

Zinc Deficiency with Cheilitis: A Report of Five Cases

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Zinc deficiency has long been known as acrodermatitis enteric dermatitis (congenital zinc deficiency). On the other hand, acquired zinc deficiency has attracted attention as a familiar disease in recent years. Epidemiological studies in Japan have shown that acquired zinc deficiency is more common than expected. It is also known that serum zinc levels fall markedly with age. In this report, several cases of acquired zinc deficiency that caused cheilitis are described. In all cases, the only symptom was cheilitis, the serum zinc level was low, and all cases were relieved by zinc supplementation. Zinc deficiency is associated with a range of pathological conditions, including mucocutaneous symptoms, delayed wound healing, dysgeusia, anemia, impaired immunity, and retarded growth development disorders. However, zinc deficiency may be overlooked even in cases of cheilitis alone. Especially in intractable cases, it is important to suspect zinc deficiency as one at the differential diagnoses.

Key words: Zinc Deficiency, Cheilitis, Zinc replacement therapy

INTRODUCTION

Zinc (Zn) is one of the essential trace elements that play a key role in the development, differentiation, and growth of various human tissues. Therefore, when zinc is deficient, functions deteriorate in various parts of the body, resulting in systemic dysfunction of the skin and its appendages and the gastrointestinal system, central nervous system, and immune system, with dermatitis, alopecia, impaired wound healing, cheilitis, glossitis, diarrhea, dysgeusia, dysosmia, cognitive impairment, and infectious diseases [1]. In particular, the skin contains high zinc levels in the body, and mucocutaneous symptoms appear around openings. The detailed mechanism of mucocutaneous symptoms caused by zinc deficiency has also been elucidated in recent years [2, 3]. In addition, zinc deficiency may not be as rare as one might think. Especially in elderly persons, serum zinc levels fall significantly with age [4], and they are prone to zinc deficiency. Five cases of zinc deficiency that caused cheilitis as a mucocutaneous symptom that was relieved by oral administration of zinc are described.

CASE REPORTS

Case 1: A 90-year-old man had a 2-week history of erosions on his lips. He was suspected of having a bullous disease by a local dermatologist and was treated with topical and oral corticosteroids. However, the enanthem spread, and he was referred to our hospital. On clinical examination, erosions and scabs with white moss were observed on the lips (Fig. 1). A direct fungal test using 10% KOH was negative. Laboratory data showed a decrease in the serum zinc level to 62 (normal, > 80)

µg/dL. Alkaline phosphatase (ALP) was within the normal range. Serum anti-desmoglein antibodies and anti-BP180 antibody were negative. On histopathological examination, necrosis and ulcers in the epithelium were observed. Infiltration of inflammatory cells, mainly lymphocytes, was seen around blood vessels and in the stroma in the dermis. No infiltration of eosinophils was detected (Fig. 2a, b). Treatment with oral zinc acetate hydrate at 50mg/day was started. Two weeks later, the erosions began to partially epithelialize. After three months, the enanthem and pain of the lips improved (Fig. 3), and the serum zinc level increased to 75µg/dL. Oral medication was continued for five months. There was no clinical recurrence after the end of oral administration.

Case 2: An 81-year-old man had an 8-month history of erosion on his lower lip. He was treated with topical petrolatum by a local dermatologist. However, despite the treatment, the erosion did not improve, and he was referred to our hospital. On clinical examination, mild erosion was observed on the mucosal side of the lower lip. Laboratory data showed a decrease in the serum zinc level to 51 (normal, > 80) µg/dL. Laboratory data except for the serum zinc level were all within normal limits. Treatment with oral zinc acetate hydrate at 50mg/day was started. Two weeks later, the pain of the lips improved, and the erosion began to partially epithelialize. After two months, the serum zinc level increased to 63 µg/dL. Oral medication was continued for two months. There was no clinical recurrence after the end of oral administration.

Case 3: A 54-year-old woman had a 2-month history of swelling and pain of the lips. The enanthem did not improve despite treatment with topical corticosteroids



Fig. 1 Clinical features
Erosion and scabs with white moss are observed on the lips.

