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Case report

Orange discoloration of the skin in mother and newborn with SARS-CoV-2 infection: is hypercarotenosis a sign of COVID-19?

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Abstract

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) and represents a potentially fatal disease. Recently, dermatological manifestations have been reported to be signs of COVID-19. We describe a case of a newborn and her mother affected by SARS-CoV-2, that developed hypercarotenosis (HC) about 5 weeks after delivery. The aim of this report is to identify the pathological mechanism of this association and to underline the importance of investigating any dubious skin manifestation in case of contact with patients with suspected or confirmed COVID-19, because it may be a clinical sign of infection. Even if not previously described in the literature, this case report suggests a possible association between HC and SARS-CoV-2 infection.

Keywords

Hypercarotenosis, newborn, skin, COVID-19, SARS-CoV-2.

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Introduction

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) and represents a potentially fatal disease, due to the fact that it may cause serious respiratory illness such as pneumonia and lung failure. Since the first cases in China, COVID-19 has rapidly progressed to a pandemic on a planetary scale [1]. Recently, dermatological manifestations have been reported to be signs of COVID-19 [2]. Urticaria, livedo reticularis, acral ischemia, erythema pernio-like lesions, petechial or vesicular rash like chicken pox have been associated to COVID-19 [3]. These dermatological lesions may be the first clinical signs of the SARS-CoV-2 infection and, even if they usually are benign and self-limited, they should be promptly identified to prevent mother-to-child transmission [2]. One of the major clinical and public health issues is now represented by COVID-19 during pregnancy and the risk of transmission of the infection from mother to child before, during and after delivery.

Case report

We present the case of a mother-infant dyad with probable hypercarotenosis (HC) during SARS-CoV-2 infection. The pregnancy was physiological and the infant was born by spontaneous full-term vaginal delivery complicated by shoulder dystocia and right brachial plexus injury. Sixteen days after childbirth, the mother developed anosmia and dysgeusia after a contact with a nurse and a gynecologist who tested positive for COVID-19. Therefore, rhino-pharyngeal swabs were performed in the newborn and her mother resulting positive for the new Coronavirus. The father and the 3-year-old sister were also tested and resulted negative. The infant and her mother were immediately hospitalized, but they did not require any medications and no significant laboratory test abnormalities were detected. After fourteen days, the infant's rhino-pharyngeal swab resulted negative, nevertheless SARS-CoV-2 continued to be excreted through the stool and the mother continued to be positive. Eight days later, the mother was noticed to have a yellow-orange color on the palms of the hands, periungual skin and on the feet (**Fig. 1A**). The day after, the newborn presented yellow-brown macules on her arms (**Fig. 1B**) and legs (**Fig. 1C**) and in the periumbilical area. After a week, the lesions spontaneously disappeared in both cases. Forty-eight days after childbirth, the father and the 3-year-old sister also presented the same isolated pattern of skin manifestations: a yellow-orange color on the palms of the hands in both cases (**Fig. 1D** and **Fig. 1E**) and on the tibial tuberosity and the inner thigh in the sister (**Fig. 1F**). For this reason, rhino-pharyngeal swabs and rapid serological test for SARS-CoV-2 were performed, resulting negative in both cases.

Discussion

Beta-carotene is one of the major antioxidants of fresh fruits and vegetables [4] and it is converted into vitamin A through two enzymes, 15-15'-carotenoid dioxygenase and beta-carotene-15-15'-dioxygenase. Carotene is mainly absorbed in the proximal small intestine and has a high affinity to fat. If its blood levels are excessively high, it gets deposited in the corneum, sweat and sebum, contributing to yellow-orange skin pigmentation that does not affect the mucous membranes [5]. This pigmentation is more evident in areas richer in sweat glands, such as the palms of hands and feet. An excessive dietary intake (greater than 30 mg a day) for a protracted period can lead to carotenemia and it is the first cause of HC. HC may also be associated with hyperlipidemia, impaired conversion of carotene to vitamin A, hypothyroidism, hypopituitarism, diabetes mellitus, nephrotic or nephritic syndrome, hypothalamic amenorrhea, liver disease or restrictive eating disorders (**Tab. 1**) [6-8]. An abnormal dietary intake of carotene was excluded in our cases, because the mother received a controlled diet by the Pediatric COVID Center, the infant was breastfed and the usual Mediterranean diet was not modified at home. The other medical conditions associated with HC were excluded. SARS-CoV-2 infection and stress factors were the only common features between mother and infant. Protracted hospitalization, quarantine and inappropriate responses of the immune system induced by SARS-CoV-2 infection may cause a homeostasis perturbation and induce numerous protein hormones and cytokines release [7]. These cytokines can activate the hypothalamic-pituitary-adrenal axis (HPA axis), stimulating the adrenal glucocorticoids

