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Carotenoderma due to lycopenemia: A case report and evaluation of lycopene deposition in the skin

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Abstract

Carotenoderma is a yellow-orange coloration of the skin caused by high levels of serum carotenoids mostly due to the excessive intake of carotenoid-rich foods. The yellowish coloration is typically observed on the palms, soles, and nasolabial folds. Although the physical appearance is prominent, the condition itself is benign and harmless. Diagnosing carotenoderma is not difficult because of its unique manifestations, but its pathophysiology remains unclear. We report a relatively rare case of carotenoderma due to lycopenemia caused by the excessive intake of lycopene-rich vegetables and fruits. Lycopene is a carotenoid component that is distinguished by the high absorption of light around 488 nm. Given these characteristics, we examined hematoxylin–eosin stained specimen from the patient and tape stripping samples by florescent microscopy with 488-nm wavelength emission and compared them with normal skin samples. Notably, the patient's samples showed a weaker autofluorescence in the stratum corneum and sweat glands. Furthermore, we measured carotenoid concentrations in the patient's skin non-invasively with Vegecheck® (Kagome Co.) and found a higher score than the average of 24 healthy volunteers. These results support the long-held hypothesis that carotenoids are secreted in sweat and are deposited in the stratum corneum. To the best of our knowledge, no previous reports have measured the

skin carotenoid levels nor detailed the pathological findings of carotenoderma patients. This case further highlights that the excessive intake of lycopene causes carotenoderma and demonstrates that carotenoid deposition is particularly pronounced in the stratum corneum of the skin.

Introduction

Carotenoderma is a well-known skin condition characterized by yellow-orange discoloration of the skin.[1] The skin change is typically observed on the palms, soles, and nasolabial folds.[1,2] Although the physical appearance is prominent, this condition itself is benign and harmless and its diagnosis is not difficult because of the unique manifestations.[1] It is associated with high levels of serum carotenoids, which are fat-soluble antioxidants found in fruits and vegetables.[1,2] The most common carotenoids are α-carotene, β-carotene, lycopene, lutein, and zeaxanthin.[2] As carotenoids are not synthesized in the human body, food is the only source.[1] Carotenoderma with lycopenemia is relatively rare, and most cases are caused by the excessive intake of lycopene-rich foods.[3]

We report a case of carotenoderma due to lycopenemia caused by the excessive intake of lycopene-rich foods, in which we investigated the pathophysiology by evaluating the symptoms through a skin biopsy, tape stripping, and serum and cutaneous carotenoid measurements.

Case report

A 26-year-old female presented to our hospital with a 2-month history of the yellow

coloration of both palms. She had started consuming 20 to 30 cherry tomatoes per day 2 months before the symptoms appeared. She also had a daily routine of drinking 180 ml of tomato juice for 10 years, and of consuming vegetables and fruits for 2 years such as pumpkins, carrots, blueberries, and green vegetable juice. She has endometriosis and had been taking oral contraceptives for 6 months. She was taking no nutritional supplements and had no changes in topical agents such as sunscreen or skin care ointments. Physical examination showed yellow-orange coloration on both palms and fingers but not on the sclerae, nails, soles, or elsewhere (Fig. 1a-c). She had no pruritus, paresthesia, nor hyperhidrosis. A skin biopsy from the colored palm showed no inflammatory infiltrates nor considerable hyperkeratosis (Fig. 2a-c). Blood tests showed normal results for full blood count, liver function, thyroid profile, renal function, lipids, and C-reactive protein. Additional blood tests showed high levels of carotenoids—especially of lycopene, at 272.2 μg/dL (normal range, ≤ 44.3 μg/dL) (Table 1).

