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Red-purple gingival enlargements in a pediatric patient

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CLINICAL PRESENTATION

A 9-year-old boy was admitted to the pediatric unit of the Hospital das Clínicas of Universidade Federal de Minas Gerais for diagnostic investigation. The patient had consanguineous parents and 2 healthy siblings (aged 8 and 25). His family medical history revealed that the father and an aunt were affected by cutaneous psoriasis.

A year ago, the patient developed pruritic skin lesions with a rough surface on his lower and upper limbs. Persistent backache and diffuse pain in the lower limbs associated with calcaneodynia and pain in the Achilles tendon topography started about 4 months before he was admitted. None of these aggravated conditions responded to common analgesics, resulting in impaired ambulation. The patient also complained of progressive weakness and difficulty when ascending stairs. He also mentioned diffuse pain within the rib cage when taking a deep breath and coughing, in addition to hyporexia associated with a significant weight loss (7 kg, 15% of total weight) in the last month and reddish diuresis. He also had oral bleeding for approximately 3 months.

After his hospitalization, a multidisciplinary team including personnel from pediatrics, nutrition, pediatric hematology, dermatology, rheumatology, psychiatry, orthopedics, and dentistry evaluated the patient. The patient's oral signs and symptoms were significant. The dental evaluation revealed gingival bleeding associated with edema and diffuse reddish-purple coloration of the gums. There was limited mobility of the tooth. The interdental papillae were predominantly affected in both the mandible and maxilla, but the posterior regions exhibited conspicuous spongy gingival enlargements involving dental surfaces (Figure 1A-D). Bilateral ecchymosis was observed on the hard palate that extended to the soft and hard palate limit (Figure 1C).

Laboratory examinations during the initial consultation revealed an elevated erythrocyte sedimentation rate (40 mm/h) and C-reactive protein (38.7 mg/L), possibly suggesting an inflammatory condition. Hypochromic microcytic anemia with reticulocytosis and iron deficiency were also identified in the initial tests that revealed low levels of hemoglobin (7.4 g/dL) and serum iron (23 μg/dL).

Abdominal computed tomography (CT) revealed reduced height of multiple vertebral bodies. Magnetic resonance imaging of the spine showed depressions in plates of thoracic and lumbar vertebrae, raising the possibility of infectious spondylodiscitis or sickle cell anemia. Edema in the posterior apophysis of the calcaneus was associated with slight alteration of the sign in the bony trabeculate (osteopenia), tibiotalar and posterior subtalar joint effusion, a mild peri-insertional Achilles tendinopathy, paratendinitis and slight fluid distension in the third intermetatarsal space bursa were observed on magnetic resonance imaging of the foot.

A CT scan of the chest showed small centrilobular nodules in the pulmonary parenchyma bilaterally. Sometimes a sprouting tree pattern associated with discrete ground-glass opacities was observed, notably in the anterior segments of the upper lobes and in the

Statement of Clinical Relevance

The oral manifestation and the correlation with the severe systemic manifestations of this rare disease nowadays helped the diagnosis through a multiprofessional approach.