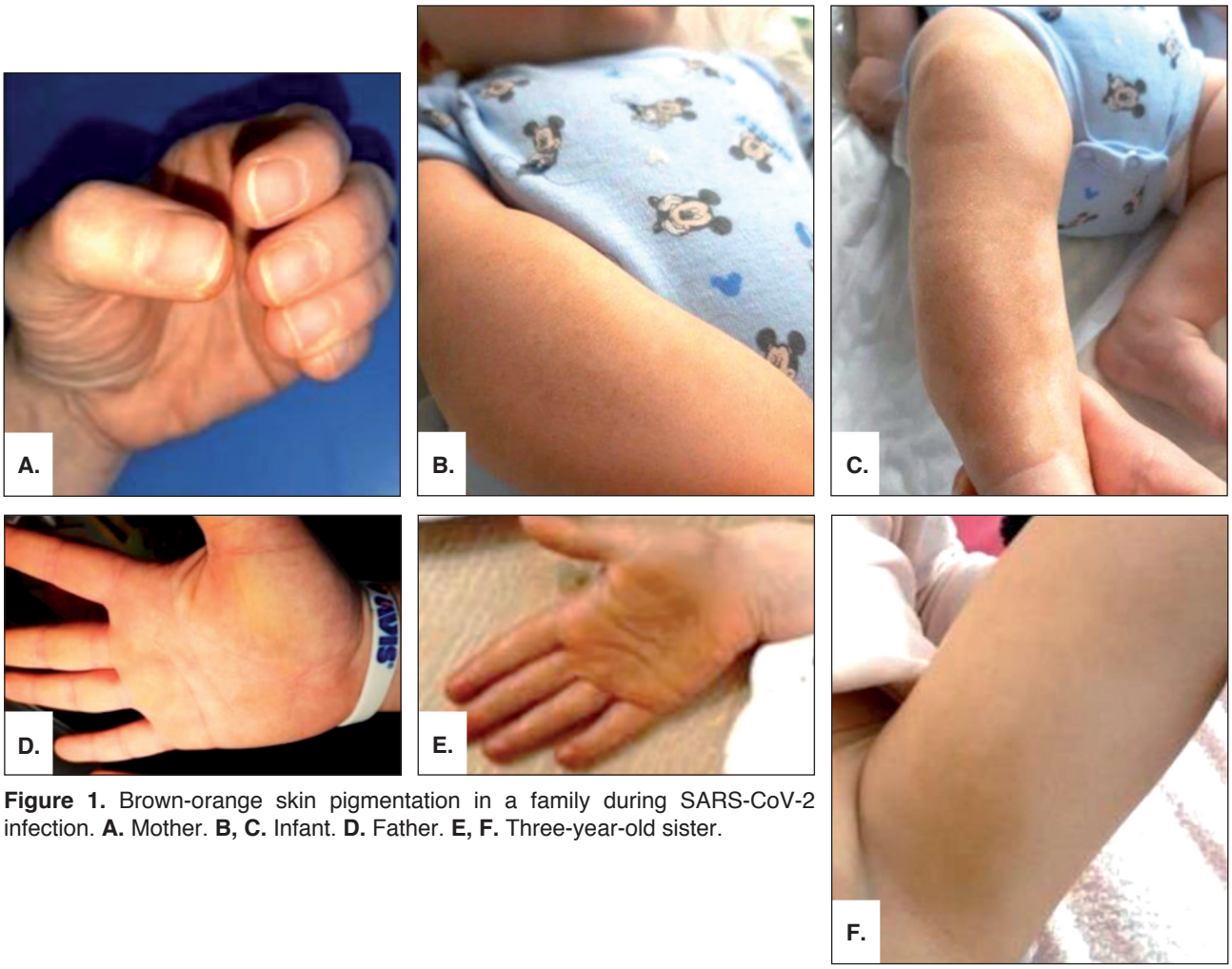

Figure 1. Brown-orange skin pigmentation in a family during SARS-CoV-2 infection. **A.** Mother. **B, C.** Infant. **D.** Father. **E, F.** Three-year-old sister.

Table 1. Different diagnosis of carotenemia.

