

Nail Matrix Pathology in Cronkhite–Canada Syndrome: The First Case Report

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Abstract: Cronkhite–Canada Syndrome (CCS) presents with gastrointestinal polyposis and the triad of cutaneous abnormalities including nail dystrophy, alopecia, and hyperpigmentation of the skin. The etiology is not well understood. The histology of skin lesion in CCS has not been routinely described. Especially, the nail matrix pathology has not been reported. In this study, the authors report the nail matrix pathology in a patient with CCS. Interestingly, the histologic evaluation revealed matrix hypergranulosis. Because matrix hypergranulosis is commonly found in several inflammatory nail diseases, this discovery points out that an inflammatory process is probably one of the important pathogenesis in CCS.

Key Words: Cronkhite–Canada Syndrome, pathology, nail, nail matrix

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INTRODUCTION

Cronkhite–Canada Syndrome (CCS) is characterized by gastrointestinal (GI) polyposis and the triad of cutaneous manifestations including nail dystrophy, alopecia, and hyperpigmentation of the skin.¹ In a dermatopathologic view, scalp and hyperpigmented skin pathology has been described in some studies; nevertheless, nail histopathology has not been previously reported. Herein, we report some interesting findings from a nail matrix biopsy in 1 CCS patient.

CASE REPORT

A 53-year-old Thai man presented with chronic diarrhea and hypogeusia for 2 months. He also noticed hyperpigmentation on his palms and soles, alopecia, and abnormal nails. The physical examination showed generalized nonscarring alopecia (Fig. 1A), multiple dark brownish macules, and patches on both palms and soles (Fig. 1B). All 20 nail plates were lost and replaced with a thin and soft triangular area in the proximal portion (Figs. 1C, D). CCS was the provisional diagnosis. Endoscopic

study was performed and revealed multiple polypoid lesions scattered throughout the GI tract, sparing the esophagus. A polyp biopsy was performed and the pathological diagnosis was hamartomatous polyposis, consistent with CCS-associated polyps. In the meantime, a biopsy from the lunula of the right thumb nail was performed using a 3-mm punch. The histopathology showed a compact eosinophilic layer of stratum corneum, the presence of a granular layer, and multilayered germinative basal cells in the epidermis. Scanty perivascular lymphocytic infiltration was noted in the superficial dermis (Figs. 2A, B). With a higher magnification, more than 10 adjacent keratohyaline (KH) granules containing keratinocytes were identified in the upper epidermis, representing nail matrix hypergranulosis (Fig. 2C). The p16 immunohistochemistry staining was negative.

Prednisolone and azathioprine were prescribed, with a good response. The diarrhea and hypogeusia improved 3 months after the treatment. Hair and nail regrowth (Fig. 1E) with disappearance of skin hyperpigmentation of the palms and soles were noted 6 months after the treatment.

DISCUSSION

CCS was first described by Cronkhite and Canada in 1955.¹ This uncommon syndrome has an estimated 500 cases reported worldwide.² Most of the patients were from Europe or Asia, especially Japan.³

The pathogenesis of CCS is still unclear. Boland et al⁴ suggested that genetics may play a role in the pathogenesis of CCS. However, some studies have shown no strong evidence to support a familial predisposition.⁵ Sweetser et al found that CCS polyps had significantly higher IgG4 antibody staining than diseased and normal control tissues. Positive antinuclear antibodies and anti-Saccharomyces cerevisiae antibodies have also been reported in some studies. The good response to immunosuppressive drugs supports the idea that CCS may have an autoimmune mechanism.⁶ Moreover, *Helicobacter pylori* infection has been proposed to be one of the causative factors.

The GI symptoms in patients with CCS vary from diarrhea, abdominal pain, weight loss, nausea, anorexia, haematochezia, vomiting, hypogeusia, and dysgeusia.⁷

The characteristic dermatologic triad of cutaneous manifestation in CCS comprises onychodystrophy, skin hyperpigmentation, and hair loss.¹ Onychodystrophy, including nail thinning, nail splitting, onycholysis, and onychomadesis, has been found in 98% of patients.⁸ However, nails with a thin and soft triangular area in the proximal half, that is bordered by a thick and ridged nail plate, is considered the typical nail change,⁹ which was found in our patient.

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The authors declare no conflicts of interest.