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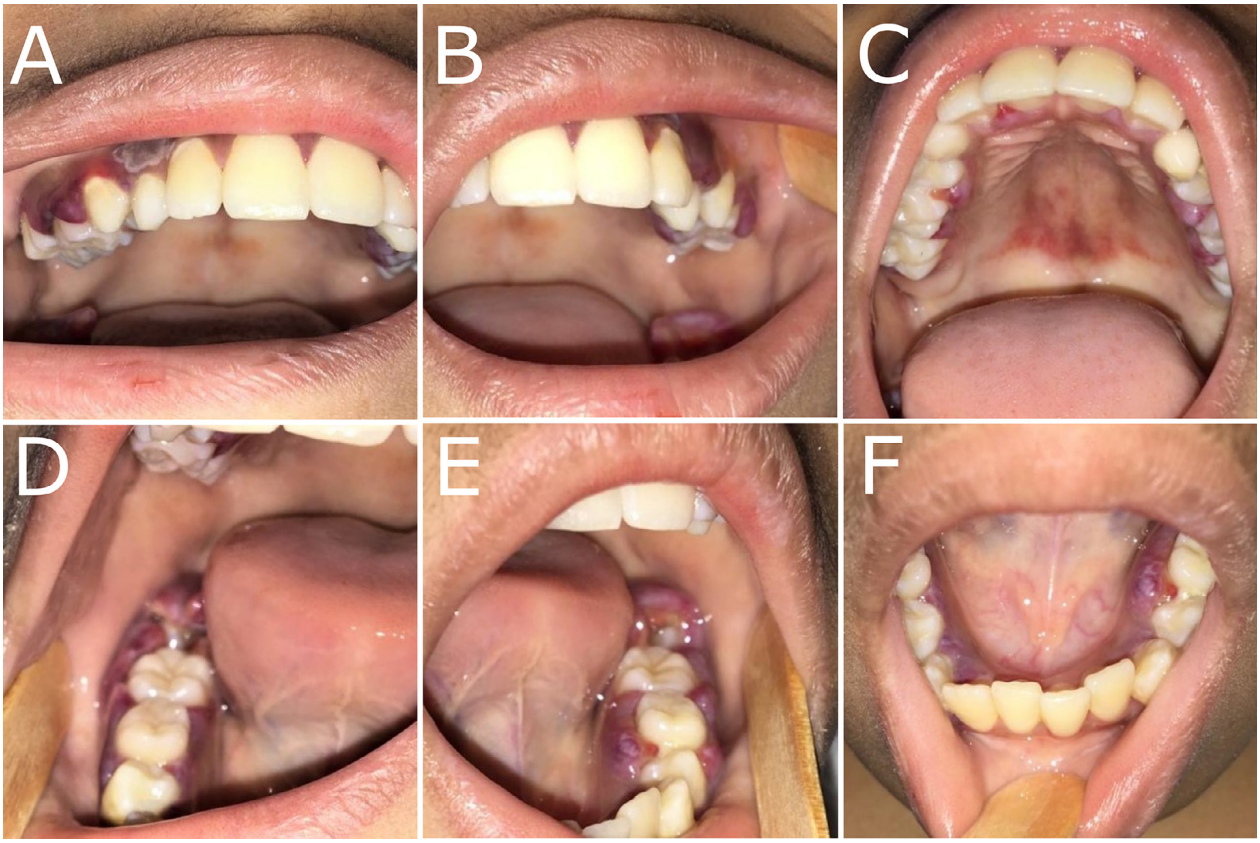

Fig. 1. Intraoral clinical aspect of scurvy-associated gingival enlargements. Lesions were present mainly in regions of interdental papillae, with purple-red color in the **(A-C)** maxilla and **(D-F)** mandible. On the palate, ecchymosis was observed bilaterally.

lower lobes. Observations from the imaging studies suggested the possibility of an inflammatory or infectious condition. The patient was placed in respiratory isolation because tuberculosis was hypothesized as 1 possible ailment. Morphine and ketoprofen were prescribed for pain alleviation. After 19 days of hospitalization, the patient developed a persistent fever that was associated with a cough. A combined dose of amoxicillin and clavulanate (50 mg/kg) was administered orally 3 times a day. The sputum test detected gram-positive cocci. Tuberculosis was ruled out after the acid-fast staining and tuberculin purified protein derivative skin test came back negative.

Dermatologic evaluation revealed a perifollicular purpuric skin rash with follicular hyperkeratosis and "corkscrew" hairs in the lower limbs. Vertebral changes were diagnosed by the orthopedic team as osteomalacia or osteoporosis without acute instability. Thus, a thoracic lumbar sacral orthosis was recommended to the patient for walking.

DIFFERENTIAL DIAGNOSIS

The correlation of physical and oral manifestations raised concerns about the possibility of leukemic infiltration in the gums. Leukemia is a hematopoietic malignancy that is clinically characterized by multiple signs and symptoms that overlapped with the symptoms in the present case. Notably, progressive fatigue, anemia, diffuse bone pain, and propensity to opportunistic infections are common in patients with leukemia.[1] Oral indications might also be present, including gingival bleeding, petechiae, and paleness of mucous membranes. In addition, in myelomonocytic types, infiltration by leukemic cells might cause generalized gingival enlargements.[1,2] Although the frequency of myeloproliferative disorders is higher in adult individuals,[3] pediatric cases have also been reported, including extramedullary manifestations involving the gums.[2] Among the spectrum of malignancies, non-Hodgkin lymphomas are lymphoproliferative disorders that include the oral cavity among the extranodal sites of manifestation, although very rare in pediatric patients.[4] Primary extranodal lymphoma of the oral cavity is often painless and might represent an isolated manifestation with no systemic signs or might be progressively associated with fatigue, fever, and weight loss. Gingival involvement is characterized by multifocal massive erythematous swelling and bleeding, as observed in the present case.[4,5]