Lycopene has a high, concentration-dependent absorption of light around the 488-nm wavelength.[4] Indeed, when we used purified lycopene to check the correlation between lycopene concentration and absorption of 488 nm light, a concentration-dependent increase in absorbance was observed (Fig. 2d). Given this, we examined a hematoxylin–eosin (HE) stained specimen of colored skin from the patient by

florescence microscopy with 488-nm wavelength emission and compared it with normal skin samples (Fig. 2e-j). The patient's specimen showed weaker autofluorescence in the stratum corneum and sweat glands than the normal specimens showed (Fig. 2k, l). We also collected tape stripped samples and examined them similarly by florescence microscopy, showing weaker autofluorescence again than that of the 25 control samples (Fig. 2m, n). We measured carotenoid concentrations in the skin non-invasively with Vegecheck® (Kagome Co.), an improved version of a multiple spatially resolved reflection spectroscopy sensor, whose mechanisms were described by Darvin et al.[5] The measurement values range from 1.0 to 12.0, with values less than 6.0 indicating a lack of carotenoid intake and values exceeding 8.0 indicating a sufficient intake. Previous research has confirmed that the measurements are proportional to the blood carotenoid concentration.[4] We examined the patient's carotenoid levels 2 months after the first visit to our hospital. Even though 2 months had passed since she stopped consuming carotenoid-rich foods, she scored maximum 9.8, which was higher than the control individuals (24 volunteers, highest 7.4, lowest 3.3, average 5.2) (Fig. 2o).

Based on the findings above, we diagnosed the patient with carotenoderma from high lycopene intake. Dietary adjustments reduced the blood lycopene levels 6 months after the first test (Table 1). However, the coloration has still not changed much (Fig.

1d-f); instead, some of the yellowish areas have thickened slightly, as can be seen in spongiotic changes after about 15 minutes of exposure to water (Fig. S1).

Discussion

Yellow coloration of the skin are seen when the serum level of β-carotene is over 250 μg/dl,[1] but the value of the present case wasn't as high enough to induce coloration. Previous cases of lycopenemia were induced by the excessive intake of persimmons (1 kg daily)[3] or by the heavy intake of 4 or 5 large red tomatoes and pasta with tomato sauce daily for 3 years.[6] Based on these cases, the clinical features of carotenoderma due to lycopenemia seem similar to those of β-carotenemia. It is characteristic and unique, compared to previous cases that the symptoms of our case persisted even after the blood levels of lycopene normalized and that the patient showed partial thickening and spongiotic changes. Prolonged skin coloration might be predictable because of fat-soluble nature of lycopene,[1] but we cannot explain the spongiotic findings, and the detailed pathogenesis of this disease remains unknown. Although no thresholds for skin coloration were reported for lycopene concentrations, its value in our case was largely over the normal limit, which was highly likely to be responsible for the skin symptoms.

There is almost no information on the pathological features of carotenoderma. In the

present case, we performed a skin biopsy that showed normal findings in HE staining. However, fluorescence examination of the HE-stained specimen revealed findings suggesting the carotenoid deposition in the stratum corneum. Palleschi et al. reported a punch biopsy specimen from the palm of a carotenoderma patient showed intercellular autofluorescence in a pemphigus-like pattern.[7] Indeed, a similar finding was observed in our case, but the meaning of this finding is unclear. Furthermore, the autofluorescence intensity was lower in the stratum corneum and sweat glands than in normal-appearing skin. Carotenoids are thought to diffuse from the subcutaneous fat tissue and to be released to the skin surface, penetrating with sweat and sebum that results in their deposition in the intercellular lipids of the stratum corneum.[1] Our fluorescence results support this idea and were confirmed by tape stripping.