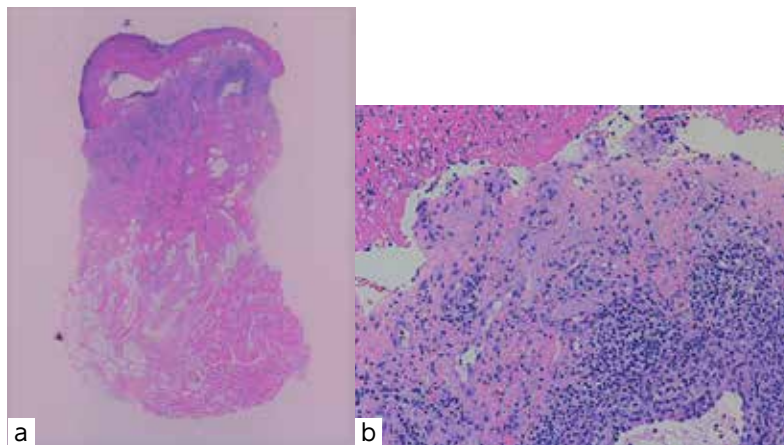


Fig. 2 Histopathological findings
×40. Necrosis and ulcers in the epithelium are observed.
×200. Infiltration of inflammatory cells, mainly lymphocytes, is seen around blood vessels and in the stroma in the dermis. No infiltration of eosinophils is seen.



Fig. 3 Clinical features after treatment
The enanthem and pain of the lips have improved.

Table 1 Etiology of zinc deficiency

Insufficient intake	Low zinc breastfeeding Low zinc diet: a low animal protein diet (Vegetarian) Intravenous nutrition Undernutrition Elderly individuals
Malabsorption	Congenital acrodermatitis enteric dermatitis Chronic hepatic dysfunction (Chronic hepatitis, Liver cirrhosis) Inflammatory bowel diseases Short bowel syndrome High intake of phytic acid and fiber
Increased requirement	Low-birth-weight infant and Breastfeeding Pregnancy
Increased loss	Chelating drugs Diabetes mellitus Renal diseases Hemolytic anemia Hemodialysis
Other	Sports

by a local dermatologist. She was referred to our hospital. On clinical examination, swelling and mild scales were observed on the lips. Laboratory data, except for a decrease in the serum zinc level to 71 (normal, > 80) $\mu\text{g}/\text{dL}$, showed normal findings. On histological examination, spongiosis of the epithelium and infiltration of inflammatory cells such as lymphocytes and plasma cells around the blood vessels in the superficial to deep dermis were observed. Treatment with oral zinc acetate hydrate at 50 mg/day was started. The skin lesions improved in 3 months, and the serum zinc level returned to the normal range. There was no recurrence after the end of oral administration.

Case 4: A 73-year-old man had had an erosion since he burned his lower lip one year earlier. A mucosal cancer was suspected by a local dermatologist who referred him to our hospital. On clinical examination, mild erosion was observed in the center of the lower lip. Laboratory data, except for a decrease in the serum zinc level to 77 (normal, > 80) $\mu\text{g}/\text{dL}$, showed normal findings. Treatment with oral zinc acetate hydrate at 50 mg/day was started. The erosion disappeared after a month, with no clinical recurrence after the end of oral administration.

Case 5: A 62-year-old woman had a 1-month history of desquamation and fissures in her lips. She was treated with topical dimethylisopropylazulene ointment and oral corticosteroids by a local dermatologist. However, the enanthem did not improve, and she was referred to our hospital. On clinical examination, swelling, desquamation, and fissures were observed on the lips. Laboratory data, except for a decrease in the serum zinc level to 75 (normal, > 80) $\mu\text{g}/\text{dL}$, were normal. Histological examination showed spongiosis of the epithelium and infiltration of inflammatory cells such as lymphocytes around the blood vessels in the superficial dermis. Treatment with oral polaprezinc at 150 mg/day was started. The desquamation and fissures of the lips tended to improve after one month. The serum zinc level increased to 143 $\mu\text{g}/\text{dL}$, and the enanthem improved in five months.

DISCUSSION

Zinc is one of the essential trace elements. Over 300 enzymes require zinc for their activation, and nearly 2,000 transcription factors require zinc for gene expression [5]. Zinc plays a key role in the development, differentiation, and growth of various human tissues [1]. In the adult human body, there are a total of 2–3 grams of zinc [6]. Zinc deficiency is associated with a range of pathological conditions, including mucocutaneous symptoms, hair loss, delayed wound healing, dysgeusia, anemia, impaired immunity, retarded growth, and brain development disorders. In particular, the skin contains the third highest amount of zinc in the body after skeletal muscle and bone (skeletal muscle 60%, bone 30%, skin 5%, and liver 5%) [6]. The association of skin symptoms and zinc deficiency is well known, because the skin is one of the abundant zinc-containing organs and is susceptible to zinc deficiency. Similar to hereditary zinc deficiency (acrodermatitis enteric dermatitis), the typical lesions occur primarily around openings such as the eyelids, mouth, ears, nostrils, anus, and vulva, as well as the distal portion of the extremities. The mechanism has been elucidated in recent years. Kawamura *et al.* investigated the mechanisms by which zinc deficiency induces dermatitis in dietary zinc-deficient mice. Zinc deficiency reduced CD39-positive Langerhans cells and increased the adenosine triphosphate (ATP) release induced by exposure of the skin to irritant stimulation, resulting in severe and prolonged dermatitis [2, 3]. The high prevalence of zinc deficiency eruptions around openings suggests that the area is susceptible to mechanical stimuli, including primary irritants such as feces and food.