Gingival hypertrophies could also be an adverse effect of some classes of drugs, such as anticonvulsants, cyclosporine, and calcium channel blockers.[6] The onset and severity of gingival enlargements have a dose-dependent relationship with the medications used.[7] Although drug-induced gingival hypertrophy in general has a fibrous, firm, lobulated, pinkish clinical appearance, the presence of secondary inflammation might cause a reddish surface with a tendency to bleed.[6] In the present case, however, the patient had no history of using medications associated with gingival hypertrophy and systemic findings did not corroborate this diagnostic possibility.

Tuberculosis, a granulomatous disease with a chronic course, is a major public health issue in developing countries.[8] Oral lesions are included in the set of possible clinical manifestations of tuberculosis and, albeit very rare, can be primary lesions of this disease. Oral tuberculosis is classically described as a nonhealing ulcer, but gingival enlargement has been reported in a small number of cases, including pediatric patients.[9,10] Clinically, gingival involvement is characterized by diffuse swelling, a tendency to bleed, and unresponsiveness to oral hygiene care. Chronic evolution might be accompanied by feverish states, weakness, hyporexia, and weight loss, as well as increased erythrocyte sedimentation rate.[9-11] The patient's clinical manifestations associated with pulmonary findings in CT scans corroborated the hypothesis that oral lesions would be secondary to pulmonary tuberculosis, despite the uncommon clinical presentation.

Disorders in the sickle cell spectrum seemed relevant in this case because of the abundance of symptoms, including pain in the limbs and back, vertebral deformities, osteopenia, and anemia. This condition is associated with chronic anemia and low bone mineral density in the lumbar spine and femoral neck in children.[12] Hemoglobinopathy results in altered erythrocytes shape, which causes vascular occlusions and various manifestations, including orofacial. Gingival enlargements associated with this condition have been described as a possible result of chronic bleeding and often consist of a thickening that extends from the marginal gingiva to the mucous-gingival junction,[13] although a case with more prominent gingival enlargement has also been reported.[14] Microscopically, chronic inflammatory infiltrate is observed in fibrous connective tissue with focal areas of scar-like fibrosis.[13,14] In the present case, the prominent red-purple gingival enlargement associated with bleeding differs from the usual gingivitis-like aspect, with slight thickening, as seen in sickle cell disease. Nevertheless, the family reported normal neonatal screening that included a sickle cell test.

The present patient was the offspring of consanguineous parents, increasing the likelihood of inherited genetic disorders, such as mucopolysaccharidosis, a multisystem disease caused by deficient lysosomal enzymes.[15] Spinal deformities observed in CT scans in this case might be suggestive of mucopolysaccharidosis, which demonstrates a wide phenotypic variability.[15] Gingival overgrowth is also seen in pediatric patients with this disorder.[16] Considering that the patient had no neurologic disorders, cognitive deficit, or evident dysmorphism, this possible diagnosis becomes even more remote. In the spectrum of this disease, type VI is related to milder phenotypes and therefore could be suggested in the present case.[15] The main oral manifestations of this condition include anterior malposition of unerupted teeth, open bite, large dental follicles, and macroglossia, in addition to gingival hyperplasia.[16] Because in the present case only spinal bone deformities and gingival hyperplasia could be indicative of mucopolysaccharidosis, this was not considered a relevant provisional diagnosis.

The family history of psoriasis was also taken into account in this case because of a genetic predisposition. Joint symptoms observed in the present case might be present in psoriasis, as a reflex of joint inflammation.[17] Oral manifestations mainly include the geographic tongue, with white plaques associated with red areas, and although gingival involvement occurs, it is clinically characterized by well-defined erythematous areas, with no evident enlargement.[18]

The presence of gingival bleeding and perifollicular hemorrhages associated with fatigue and progressive weakness also reminded clinicians of an often-forgotten disease: scurvy. In this disease, vitamin C deficiency compromises collagen synthesis, resulting in multiple progressive signs and symptoms.[19,20] In the present case, petechiae and ecchymosis might be present, and iron deficiency anemia is also a common finding in pediatric cases.[21,22] However, this is a rare disease, especially in pediatric patients without comorbidities.