As mentioned above, previous cases of carotenoderma were generally diagnosed from clinical findings and the carotenoid levels in the blood were examined in only a few cases. Besides measuring the carotenoids in the serum, we used Vegecheck® to demonstrate the deposition of carotenoids in the patient's skin directly and non-invasively. The device emits laser light at 488 nm while picking up scattered light and detecting the cutaneous concentrations of carotenoids such as α-, β- and γ-carotenoids, sigma-carotene, lutein, zeaxanthin, and lycopene, and their isomers.[5] From the health-

promotion perspective, cutaneous carotenoid measurements have become increasingly common, and Matsumoto et al. revealed skin carotenoid levels to correlate significantly and positively with serum total carotenoids and vegetable intake.[8] Hayashi et al. demonstrated with this sensor that vegetable juice consumption significantly increases cutaneous carotenoid levels and blood levels of α-carotene, β-carotene, and lycopene.[9] Previous studies have shown that a certain number of subjects show high values with this sensor, but it was not reported whether these individuals had yellow coloration on their palms. Although our patient's skin showed a higher value than that of the control volunteers' skin, the correlation between color change and measurement results is currently unknown, and it is assumed that not everyone with high values actually has carotenoderma. Therefore, there should be no doubt that there are specific mechanisms causing the clinical symptoms.

In summary, we further confirmed that the excessive intake of lycopene causes carotenoderma due to lycopenemia. Moreover, analysis of a biopsy specimen and the patient's skin demonstrated carotenoid deposition, revealing part of the pathogenesis. Although this disease does not cause any major physical issues other than appearance, the exact pathogenesis remains unclear and further studies are warranted.

Figure Legends

Figure 1. Clinical findings of the present case.

(a-c) Yellow-orange colorization on the palm and fingers on presentation.

(d-f) Clinical findings after 6-month follow-up. Some parts of the yellowish areas have slightly thickened (arrowheads).

Figure 2. Pathology and carotenoid level in the skin.

(a-c) A skin biopsy from the right palm. (b) is a high magnification of the inset in (a). Hematoxylin and eosin staining. Scale bars: 200 μm (a), 50 μm (b), and 100 μm (c).

(d) Purified lycopene (Sigma-Aldrich, SMB00706) was dissolved in dimethyl sulfoxide, and a dilution series with a maximum concentration of 10 μg/ml was prepared in 96-well microplates (n = 3). Absorbance was measured at 488 nm with a microplate reader (Tecan Group Ltd.). A concentration-dependent increase in absorbance was observed.

(e-h) Fluorescence microscopic findings of the epidermis of the patient (e, g) and a healthy control (f, h). The patient's specimen shows intercellular autofluorescence in a pemphigus-like pattern localized to the upper epidermis (g). (g) and (h) are high magnifications of the insets in (e) and (f). Scale bars: 200 μm (e, f), and 50 μm (g, h).

(i, j) Fluorescence microscopic findings of the sweat glands of the patient (i) and the healthy control (j). Scale bars: 100 μm.

(k, l) Fluorescence intensity was measured with Fiji software. The values for the stratum corneum (k) and sweat glands (l) were normalized to those of epidermis and collagen fibers, respectively. Examples of measurement points are indicated by "*" and "◊" in Fig. 2e, f, i, and j. Error bars represent SEM. Statistical significance was calculated using a two-tailed t test. # $p < 0.0001$.

(m, n) Fluorescence microscopic findings for tape stripping samples from the palm of the patient (m) and the healthy control (n). Scale bars: 100 μm.

(o) Carotenoid deposition level in the skin of the patient and healthy controls measured with Vegecheck®. Patient dots represent the data obtained from four sites on her right palm and control dots from 24 volunteers.

Table 1. Summary of the serum levels of carotenoids.

Blood tests were performed at 1 and 6 months after the first presentation. Aberrant values are indicated by boldface with underbars.

Supplemental Figure 1.

Spongiotic changes in the affected areas following exposure to water.