Serum level	Mechanism		
	Excessive dietary intake	**Hyperlipidemia**	**Failure of conversion carotene to vitamin A**
	• Carotene-rich foods • Dietary supplements • Tanning pills • Palm oil	**• Hypothyroidism • Type 2 diabetes mellitus • Restrictive eating disorder • Nephrotic syndrome**	**• Hypothyroidism • Restrictive eating disorder, liver disease • Enzyme deficiency**
Carotene	Elevated	Elevated	Elevated
Vitamin A	Elevated	Elevated/normal	Decreased/normal
Lipids	Elevated	Elevated	Normal

production. Viral infections can be physiologically stressful, as indicated by the concomitant activation of the HPA axis. Activation of the HPA axis begins with the release of corticotropin-releasing hormone (CRH) that acts on CRH-R1 receptors on anterior pituitary corticotrophs. This stimulates the rapid release of adrenocorticotropic hormone (ACTH) from cellular stores and the synthesis of the ACTH precursor peptide proopiomelanocortin (POMC) to replenish ACTH stores [9]. ACTH is released into the peripheral circulation and stimulates the release of glucocorticoids from the adrenal cortex by acting on the MC2-R (type 2 melanocortin receptor) [10]. The immune response to viral infection includes the role of relevant cytokines that have different characteristics than in bacterial or parasitic infections, including cellular and cytokine responses to viral infection and potential immunomodulatory effects of glucocorticoids [11-13]. It is relevant the role of synergistic actions of

these pro-inflammatory cytokines in stimulating a complete lipopolysaccharide-induced ACTH response and greater HPA axis activity generating a pro-inflammatory state [11]. ACTH can bind to the melanocyte stimulating hormone (MSH) receptors expressed by the melanocyte, acting directly on the melanocyte to enhance melanogenesis. This mechanism may account for the newborn's yellow-brown dermatological manifestations, whereas the immaturity of sweat glands may explain the absence of yellow palm hands in her. Furthermore, the virus colonization of the proximal small intestine may result in carotene to vitamin A conversion failure or vitamin A impaired transport, especially through lipoprotein carriers. Therefore, the potential immunomodulatory effects and pro-inflammatory state of glucocorticoids caused by viral infection, directly or by a systemic stressful state, may account for the simultaneous presence of dermatological manifestations in this family. This condition is known to occur during viral infection such as human immunodeficiency virus-1 (HIV-1). The correlation between serum vitamin A and beta-carotene levels in pregnant women infected with HIV-1 was described. Its link with CD4 count is consistent with the relationship between markers of HIV-1 disease progression and serum beta-carotene [12, 13]. Lin et al. demonstrated *in vitro* the possible anti-inflammatory effect of beta-carotene in DNA viruses such as Herpes Simplex Virus. Their results indicate that beta-carotene inhibits Nitric Oxide (NO) production in virus-infected macrophages by the down-regulation of iNOS, COX-2, IL-1b, IL-6, TNF-a, and MCP-1 expression via the suppression of NF-kB activation pathway [6].

In our opinion, although it was not possible to obtain virus detection in all family members through rhino-pharyngeal swab, the epidemiological link and similar clinical symptoms suggest a SARS-CoV-2 infection in the whole family. Several reasons may provide an explanation for this finding. Firstly, the sensitivity of the rhino-pharyngeal swab depends on the appropriate collection procedures and a low viral load may not be detected by current laboratory methods. Secondly, the phenomenon of SARS-CoV-2 positive in the stool samples but negative in rhino-pharyngeal swab specimens should be taken in account, especially in the hypothesis of faecal-oral transmission. Lastly, real-time reverse transcriptase-polymerase chain reaction (RT-PCR) can achieve a sensitivity up to 60% and several reports suggest collecting samples from multiple sites in the different stages to improve the positive rate [14]. All these factors may have contributed to false-negative tests. Only by deepening our knowledge on the pathophysiology of the new Coronavirus infection we will soon be able to clarify many of these aspects.

Conclusion

Even if not previously described in the literature, this case report suggests a possible association between HC and SARS-CoV-2 infection. The description of a 4-member family, two of them with positive swab for COVID-19, with similar dermatological manifestations provides a possible evidence of this association.

Spreading our experience can be a starting point for a more in-depth study on the different mechanisms underlying the various dermatological manifestations during SARS-CoV-2 infection.

Statement of Ethics

The patient provided written informed consent. The study adhered to the tenets of the Declaration of Helsinki.

Declaration of interest

The Authors have no conflicts of interest to declare. No funding was obtained.

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