DIAGNOSIS

Based on clinical and imaging findings, tests for the diagnosis of leukemia, rheumatic diseases, tuberculosis, and other infectious conditions were requested, and the results of these laboratory tests are listed in Table I. Additional tests for investigation of hematological status and kidney and liver functions were also performed (Table II).

The investigation to determine the possible cause of the patient's clinical condition revealed a history of diet selectivity and food refusal, as well as persistent cough and occasional vomiting, suggesting the possibility of gastroesophageal reflux disease, nutritional deficiency,

Table I. Laboratory tests for diagnostic investigation of rheumatic diseases and infectious conditions

Test	*Result*
Direct antiglobulin test (Coombs direct)	Negative
Anti-HTLV I/II	Nonreagent
Toxoplasmosis	
IgG	Negative (0.00 UI/mL)
IgM	Negative (0.23)
Rubella	
IgG	Negative (8.03 UI/mL)
IgM	Negative (0.24)
Epstein-Barr VCA	
IgG	Non-reagent (0.02)
IgM	Non-reagent (0.02)
HBsAg	Negative (0.11)
Anti-HCV	Negative (0.02)
Anti-Trypanosoma cruzi	Negative
Cytomegalovirus	
IgG	Positive (64.20 U/mL)
IgM	Negative (0.24)
VDRL	Non-reagent
Anti-HIV 1 and 2	Non-reagent (0.07)
Anti-HBc	Negative (3.12)
Lupus anticoagulant	Negative
Anti-Ssb antibodies	Negative (1.97 U/mL)
Anti-Ssa antibodies	Negative (7.11 U/mL)
Anti-Sm antibodies	Negative (<1.0 U/mL)
Anti-Rnp/Sm antibodies	Negative (<1.0 U/mL)
ANA-Hep-2	Non-reagent
Anti-neutrophil cytoplasm	Negative
Anti-cardiolipin	
IgG	Negative (1.74 GPL)
IgM	Negative (3.19 MPL)

ANA-Hep-2, Antinuclear Antibody with HEp-2 Substrate; GPL, G phospholipid unit; Anti-HBc, hepatitis B core antibody; HBsAg, Hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLTV, human T-lymphotropic virus; MPL, M phospholipid unit; Rnp, ribonucleoprotein; anti-Ssa, anti−Sjögren's-syndrome-related antigen A autoantibodies; Ssb, anti−Sjögren's-syndrome-related antigen B autoantibodies; anti-Sm, Anti-Smith; VCA, Viral capsid antigen; VDRL, Venereal disease research laboratory test.

Table II. Laboratory tests performed at the patient's hospital admission for diagnostic investigation.

