

Scurvy as cause of purpura in the XXI century: a review on this “ancient” disease

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Abstract. – OBJECTIVE: Scurvy is defined as a deficiency of ascorbic acid, which is an essential exogenous vitamin in humans. Vitamin C is involved in collagen synthesis and its deficit can cause disorders of connective tissue. The most frequent symptoms are weakness, arthralgias, anorexia and depression, commonly associated with follicular hyperkeratosis and perifollicular hemorrhage, with purpura.

PATIENTS AND METHODS: A young woman, with a history of malnutrition, manifested purpura and hematoma of the left lower limb. The laboratory tests didn't detect alterations either in coagulation, the platelet count or in the autoimmunity. The total body TC scan didn't show neoplasia or other suspected lesions. Excluding the most important causes of purpura, in consideration of malnutrition, scurvy was suspected.

RESULTS: A skin biopsy confirmed the diagnosis. Accordingly to this finding, a treatment with a daily intravenous infusion of vitamin C was started with consequent improvement of hematoma and purpura.

CONCLUSIONS: Scurvy is a re-emerging disease, also in western countries. When purpura appears in young adults, scurvy has to be investigated, especially when a history of malnutrition is present. The treatment with vitamin C infusions should be started as soon as possible in order to prevent any complications.

Key Words:

Scurvy, Purpura, Vitamin C, Ascorbic acid.

Introduction

Scurvy is a clinical syndrome linked to ascorbic acid deficiency, largely due to impaired collagen synthesis with consequent disorder of connective tissue¹. Although scurvy is considered a disease of the era of great maritime expeditions,

it is re-emerging in Western Countries population with unusual eating habits². Ascorbic acid is a reversible biologic reductant that involves a great number of biochemical reactions and metabolic processes. Particularly, it provides electrons needed to reduce molecular oxygen, functioning as an anti-oxidant factor capable of stabilizing a number of other compounds, including vitamin E and folic acid. In addition, it functions as a co-factor for hydroxylation reactions of mono- and di-oxygenase enzyme iron and copper dependent. In fact it acts like an enzyme complement for lysyl- and prolyl-hydroxylase that catalyzes formation of hydroxyproline and hydroxylysine in collagen synthesis³. The failure in this step results in impaired wound healing and deficient osteoblast and fibroblast function. Ascorbic acid is also an enzymatic cofactor of dopamine-beta-hydroxylase. Hence it is involved in the synthesis of catecholamines and in biosynthesis of carnitine, necessary for the long-chain fatty acids transport across the mitochondrial membrane⁴.

For these reasons the vitamin C deficit can induce different and various clinical presentations. They are preceded from weakness, malaise, arthralgias, anorexia and depression. Then, follicular hyperkeratosis and perifollicular hemorrhage with petechiae (typically on the skin of lower limbs) and coiled hairs appear. Other common symptoms include subungual multiple hemorrhages (more extensive than in bacterial endocarditis), ecchymosis, gingivitis with bleeding and receding gums, edema, and anemia⁵. Moreover, muscle-skeletal pain can develop, caused by hemorrhages in the muscles or periosteum⁶.

At present, because of the variety of clinical manifestations, the diagnosis of scurvy is frequently misunderstood with both clinical evalu-

ation and diagnostic imaging⁷. Imaging studies could detect osteolysis, joint space loss, osteonecrosis, osteopenia or osteoporosis, periosteal proliferation and/or subperiosteal bleeding⁸. Biological signs are represented by abnormalities including anemia and low levels of cholesterol and albumin. Finally, a serum ascorbic acid level lower than 2.5 mg/l allows to diagnose scurvy⁹. When the vitamin C dose is not available, skin biopsy is a valid alternative to diagnosis¹⁰.

The aim of this review is to underline the importance of recognizing purpura as a clinical manifestation of scurvy, with the purpose to reach the diagnosis of ascorbic acid deficiency before the development of complications. In particular, we start describing a case report of scurvy in a middle-aged woman.

Case Report

A 51 years old female patient was admitted in the Department of Internal Medicine with the diagnosis of purpura of the left leg in association with hematoma. The patient reported a clinical history of multi-allergies in bronchial asthma, recurrent tonsillitis and mitral valve prolapsed. She denied taking drugs at home. In the last three years, the patient reported a liquid/semi-liquid nutrition for a referred disturbance of mastication and gingivitis, associated with weight loss of about thirty kilograms. For four months she reported the appearance of purpura in the lower limbs with progressive and upward trend. The bruising and swelling of the left lower limb was present at the same time (Figure 1).

