of pellagra is based on typical clinical presentation and rapid response to niacin supplementation. The primary management is replacement of nicotinamide, with the initial dose of 100 mg orally every 6 hours, tapering to 50 mg every 8–12 hours until resolution of all the symptoms. Parenteral nicotinamide administration of 1 g, 3–4 times daily, is recommended for severe cases.[4] Supplementation of other B vitamins, zinc, and magnesium, as well as a diet rich in niacin, calories, and protein, is also recommended.[4]

In the present case, chronic alcoholism and prolonged isoniazid/pyrazinamide administration constitute inducing factors of niacin deficiency. The diagnosis of pellagra was based on the patient's history and the presence of dermatitis, diarrhea, and neuropsychological manifestations. Given the severe erosion on skin and enteral mucosa, our patient was prescribed with a larger dose of oral nicotinamide (150 mg every 6 hours). Rapid resolution of symptoms after supplementation of nicotinamide and other B vitamins further confirmed the diagnosis of pellagra.

This case raised attention and awareness on niacin deficiency, not only in an impoverished population, but also under other clinical conditions that may interfere with the intake, absorption, and metabolism of niacin. Pellagra is easily cured and usually has a desirable prognosis when recognized early, but it can be fatal[25] if not identified in time. Risk of pellagra should not be overlooked in special clinical arenas—for example, when patients are administered with combined antituberculosis therapy consisting of isoniazid and pyrazinamide. Under such circumstances, it is necessary for patients to avoid alcohol use, maintain proper diet and sufficient nutrient intake, and supplement nicotinamide, pyridoxine, and other B vitamins simultaneously.

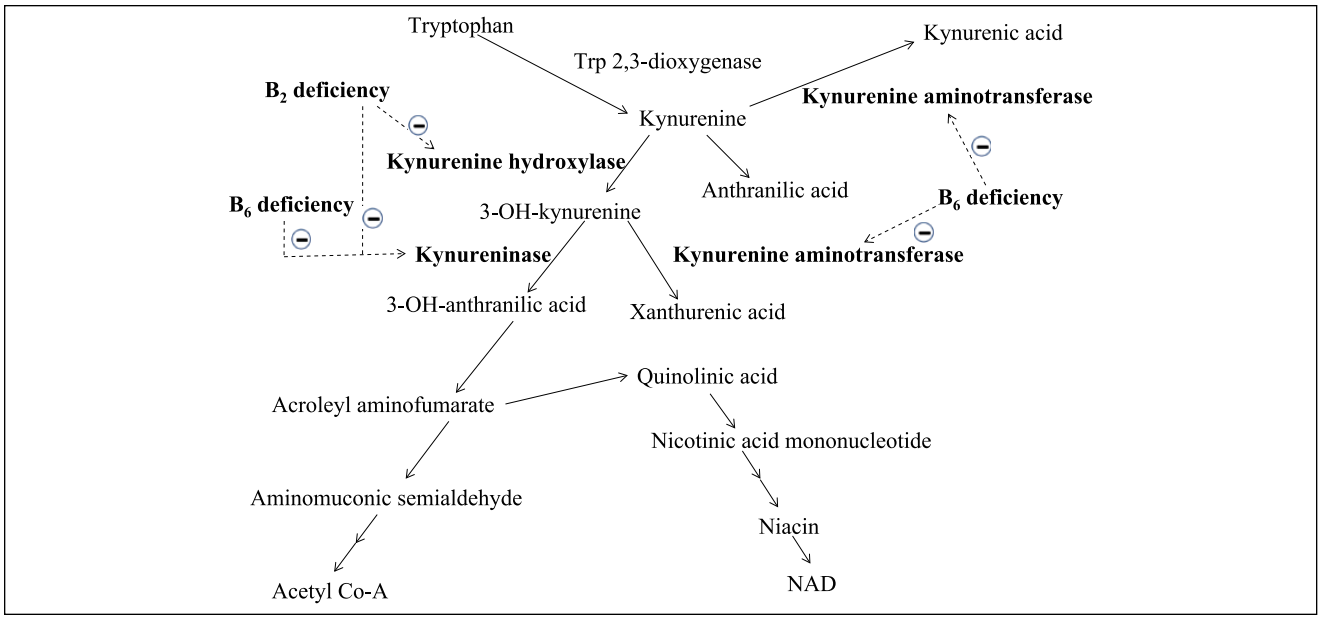


**Figure 3.** The kynurenine pathway and the effects of vitamin $B_2$ and $B_6$ deficiency on it. Enzymes that can be inhibited by vitamin $B_2$ and $B_6$ deficiency are in bold. Co-A, coenzyme A; NAD, nicotinamide adenine dinucleotide; OH, hydroxide; Trp, tryptophan.

## Statement of Authorship

R. Li, K. Yu, and Q. Wang equally contributed to the conception of the research; R. Li contributed to the acquisition of the data; and R. Li, K. Yu, and Q. Wang contributed to the interpretation of the data. All authors contributed to the design of the research and to the analysis of the data, drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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