Test	*Result*	*Reference values**
Blood count		
Leukocytes	3.78 × $10^3/\mu$L	4.5-13.5 × $10^3/\mu$L
Red Cells	3.39 millions/μL	4.0-5.2 millions/μL
Hemoglobin	7.4 g/dL	11.5-15.5 g/dL
Hematocrit	24.4%	35%-45%
MCV	72.0 fL	77-95 fL
MCH	21.8 pg	25-33 pg
CHCM	30.3 g/dL	31.5-36.5 g/dL
RDW	15.6%	11.5%-14.6%
Platelets	208 × $10^3/\mu$L	150-450 × $10^3/\mu$L
Reticulocyte count	3.6%	0.5%-1.5%
Liver profile		
Aspartate aminotransferase	20 U/L	15-40 U/L
Aminotransferase	11 U/L	10-35 U/L
Alkaline phosphatase	128 U/L	55-425 U/L
Gamma-glutamyltransferase	17 U/L	6-44 U/L
Total bilirubin	0.63 mg/dL	0.2-13 mg/dL
Direct bilirubin	0.20 mg/dL	0.0-0.3 mg/dL
Indirect bilirubin	0.43 mg/dL	0.0-1.1 mg/dL
Kidney function		
Uric acid	8.4 mg/dL	3.5-8.5 mg/dL
Urea	27 mg/dL	11-45 mg/dL
Creatinine	0.49 mg/dL	0.2-0.7 mg/dL
Sodium	137 mmol/L	137-145 mmol/L
Potassium	3.9 mmol/L	3.5-5.1 mmol/L
Total calcium	8.9 mg/dL	8.8-10.8 mg/dL
Phosphor	6.49 mg/dL	3.7-5.8 mg/dL
Lactic dehydrogenase	248 U/L	120-246 U/L
Coagulogram		
Partial thromboplastin time	Control: 30.9 s Patient: 25.1 s	Patient/control <1.25
Prothrombin time and activity	Control: 11.5 s Patient: 13.5 s Activity: 78.0% INR: 1.17	Patient/control <1.25 Activity: 70%-110%
Fibrinogen	289 mg/dL	180-400 mg/dL
Serum iron	23 μg/dL	49-181 μg/dL
Ferritin	33.2 ng/mL	179-464 ng/mL
Rheumatoid factor	<8.6 UI/mL	<12 UI/mL
Complement C3	132 mg/dL	88-165 mg/dL
Complement C4	55 mg/dL	14-44 mg/dL

CHCM, cellular hemoglobin concentration mean; MCH, mean corpuscular hemoglobin; RDW, red cell distribution width; INR, international normalized ratio; MCV, Mean Corpuscular Volume.
*Reference values adjusted for age and sex.

and hypovitaminosis—mainly vitamin C deficiency and scurvy.

MANAGEMENT

Based on the presumptive diagnosis of scurvy, immediate vitamin C supplementation (100 mg 3 times a day) was initiated. Because of the patient's dietary restrictions, the possibility of other hypovitaminosis was very likely. Therefore, clinicians also started supplementation of thiamine (100 mg/d), zinc sulfate (5 mL/d), ferrous sulfate (2 mg/kg 2 times a day), vitamin D (2000 IU/d), and vitamin B12 (1000 μg/d intramuscular). The management of oral lesions was based on oral hygiene guidance and clinical follow-up. Within 48 h of vitamin C supplementation, the patient displayed improvement in back and lower limb pain and good tolerance to ketoprofen suspension. Oral changes showed complete resolution after 2 weeks of treatment (Figure 2).

One month after the initiation of multivitamin supplementation, the patient showed regularization of serum iron levels (59 μg/dL), hemoglobin (12.9 g/dL), hematocrit (41.7), red blood cell count (5.30 million/μL), leukocytes (8.84 × $10^3/\mu$L), reticulocytes (0.6%), vitamin B12 (767 pg/mL), and vitamin D (39 ng/mL).

