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Pellagra and anorexia nervosa: a case report

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Abstract

Background—While pellagra appears to be a rare entity currently, it may still develop. It is important to recognize how the disease manifests to ensure adequate and timely treatment.

Case presentation—We present a case of pellagra secondary to anorexia nervosa in a 28-year-old woman. We observed the classical signs: erythema in the neck region, diarrhea, and neurologic symptoms. Diagnosis was made on a clinical basis, and the patient had a rapid recovery after undergoing therapy with nicotinamide and tryptophan.

Conclusions—In our case, the patient did not exhibit any sign of being severely underweight with marked malnutrition such as the typical manifestation expected in pellagra. This case demonstrated that clinicians should have a high level of suspicion in making a diagnosis of pellagra, especially in patients with a history of eating disorders.

Level of evidence IV—(case study).

Keywords

Pellagra; Niacin deficiency; Anorexia nervosa; Case report

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The reported case report was drafted after acquisition of written informed consent signed by the patient.

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Introduction

Pellagra is a condition characterized by the lack of niacin (vitamin B3) or tryptophan (precursor of niacin, 60 mg is equivalent to 1 mg of niacin) [1]. Niacin has two forms (niacin and niacinamide) and is fundamental in nicotinamide adenine dinucleotide (NAD) biosynthesis which has a central role in cellular homeostasis and energy regeneration [2]. In the past, pellagra was caused by a diet which consisted of corn or other plants [3]. Flour fortification with niacin and access to more diverse food sources have essentially led to its eradication in western countries [4]. However, there seems to be a reemergence of pellagra, which has been observed in patients with anorexia nervosa (AN) or HIV [5].

Three different etiopathogenetic mechanisms of pellagra can be described: (i) an alteration of the tryptophan intake, absorption and/or metabolism due to prolonged diarrhea, severe dietary restriction, chronic alcoholism, malabsorption states, hepatic cirrhosis, Hartnup's syndrome, HIV infection; (ii) impaired serotonin metabolism related to the presence of malignant carcinoid; (iii) iatrogenic pharmacological factors (isoniazid, ethionamide, 6-mercaptopurine, acetylpyridine, thiosemicarbazone, methopterin, 5 fluorouracil, azathioprine, pyrazinamide, hydantoin, phenobarbital, chloramphenicol) [1, 3, 6, 7].

Pellagra is characterized by the classic triad of pellagra: dermatitis, diarrhea, and dementia ("the three D disease") which can be expanded to include a fourth "D" for death— if left untreated [4]. The disease is characterized by a prodromal period of variable duration with asthenia, fatigue, paresthesia, nausea, gastrointestinal discomfort, diarrhea, irritability, anxiety, and depression. This symptomatology slowly progresses with deleterious effects on the skin, digestive, and nervous systems [3].

Dermatitis occurs with itching, burning, erythema, and edema, and it affects the sun-exposed areas: face, neck, upper part of the thorax ("Casal's necklace"), back of the hands, and feet. Photosensitive dermatitis may occur, whose mechanism remains unclear, but it is considered to be of phototoxic origin [8]. After several weeks, the skin becomes dry, rough, pigmented, and exfoliation follows.

The symptoms of the digestive system include: stomatitis, gingivitis, glossitis and severe diarrhea (up to ten stools per day) with liquid, foamy, sometimes loose stools. This results in dehydration and weight loss.

The symptomatology of the nervous system includes: mental decay, apathy, memory loss, stupor state, hallucinations, sometimes delirium tremens and dementia.

The course of untreated pellagra is chronic, with spontaneous regressions and flare-ups, most often in the spring. These become increasingly serious, leading to pellagrous dementia, cachexia, and death [3].

Due to the limited cutaneous manifestations of the disease at the beginning, the differential diagnosis includes: with pellagroid erythema (due mostly to photosensitizing drugs), atopic dermatitis, systemic lupus erythematosus, pemphigus vulgaris, porphyria cutanea tarda and porphyria variegata.