Acquired zinc deficiency is a disorder associated with various etiologies and causes (Table 1) [7]. Depending on the patient's age, background illnesses, and life history, a multitude of causes should be considered. In the present cases, it affected a relatively large number of elderly persons (average age 72.4 years), but there was no underlying disease that was likely to cause zinc deficiency. These findings suggest

Table 2 The diagnostic guideline for zinc deficiency

1. One or more symptoms and laboratory data
1) Symptoms and signs : dermatitis, stomatitis, hair loss, pressure ulcer, alopecia, growth disturbances in terms of weight and height in children, hypogonadism in males, increased susceptibility to infection, taste disorder, anemia, infertility
2) Laboratory data : low levels of serum alkaline phosphatase (ALP)
2. Ruling out other diseases associated with the above
3. Serum zinc levels
3-1 : < 60 µg/dL : zinc deficiency
3-2 : 60-80 µg/dL : marginal zinc deficiency
4. Alleviation of symptoms upon zinc administration
Definitive diagnosis:
If all of the above items 1. 2. 3-1 and 4 are satisfied, zinc deficiency
If all of the above items 1. 2. 3-2 and 4 are satisfied, latent zinc deficiency
Probable: Before zinc supplementation 1. 2. 3. Indications for zinc supplementation

Table 3 Summary of 5 cases

Mean age	72.4 years (54-90 years)
Sex	Male : 3 cases Female : 2 cases
Location	Upper lip : 0 cases Lower lip : 2 cases Both : 3 cases
Pretreatment	Topical : 2 steroids 1 petrolatum 1 azulene 1 bacitracin/fradiomycin sulfate Oral : 2 steroids 1 tranexamic acid 1 oral valacyclovir (There is duplication)
Serum zinc levels	67.2 µg/dL (51-75 µg/dL) < 60 µg/dL (zinc deficiency) : 1 case 60-80 µg/dL (marginal zinc deficiency) : 4 cases
Serum ALP levels	Normal : 3 cases Unknown : 2 cases
Treatment	Zinc acetate hydrate : 4 cases Polaprezinc : 1 case

that elderly persons are prone to zinc deficiency because of inadequate intake and decreased intestinal tract absorption.

The Japanese Society of Clinical Nutrition issued the Japanese Practical Guideline for Zinc Deficiency 2018 setting forth criteria for diagnosing zinc deficiency (Table 2) [7]. The practical guideline proposed that a serum zinc level < 60 µg/dL indicates zinc deficiency, 60-80 µg/dL indicates marginal zinc deficiency, and > 80 µg/dL indicates normal zinc status. ALP is also sometimes helpful. The only symptom was cheilitis in the present cases. In these cases, the zinc drop was mild, with a serum zinc level < 60 µg/dL (zinc deficiency) in 1 case and 60-80 µg/dL (latent zinc deficiency) in 4 cases, with an average of 67.2 µg/dL (Table 3). Even if only cheilitis is presented, it is recommended that the serum zinc level be measured if it is intractable.

Zinc deficiency is improved by zinc supplementation. Ishikawa *et al.* reported that zinc deficiency symptoms improve in days to months with zinc replacement therapy [8]. However, there is no rule for the end of administration. Zinc-rich foods such as oysters, pork

liver, and cashew nuts are also recommended. The zinc content is low compared to the recommended zinc intake specified by the Ministry of Health, Labour and Welfare of Japan the reference values for optimum zinc intake per day are approximately 11.0 mg for adult men and 8.0 mg for adult women [9]. For example, eating 5 oysters is 7.9 mg, which is not enough to reach the daily zinc recommendation. If zinc deficiency symptoms are present, diet alone is not enough, and zinc supplementation is required.

Zinc deficiency has been said to be common mainly in developing countries, but it is expected that it will continue to increase in Japan due to the increase in chronic diseases such as aging and diabetes mellitus. We hope to contribute to improving the understanding of all physicians who may treat zinc deficiency, not to mention dermatologists.

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