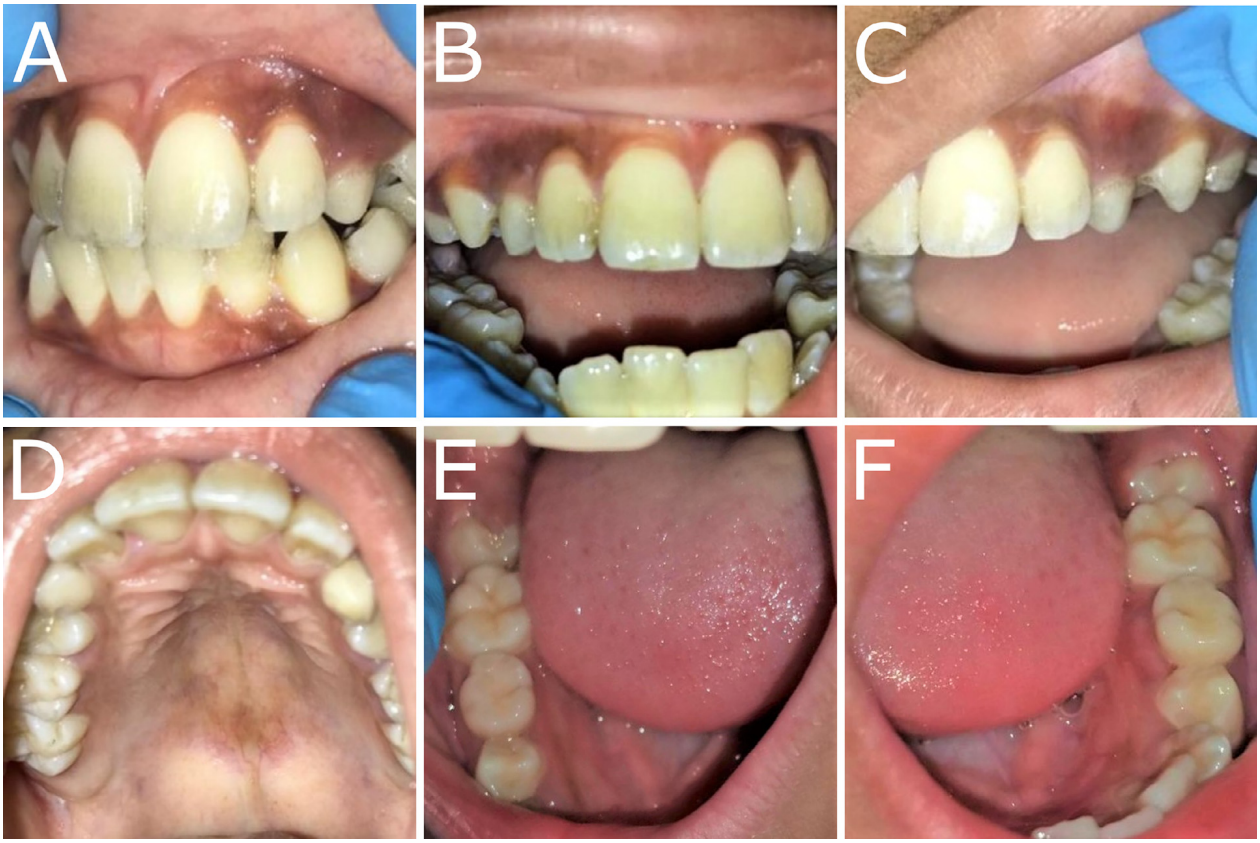

Fig. 2. Intraoral clinical aspect after treatment. Vitamin C supplementation promoted complete resolution of lesions in the **(A-C)** maxilla, **(D)** palate, and **(E,F)** mandible.

DISCUSSION

Vitamin C is an essential dietary nutrient because its synthesis requires L-gulono-ɣ-lactone oxidase, an enzyme deficient in humans at the gene level because of the accumulation of several mutations during evolution. The enzyme missing in humans promotes an oxidation step crucial for the synthesis of vitamin C, making humans prone to scurvy, a historically well-known disease that decimated many people on long sea voyages.[19]

Clinically, the initial signs occur when the plasma vitamin C concentration reaches below a critical level and include fatigue and precluded collagen synthesis, resulting in capillary fragility. This is clinically evidenced by ecchymoses, purpura, and bleeding gums.[21] The progression is usually followed by joint pain, loosening of teeth, and iron deficiency anemia.[23] The signs and symptoms are variable and influenced by the level of vitamin C deficiency, as well as its duration, and might even mimic malignancies such as leukemia.[23,24] The present report describes a case of advanced pediatric scurvy associated with other hypovitaminosis that represents a diagnostic challenge because of multiple symptoms.

Pediatric scurvy as a result of deficient diet is uncommon, and most cases are associated with special medical conditions, mainly with autism spectrum disorder.[25,26] Conditions that require special care, such as motor and intellectual disabilities and enteral tube feeding, have also been reported to cause vitamin C deficiency and scurvy.[27] Children with typical development affected by scurvy are even less common and, in general, the condition results from food selectivity.[22] In the present case, the patient was healthy, but his selective diet and refusal of various foods resulted in severe vitamin deficiencies and scurvy. He was evaluated by a psychiatrist, who ruled out a diagnosis of severe restrictive eating disorder.

The eating habits of these selective children exclude fresh foods such as fruits and vegetables in addition to eating small portions and preferring dairy products and processed foods. Consequently, other nutritional deficiencies are possibly associated, and iron deficiency anemia is common in cases of pediatric scurvy.[22] In this case, microcytic hypochromic anemia was found in initial tests and was characterized by low levels of hemoglobin, hematocrit, and serum iron and low red blood cell count. Ascorbic acid favors the conversion of the iron consumed in a ferric state to ferrous ions before its absorption and participates as an active molecular factor in iron cellular metabolism and

homeostasis.[28] The anemic condition of the present patient was complemented by an increase in the proportion of reticulocytes, possibly indicating a delay in the maturation of erythrocytes, and the marrow started releasing cells early.

