

A Woman with Treated Breast Cancer, Recent Neurological Symptoms and Xanthoderma

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Abstract- We describe a 69-year-old-woman with antecedent of breast cancer and recent transitory neurological symptoms. Physical examination showed yellow to orange skin pigmentation, more conspicuous on her palms and soles, while discoloration changes were absent in the eye and oral mucous membranes. Routine laboratory findings were not indicative of hemolytic anemia, liver or bile disorders, nephrotic syndrome, hypothyroidism or diabetes mellitus. We emphasize the role of her excessive ingestion of papaw and tomato. These foods are rich in carotenoids (β -carotene and lycopene), which are associated with pigmentation disorders. The skin discoloration improved in about two months after correction of the inadequate diet. Major concerns about differential diagnosis of yellow skin pigmentation are also highlighted.

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Introduction

Xanthoderma results from an increased concentration of carotenoids (1), which are antioxidants. Dietary antioxidants, in special β -carotene and lycopene, are frequently preconized in the prevention of coronary heart disease, as well as of breast and brain cancers. Yellowish skin discoloration due to deposits of β -carotene (carotenemia) is probably under reported. It was first described in 1919 as a discoloration that developed in 5 to 7 weeks after an excessive ingestion of carrots, and gradually disappeared after omission of this food from the diet (2). Lycopene is an isomere of carotene related to yellow-orange discoloration (lycopenemia). Carotenemia and lycopenemia are more accentuated on the palms and soles because the stratum corneum is thicker in these regions, while in areas of mucosa, submucosa and subconjunctiva, these discolorations are not observed (3,4). In addition to eggs, butter and apple juice, fruits and vegetables (*e.g.* oranges, peaches, apricots, papayas; carrots, pumpkins, yellow beans, yellow corn, yellow squash, yellow turnips, rutabagas, sweet potatoes), hypothyroidism, nephrotic syndrome and diabetes mellitus may be

associated with carotenemia. Lycopenemia can be due to an excessive ingestion of lycopene rich-foods as tomato, guava, grapefruit, beet, kaki, water melon or dried parsley (3-5). Both carotenemia and lycopenemia can be easily reversed after correction of the inadequate diets (2,3), and may be mistaken by mild jaundice or other condition associated with yellow-orange skin changes.

Case Report

A 69-year-old white woman was admitted for investigation of recent episodes of transitory loss of the anterograde memory, and the main diagnosis hypothesis was epilepsy of the temporal lobe. An Echo-Doppler of the cervical and cerebral arteries, dosage of serum vitamins (A, B12 and folate), and lipidogram accomplished before the actual hospitalization were normal. She had antecedent of an infiltrating mixed tubular carcinoma in the right breast (treated by surgery in 1995, plus use of tamoxifen for five years), and glaucoma. Moreover, one of her sons had a benign brain tumor. Medicines in use were aspirin, duloxetine, flurazepam and eye drops (brimonidine, pilocarpine and travoprost). She was not using multivitamins or energy

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drinks, and denied alcohol abuse and tobacco smoking. Because of her intestinal constipation (up to five days), which developed in the past three years, she started a high ingestion of green vegetables, papaw, and tomatoes. Figure 1 shows the amounts of papaw “Formosa” and tomato “red kaki” that she had been eating daily. The increased intake of carotenoids and green vegetables gradually normalized her bowel rhythm. Physical examination was normal, except for yellow to orange discoloration of the skin, with higher intensity in the palm and sole areas (Figure 2).



Figure 1. Illustrative images of the daily amounts of papaw “Formosa” (~ 500 grams) and tomato “red kaki” (~ 300 grams) consumed by the patient in the last three years.



Figure 2. Yellow-orange discoloration of the palms and soles.



Figure 3. Comparative images of palm and sole areas eight weeks after reduction of the excessive intake of papaw and tomato.

Worth of note was the absence of changes in the eye and oral mucous membranes. Laboratory data and normal ranges: red cells $4.44 (4.4-6.0) \times 10^{12}/\text{mm}^3$, hemoglobin 13.8 (11.1-16.1) g/dl, hematocrit 41.1 (39-53) %, MCV 93 (80-100) fl, MCHC 34 (32-36)%, white cells $4.57 (4.0-11.0) \times 10^3/\text{mm}^3$, platelets $212 (150-450) \times 10^3/\text{mm}^3$, glucose 92 (70-99)mg/dl, urea 41.6 (10-50) mg/dl, creatinine 1.0 (0.7-1.3) mg/dl, ionized calcium 1.29 (1.12-1.32) mmol/l, magnesium 2.0 (1.6-2.5) mg/dl, sodium 139 (136-145) mmol/l, potassium 3.5 (3.5-5.1) mmol/l, total bilirubins 1.2 (< 1.3) mg/dl, ALT 21.6 (< 32) U/l, AST 24.5 (< 39) U/l, TSH 0.97 (0.27-5.0) $\mu\text{UI}/\text{ml}$, rheumatoid factor 10.6 (15.0) UI/ml, C3 124 (90-180) mg/dl, C4 21,4 (10-40) mg/dl. Her urine and stools were normally colored; the urinalysis was unremarkable, including the evaluation for bile pigments, hemoglobin, and protein. Images of the brain obtained during this hospitalization were also normal by CT and MRI studies as well. Furthermore, an EEG utilizing sphenoidal electrodes did not reveal significant changes. The patient was asymptomatic and after being informed about the nature of the yellowish discoloration of her skin, she was discharged to the outpatient follow-up. Improvement of the skin change occurred two months after she was placed on a low-carotenoid diet (Figure 3). Actually, she follows without symptoms and is under ambulatory surveillance to better clear the events of transitory neurological symptoms.