Primary pellagra must be distinguished from secondary pellagra, an entity which may be seen in AN [3, 6]. Anorexia nervosa is an eating disorder characterized by significant weight loss. The cutaneous manifestations in AN depend upon different factors: energy and nutrient intake, purging behaviors, and illness duration. Due to the potential similarities, we must ensure that we distinguish between these disease entities.

Case presentation

A 28-year-old woman with a 13-year history of AN, in partial remission phase, presented with burning and blistering on the upper thorax region, with skin signs similar to the Casal's necklace, erythematous pigmented skin rash in the distribution of dermatomes C3 and C4 [3, 6]. She started to experience cutaneous manifestations during a stressful period associated with weight loss, increased physical activity, irritability, depressed mood, asthenia and diarrhea.

The patient has a long history of eating disorder, as she experienced a significant weight loss at 15: she lost about 13 kg reaching the minimum weight of 44 kg through fasting and sometimes purging behavior characterized by laxative abuse. Her previous weight corresponded to the 50th percentile, and it rapidly decreased to a level below the 10th percentile. She developed secondary amenorrhea. She was admitted to an outpatient clinic and underwent multidisciplinary treatment. During the following years, she partially recovered with slow weight gain and reappearance of menstruation, but she continued to have poor dietary intake and variable compliance to clinician recommendations which included pharmacologic therapy with anxiolytic and antidepressant medications.

A complete medical and dietary history was collected. Her diet was limited to vegetables, fruits, and a few crackers or slices of bread. No alcohol intake. Moreover, she feared eating with other people and she ate meals while standing and crumbled food into small pieces before eating. At 23, she began an intense physical activity regimen which she has sustained since that time.

When skin manifestations first appeared, the patient was 52.9 kg (BMI 19.7 kg/m²) and also had weakness, sleep disturbances, anxiety and diarrhea. Although her weight was in a normal range, she maintained a strict restriction of energy intake relative to requirements, and she showed an intense fear of gaining weight and disturbances in body image perception. According to Diagnostic and Statistical Manual of Mental Disorder—5th Edition (DSM-5) criteria, a diagnosis of anorexia nervosa in partial remission was made: she previously met full criteria for anorexia nervosa; criterion A (low body weight) has not been met for a sustained period, but either criterion B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) or criterion C (disturbances in self-perception of weight and shape) was still met. The patient previously underwent a psychiatric evaluation with consequent anxiolytic drug prescription. No other psychiatric diagnosis was made.

The clinical examination revealed erythematous and edematous areas around the neck (Fig. 1 skin lesions at the beginning) resistant to dermatological topic treatment with

corticosteroid medication and soothing ointment, arterial hypotension (100/70 mmHg) and abdominal pain. Laboratory tests showed a mild decrease in red cells ($3.44 \times 10^{12}/L$), augmented red cell volume (111 fL), vitamin B12 deficiency (170 pg/mL), vitamin D deficiency (21.5 ng/mL) and mild increase of alpha-amylase (126 U/L). The remaining routine laboratory tests were within normal range.

We performed a bioimpedance assessment (BIA) analysis that showed normal hydration (but near to lower normal value), low body cellular mass and low phase angle (4.8°). We also performed an indirect calorimetry revealing a resting energy expenditure (REE) of 1111 kcal/day, which corresponded to 84% of the predicted value, and a respiratory quotient (RQ) = 0.91. Furthermore, the patient underwent a dual-energy X-ray absorptiometry (DEXA), which showed lumbar and femoral osteopenia.

Although serologic and urinary assays confirming niacin deficiency were unavailable in our laboratory, pellagra was highly suspected and treatment was started promptly. The patient received dietary advice and an oral dose of nicotinamide 250 mg + tryptophan 600 mg per day was administered. Cyanocobalamin (vitamin B12) (5000 µg intramuscular) and cholecalciferol (vitamin D3) (10,000 UI per week orally) were administered to restore normal values. The skin lesions improved in 1 week and the remaining hyperpigmentation areas slowly disappeared in the following weeks (Fig. 2 skin appearance after treatment). In addition, the gastrointestinal disturbances resolved and the psychological alterations diminished in a similar period. She did not show any skin manifestation relapse in follow-up visits, but she did not get a full remission from AN yet.