The serum ascorbic acid level accurately reflects recent vitamin C intake, whereas leukocyte ascorbic acid assays are considered better indicators of total body levels and, consequently, more appropriate for the diagnosis of scurvy.[29] Because these laboratory tests are not readily available in routine health services, scurvy is also diagnosed by empirical administration of ascorbic acid, verifying the clinical resolution of symptoms after supplementation.[30] In the present case, vitamin C supplementation resulted in rapid clinical improvement, especially of the oral lesions, which resolved in 2 weeks.

Dietary sources of vitamin C include fruits and vegetables, and its content is reduced by 20% to 40% with cooking and long-term storage. Significant deficiency will develop after 2 to 3 months of near-zero intake and clinical signs would manifest within 6 months of deficiency.[31,32] The diagnosis is mainly made on clinical grounds, and a high index of suspicion must be maintained in children presenting with the constellation of cutaneous and musculoskeletal complaints.

Laboratory studies often reveal low or undetectable serum vitamin C levels but, unfortunately, they do not accurately assay stores of ascorbic acid because recent intake can mask longstanding deficiency. Diagnosis is confirmed by clinical response to supplementation. Though not necessary for diagnosis, cutaneous biopsy of affected corkscrew hair follicles revealed dilated hair follicles with keratin plugging and perifollicular hemorrhage, as observed in this case.[31]

Oral scurvy lesions are consistently reported in the literature and are characterized by petechiae, ecchymoses, gingival bleeding and swelling, red-to-purple gingival enlargements, progressive tooth mobility, and loss of teeth. Oral lesions might precede other signs and symptoms and may intensify food selectivity, thereby perpetuating eating disorders.[32] However, early recognition of oral lesions as a manifestation of scurvy is rare because it is an unexpected diagnosis.[21] In the pediatric population, unusual oral complications associated with scurvy have been described, such as inhaling a loosening primary molar, as well as persistent bleeding, delay, and difficulty in healing after the extraction of primary teeth.[33]

Skeletal manifestations are frequent in pediatric scurvy, but multiple and unspecific signs prevent an accurate diagnosis based on radiographic findings. Osteopenia is often seen in imaging studies of patients with scurvy.[26] In pediatric cases, some classic findings, such as metaphyseal bands of decreased density, the scurvy lines, are rarely described.[26,27] Radiographic images can also show thinning or rupture of the cortical bone, periosteal proliferation, and changes that can mimic malignant, inflammatory, or infectious processes.[23] The deformities observed in vertebral bodies in the present case were initially considered suggestive of infectious spondylodiscitis, illustrating the variability of radiographic aspects that scurvy can mimic. Periostitis and abnormal signals of the marrow were observed in a significant proportion of scurvy cases, although these are also features of chronic nonbacterial osteomyelitis.[26] Therefore, scurvy should be considered as a differential diagnosis when observing these findings, especially in cases of patients at nutritional risk.

Joint pain and tendinopathies were also relevant clinical findings in the present case. Joint symptoms characterized by pain, swelling, contractures, and restricted movement, associated with elevated levels of inflammatory markers, may primarily suggest rheumatic diseases in children with scurvy, such as juvenile idiopathic arthritis.[26] However, as observed in the present case, elevated erythrocyte sedimentation rates and C-reactive protein levels may also be a result of vitamin C deficiency and scurvy.

The present case demonstrates the complexity of diagnosing an unexpected disease in the contemporary clinical routine. Children with food selectivity may commonly show nutritional deficiencies, but the distinction between eventual situations and extreme conditions that can be life threatening can only be revealed through a detailed assessment of the dietary routine. Including scurvy among the diagnostic possibilities in cases of children with oral, musculoskeletal, and hematological manifestations proved to be fundamental in this case because this condition can be similar to various diseases. Although the literature reports that children in need of special care are at a higher risk of developing scurvy,[26] this case clarifies that this diagnosis cannot be ruled out in children with typical development and without comorbidities.

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