Discussion

Carotenoids are substances with antioxidant activity and protective effects on human health. Although more than 600 carotenoids have been described in human nutriment, only six can be utilized (β -carotene, α -carotene, β -cryptoxanthin, lycopene, lutein, and

zeaxanthin) (1,6). People from industrialized and developing countries are informed about favorable effects of carotenoids on cardiovascular, neurological and malignant conditions, on the management of diabetes mellitus, and as an anti-ageing agent (7-9). Additionally, slimming and vegetarian diets rich in carotenoids have been widely utilized by adults of both genders. Interestingly, dark green vegetables are also rich in carotenoids, but their yellow-orange pigments are covered by green chlorophyll, because it reflects the green light. The discoloration of the palms and soles is a consequence of the pigment deposit due to slow conversion of carotenoids to vitamin A (3); lycopene does not get converted into vitamin A, a fact that differs from the other carotenoids. Neither the elderly woman here reported, nor her husband had been concerned about the skin discoloration before her admission to investigate the diagnosis suspicion of temporal epilepsy. Xanthoderma was a benign condition and abated by reducing her ingestion of carotenoids; however, possible concerns in the present case would include the antecedent of breast cancer, history of a son with a brain tumor, and change in the bowel habits (progressive constipation). Liver implants from breast or bowel cancer, and bile duct obstruction can cause jaundice; notwithstanding, these hypotheses were ruled out by the laboratory tests and imaging studies. The patient had transitory deficits of anterograde memory and a feeling of *jamais vu*, with a sense of unfamiliarity, which raised the hypothesis of simple partial seizures of temporal lobe origin. Her neurological disturbances could be due to primary or secondary brain tumors, and related to local effects or paraneoplastic phenomenon (*e.g.* limbic encephalitis by lung, colon, breast, kidney, or ovary cancer). Some familial syndromes (*e.g.* Li-Fraumeni, Turcot, Gorlin, von Hippel-Lindau, and neurofibromatosis), involve tumors in the central nervous system; however, there were neither indicative clinical stigmata nor images of brain masses. Furthermore, dietary antioxidants presumably should reduce the incidence of brain tumors (10). The patient here described had a child with a benign tumor of the central nervous system. Pogoda *et al.* studied the role of maternal diet during pregnancy on childhood brain tumor risk, and found that ingestion of cruciferous and yellow-orange vegetables can prevent tumors (11). Nevertheless, her intake of carotenoid-rich foods was low during the respective pregnancy. She had an invasive breast cancer, which was excised 16 years before this hospitalization. Worth of note are the findings from studies about the serum levels and tissue

concentrations of carotenoids with relation to development and invasiveness of breast malignancy. Sato *et al.* prospectively evaluated 295 cases and the same number of normal controls and found that carotenoids may have a protective role against the development of breast cancer (12). Yeum *et al.* described lower concentrations of 9-cis- β -carotene in the normal breast adipose tissues of 46 patients with benign tumors in comparison with 44 patients with breast cancer; but there were no differences between the tissue concentrations of the major carotenoids (13). Kabat *et al.* found in postmenopausal women a direct relationship between the baseline serum α -carotene and a reduced risk of invasive breast cancer (but not with breast cancer in general); while lycopene serum levels were associated with an increased risk of the invasive type of breast cancer (14). Because some drugs can be related with skin disturbances, additional concern could be about the adverse role of medicines used by this patient, including the eye drops for glaucoma (15). Xanthoderma may be caused by drugs (*e.g.* quinacrine, sorafenib, sunitinib), but the medicines utilized by the patient are not described in association with this skin discoloration. A major limitation of the present case study is the lack of serum carotenoid analysis by high-performance liquid chromatography, and biopsy studies of fat tissue from the breast samples. The patient was more concerned about the possibility of late breast cancer metastasis and bowel dysfunction, than with skin discoloration, which was considered as cosmetic side effect. She did not agree with analysis for pigments involved on her skin changes. In addition to vitamin A, the levels of carotenoids and their metabolites should be determined (16), to better clear the specific role of the diverse carotenoids that could be involved in this case. Notwithstanding, cumbersome and more sophisticated investigations are not mandatory for characterization of this harmless condition in daily practice of the primary care attention. Clinical data and basic laboratory routine usually establish this diagnosis in developing areas. The occurrence of unnoticed xanthoderma may be growing, in special among elderly individuals with excessive ingestion of β -carotene supplements and of natural foods rich in carotenoids (7,9). Therefore, this condition seems to be under diagnosed and scarcely described. In conclusion, the main hypothesis to explain the palm and sole yellow-orange discoloration of this patient is carotenemia plus lycopenemia, due to excessive intake of papaw and tomato. Although with the inherent limitations, we believe that this report might enhance the suspicion index of primary care workers about this

probably under detected benign condition, which can pose challenges in the setting of invasive breast cancer and suspected brain tumor.

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