Discussion

In the modern age, pellagra has been reported mainly in under-resourced countries, and it is associated with a corn-based diet or general malnutrition, but secondary causes must be considered, including alcoholism, medication, inadequate dietary intake (as in AN), malabsorption, and metabolic disorders [1, 3]. Furthermore, protein deficiency, present in restrictive eating disorder, exacerbates niacin deficiency as tryptophan is used in preference to other amino acids to maintain nitrogen balance [9].

The characteristic skin lesions support the clinical diagnosis, and it is important to know that as the symptoms do not appear in a specific chronologic order, it may not represent the complete triad—dermatitis, diarrhea, and dementia. The diagnosis of pellagra rests primarily on specific skin lesions [5, 10].

The cutaneous manifestations in AN depend upon different factors: nutritional and caloric content of the diet, purging behaviors and illness duration. Protein–energy malnutrition can lead to xerosis, lanugo hair, telogen effluvium, pruritus, hypercarotenemia and acrocyanosis. Nutritional deficiency can also drive to nail dystrophy and koilonychia, angular stomatitis, acrodermatitis enteropathica, pellagra and scurvy. Some skin alterations such as erythema ab igne and trichotillomania can represent effects of behaviors. Also there are rare associations with acne prurigo pigmentosa and pili torti pernio [3].

According to recent literature, the pathophysiology of pellagra involves necrolytic damage in upper epidermidis, similarly to other malnutrition-associated dermatoses (necrolytic migratory erythema, necrolytic acral erythema, acrodermatitis enteropathica). Skin damage can be induced by autophagy and consequent to malnutrition itself [11].

Otherwise skin lesions can be due to sun exposure, infectious diseases, allergic contact dermatitis, pruritus or other nutrient deficiencies such as of vitamin B12, which was detected and properly treated in our case. That is why a proper and complete anamnesis and laboratory testing are mandatory to discriminate between conditions, which need to be treated differently.

However, if nicotinamide therapy has not already been initiated, the diagnosis of pellagra can be made by quantifying urine metabolites (niacin metabolites and 5-hydroxyindole-acetic acid) to determine recent dietary niacin intake and niacin status [1]. In case such specialized laboratory assays are not available, empirical treatment with oral nicotinamide which results in 24–48 h clinical improvement may be indicative of a pellagra diagnosis [4, 7, 10]. The main limit of our study is due to the unavailability of specific urine tests in the laboratory. Empirical specific treatment was started promptly and the final diagnosis of pellagra was based on clinical presentation and confirmed by the resolution of cutaneous, gastrointestinal, and psychological symptoms soon after nutritional treatment.

Pellagra treatment consists of exogenous administration of niacin or nicotinamide. In current literature, the recommended oral niacin dose to treat pellagra varies from 100 to 500 mg daily, divided in 2–3 administrations [4–7, 10]. The prevention of relapses is based on dietary guidelines and nutritional counseling which encourages a balanced diet, with an adequate caloric intake to meet patient's energy requirements. Diet should also be rich in foods like bran, eggs, meat, poultry, fish, legumes and seeds, aiming to provide a variety of niacin-rich sources. Refraining from alcohol consumption is mandatory [3].

Conclusion

In our case, the patient did not exhibit any sign of being severe underweight with marked malnutrition such as the typical manifestation expected in pellagra. However, she did lose a substantial amount of weight beginning in adolescence and she restricted her food choices and dietary intake into early adulthood which developed into chronic energy–protein malnutrition and vitamin inadequacy resulting in pellagra. Clinicians should have a high level of suspicion in making a diagnosis of pellagra, especially in patients with a history of eating disorders.

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Fig. 1.
Skin signs before treatment

Fig. 2.
Skin appearance after supplementation