Blood and instrumental tests

In the emergency room, the patient underwent to arteriovenous Doppler ultrasound of the lower limbs with the evidence of not-replenished hematoma, in the absence of deep vein thrombosis. Blood tests showed iron deficiency anemia and increased fibrinogen, in the absence of other prominent alterations, especially in coagulation. During hospitalization several blood tests were performed to detect the cause of purpura: research of antiphospholipid and anticardiolipin, anti nuclear, extractable nuclear antigens, anti-dsDNA, anti-neutrophil cytoplasmic, anti-liver kidney microsome, anti-smooth muscle, anti-mitochondrial, anti-*Saccharomyces cerevisiae*, anti endomysial, anti transglutaminase and anti gliadin antibodies, IgG, IgM, C3, C4, b2 microglobulin, rheumatoid factor, crioglobulin. All these results were negative. Furthermore, a total body TC



Figure 1. Hematoma and purpura of the left lower limb.

scan was performed, in the hypothesis of occult neoplasia, but nothing was discovered. Patient refused to undergo endoscopic examinations. Considering the patient malnutrition history, a vitamin deficiency was suggested. Vitamin B12 and folate levels were evaluated, resulting lower than reference interval, so parenteral infusions of these vitamins were performed. In spite of these findings, the main suspect remained a vitamin C deficiency. The ascorbic acid dosage was unfortunately not available in our laboratory. Therefore, a skin biopsy of the lesions was performed and the parenteral supplementation of vitamin C was started. In about a week, the anemia improved, as purpura and hematoma of the left limb (Figure 2).

Diagnosis

Histological examination showed specific histological changes of the follicular pilifera structure. In particular, the infundibular and isthmic ectasia with unusual phenomena of dyskeratosis of follicular epithelium were observed, showing



Figure 2. Resolution of hematoma and purpura after vitamin C infusion.

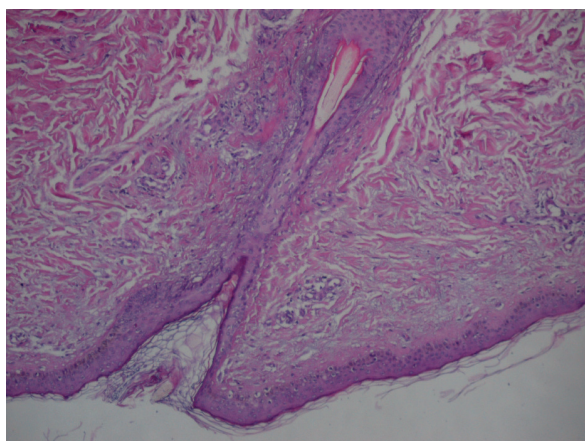


Figure 3. Infundibular and isthmic ectasia of follicular pilifera structure. 10x

the classic follicular dystrophy caused by vitamin C deficiency (Figures 3 and 4).

Discussion

This case report underlines the variety of clinical manifestations in scurvy. In particular, in our patient we have investigated purpura, since it was the prevalent sign reported. Although the most recognized causes for purpura are commonly characterized by coagulation disorders, autoimmunity alterations, antiplatelet and anticoagulant agents or drug intake, in other cases purpura can be associated with malnutrition and the development of severe vitamin C deficiency¹¹.

Roé et al¹² described the case of a 45 years old spanish male affected by asthenia, polyarthralgia and bleeding gums accompanied by a lower limb edema and follicular purpura in a patient with deficit of vegetables intake. After a skin biopsy the diagnosis of scurvy was made.

Another case of purpura of lower extremities was described in a 28 years old spanish female with a dietary restriction for epigastralgia¹³. The detection of less than 0.1 mg/dl of ematic ascorbic acid allowed to make diagnosis of scurvy. Moreover, the case of a 50 years old white woman affected by psychosis was reported by Chisholm et al¹⁴. She presented lower extremities purpura due to food disorders subordinated to psychiatric illness. The skin biopsy was performed and the histologic analysis confirmed the diagnosis. Recently, Mintsoulis et al¹⁵ described a case of scurvy in a western country. In particular, the patient presented suddenly oligoarthritis and purpura of

the lower extremities, due to insufficient fruit and vegetable intake attributed to allergies. Also in this case, the finding of a low vitamin C serum concentration permitted the diagnosis.