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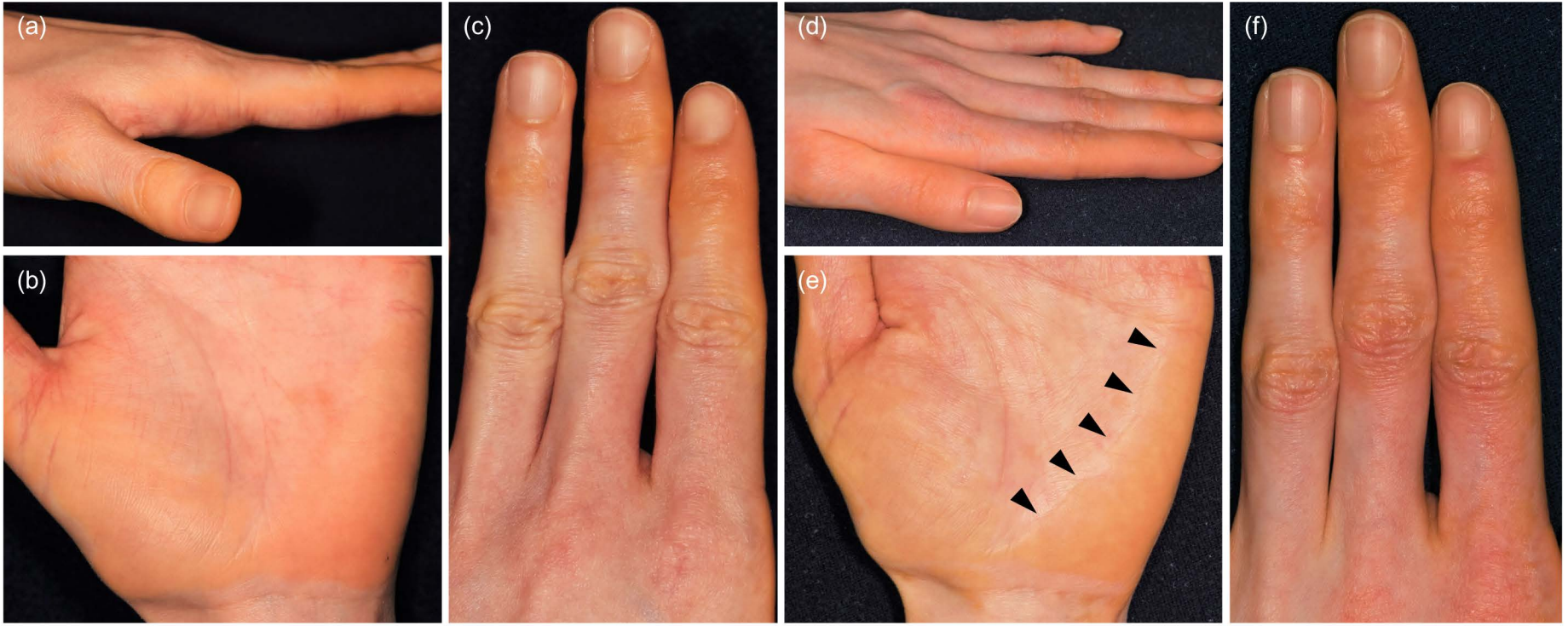
(a)
(b)
(c)
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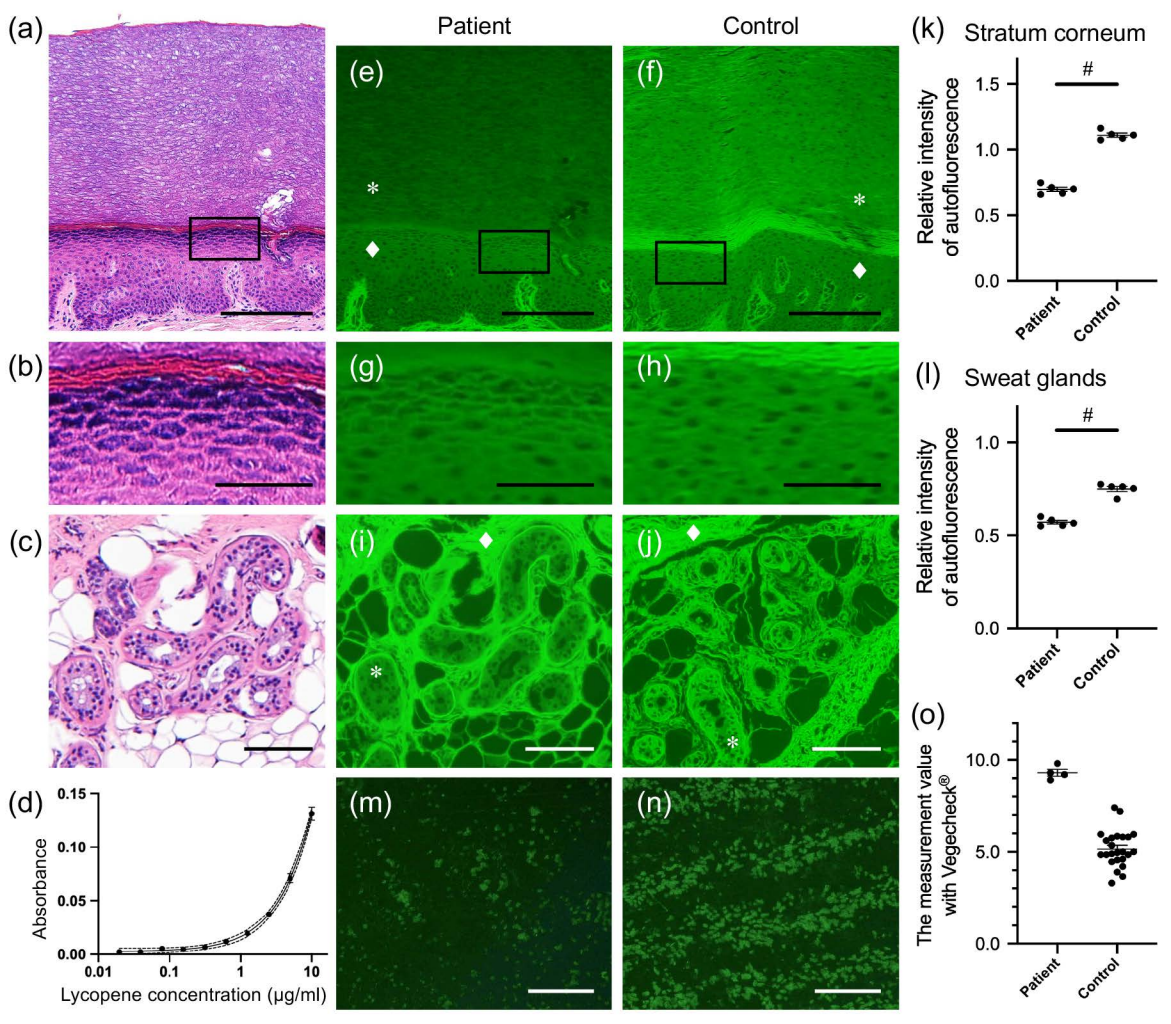
(a)
Patient
Control
(e)
(f)
(k)
Stratum corneum
#
Relative intensity of autofluorescence
1.5
1.0
0.5
0.0
Patient
Control
(b)
(g)
(h)
(l)
Sweat glands
#
Relative intensity of autofluorescence
1.0
0.5
0.0
Patient
Control
(c)
(i)
(j)
(d)
0.15
0.10
0.05
0.00
Absorbance
0.01
0.1
1
10
Lycopene concentration (μg/ml)
(m)
(n)
(o)
The measurement value with Vegecheck®
10.0
5.0
0.0
Patient
Control

Carotenoid component	Serum levels (μg/dL)		Normal range (μg/dL)
	1 month after the first presentation	6 months after the first presentation	
Lycopene	**272.2**	31.5	≤ 44.3
Lutein and zeaxanthin	88.1	86.7	≤ 104.4
α-carotene	10.6	12.5	≤ 29.3
β-carotene	**98.7**	**110**	≤ 96.4
Vitamin A	**93**	**86.2**	≤ 78.2
α-tocopherol	**1401**	**1404**	≤ 1225
δ-tocopherol	16.3	7.4	≤ 18.6
β,γ-tocopherol	59.8	49	≤ 245.8