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FIGURE 1. A, Generalized nonscarring alopecia (a surgical scar in the left parietal area from previous trauma was noted). B, Multiple dark brownish macules and patches on hyperpigmented skin on both palms. C, Loss of all finger nails with a thin, and soft, triangular area in the proximal portion. D, An asterisk on the proximal part of right thumb nail identifies the area where the nail matrix biopsy was performed. E, Nail regrowth after treatment with prednisolone and azathioprine for 6 months.

Onychokeratinization is a process in which the matrix becomes keratinized and finally produces the hard keratin that forms the nail plate.^{10,11} To investigate the mechanism that causes an abnormal nail plate, the nail matrix should be the structure of choice to be studied. The histopathology of

a normal nail matrix is composed of a papilliform germinative epithelium with no granular layer. Until now, no known study has described the nail matrix pathology in patients with CCS. In this study, we took a biopsy from the lunula area which represented the distal nail matrix so it would

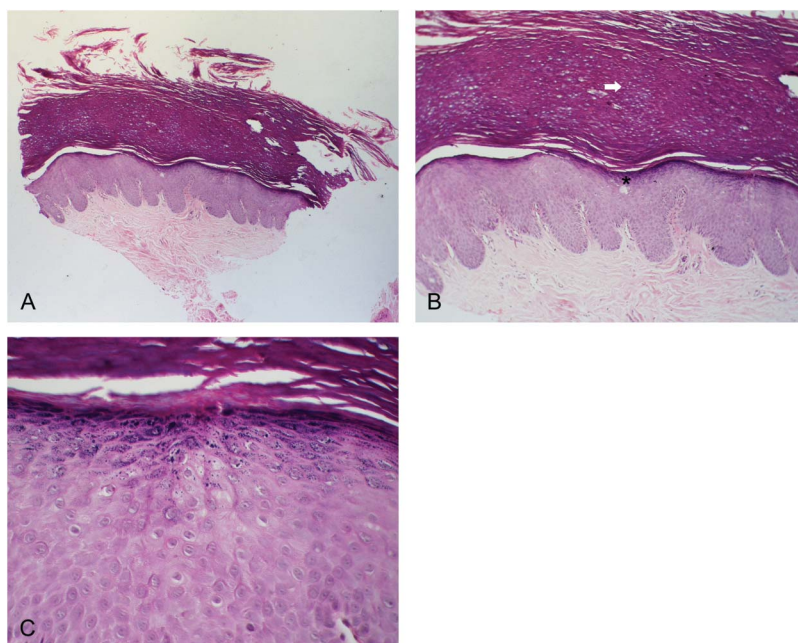


FIGURE 2. A, Nail matrix biopsy showed typical papilliform germinative epithelium (hematoxylin and eosin ×4). B, A compact eosinophilic layer compatible with orthokeratosis (arrow) and the presence of stratum granulosum in epidermis (asterisk) (hematoxylin and eosin ×10). C, More than 10 adjacent KH granules containing keratinocytes represented nail matrix hypergranulosis (hematoxylin and eosin ×40).

cause minimal nail dystrophy.¹¹ The histopathology showed typical multilayered germinative basal cells, which are the characteristic finding in the nail matrix. Compact orthokeratosis and hypergranulosis (defined by more than 10 adjacent KH granules containing keratinocytes) were also found in the epidermis. Nail matrix hypergranulosis is a common feature in inflammatory conditions, such as lichen planus, psoriasis, and spongiotic trachyonychia. Fanti et al¹² proposed that inflammatory conditions result in an imbalance of nail matrix keratinocyte kinetics which leads to replacement of the normal matrix keratogenous zone by an epidermal-like zone containing KH granules and eventually resembles epidermal keratinization. This explains the formation of so-called “soft keratin” or compact orthokeratosis resembling the stratum corneum of palms and soles, which was found in our case. These findings suggest that the nail changes in CCS might be an inflammatory reaction, and not only the malnutrition that had been previously believed. The scanty perivascular lymphocytic infiltration may be explained by the late stage of disease when the biopsy was performed.

Treatment of CCS consists of aggressive nutritional support, antibiotics, histamine receptor antagonists, cromolyn sodium, nonsteroidal anti-inflammatory drugs, immunosuppressive drugs, a tumor necrosis factor inhibitor and surgery. Corticosteroids seem to be the mainstay of medical treatment.^{2,4}

In summary, we report the first case of nail matrix pathology in CCS demonstrating matrix hypergranulosis. Based on these findings, we propose that an inflammatory process is an important pathogenesis in CCS.

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