In all these patients the early recognition of scurvy as cause of the purpura and the consequent treatment allowed the resolution of signs and symptoms.

In order to establish a correct diagnosis in case of purpura, it is firstly fundamental to distinguish unpalpable purpura (e.g., due to primary cutaneous changes, capillary fragility – including scurvy–, changes in the coagulation) from hyperkeratosis (due to deficit of vitamin A). Hence, the atypical presentations of purpura, not explained by common illnesses, should induce to suspect the vitamin C deficit. Our patient arrived with purpura of lower extremities, hematoma of the left leg, gingivitis and receding gums. The normal plate count, the normal circulating levels of von Willebrand factor and a negative anamnesis for previous hemorrhagic events (such as easy bruising, epistaxis and menometrorrhagia) led us to exclude primary haemostasis disorders. Liver function was normal, as also Prothrombin time (PT) and Partial Thromboplastin Time (aPTT), excluding coagulation disorders as cause of the hemorrhagic skin lesion. Moreover, the screening tests for autoimmunity were negative. In addition, the TC scan didn't show any occulted tumors, permitting to exclude respectively an autoimmune or a paraneoplastic vasculitis. The patient's history of malnutrition and the clinical symptoms associated, including atypical purpura, led us to consider the diagnosis of a connective tissue disease, related to vitamin C deficiency. Finally, the skin biopsy confirmed our suspicions. As for other water-soluble vitamins, the most important sources of vitamin C

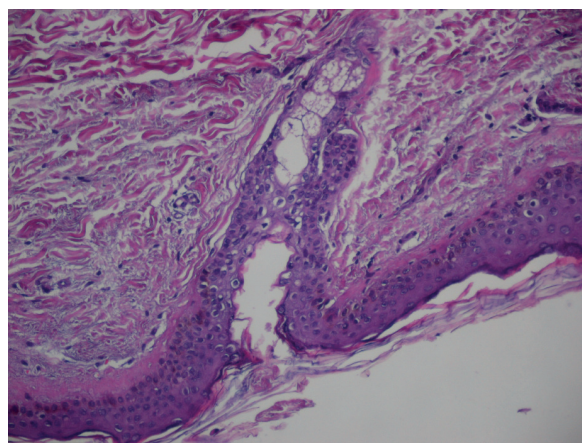


Figure 4. Dyskeratosis of follicular epithelium. 20x

is the diet. In particular, citrus fruits, tomatoes, potatoes and fresh vegetables contain large quantities of vitamin C. Primary deficiency of ascorbic acid can be manifested in a great number of situations, such as inflammatory systemic diseases, surgical interventions, burns, thyrotoxicosis or physiological status (pregnancy and nursing) which produce the vitamin C increased demand. A malabsorption disease or gastric achlorhydria can reduce ascorbic acid absorption. However, a deficiency of vitamin C in adults is generally due to the aversion against some foods or to inappropriate diets. At-risk populations also include neurologic conditions and history of chemotherapy⁷. In adults, the most specific symptoms occur after 3-6 months after the reduction of the dietary intake under 10 mg/die, therefore when the plasma concentration of ascorbic acid is less than 0.2 mg/dL (11 micromol/L)⁶.

In case of purpura suspicion by scurvy, if determination of ascorbic acid in the blood is not available, skin biopsy is the only tool to provide the correct diagnosis. The classical presentation of histologic pattern is represented by perifollicular hemorrhage, irregularly shaped hair follicles with hyperkeratosis and coiled irregular hair shafts¹⁷.

At present, there is not a standard therapeutic regimen because while the dosage of vitamin C 1 g/day per os for at least two weeks is the most used, the intake of 200-300 mg/day of vitamin C for longer periods is largely adopted^{6,8}, with the improvement of symptoms in about 72 hours.

Conclusions

Although it is customary to consider scurvy a disease of the past or of the developing countries, it is important to identify the groups of patients with a high risk of vitamin deficiencies, in order to prevent the potential deadly course of the diseases that malnutritional status can provoke. Moreover, the early vitamin C supplementation is able to revert the clinical picture. Finally, purpura confined to lower limbs must suggest scurvy when the most common causes are excluded.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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