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CASE REPORT

# Scurvy: an unusual complication of paediatric cancer treatment

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## Abstract

Scurvy is a disease that is rarely encountered in modern medicine. A condition that was classically associated with sailors, its incidence has decreased dramatically since the discovery of its association with vitamin C deficiency. We present the case of a 2-year-old boy, whose treatment for neuroblastoma was complicated by gastrointestinal disease, which necessitated enteral feeding. While still undergoing treatment, he started to complain about increasing pain in his lower limbs, which appeared to be markedly tender on palpation. Radiographic findings suggested a diagnosis of scurvy, which was subsequently confirmed on serum biochemistry. This was an unexpected finding, as the child had been receiving adequate vitamin C in his enteral feeds. However, his absorption had become severely impaired due to pseudomembranous gastritis and enteritis, leading to his deficient state. He significantly improved after intravenous ascorbic acid replacement and demonstrated a full recovery, both clinically and radiologically. This case highlights the importance of considering scurvy in the differential diagnosis for at-risk patients. Early recognition can facilitate the simple treatment of this potentially serious condition.

**Keywords** Neuroblastoma · Enteral feeding · Scurvy · Vitamin C deficiency

## Introduction

Although much decreased in incidence in the developed world, scurvy still occurs in at-risk patients, in both adult and paediatric populations. The manifestations are varied and non-specific, which frequently leads to delays in its diagnosis. The radiologist is often the first to suggest a diagnosis of scurvy, so a good awareness and understanding of its imaging features is essential.

## Case report

We present the case of a 2-year-old boy, whose treatment for neuroblastoma was complicated by gastrointestinal disease and electrolyte disturbances, which necessitated enteral feeding. While receiving myeloablative chemotherapy, he started to complain of increasing pain in his lower limbs, which were markedly tender on palpation. Radiographs of the right knee and hip revealed generalised osteopaenia, with thinning of the cortex, most marked at the epiphyses. This was associated with extensive elevation and calcification of the periosteum along the shafts of the long bones (Fig. 1). A radiograph of the left hand and wrist showed similar findings (Fig. 2). Several possible causes of the periosteal abnormality were considered (Table 1). However, many of these were excluded on clinical and biochemical grounds.

The favoured radiological diagnosis was scurvy with associated subperiosteal haemorrhage, which was presumably exacerbated by chemotherapy-induced thrombocytopaenia (platelets dropped as low as $1 \times 10^9$/L, normal range 150–450). The oncologists felt that scurvy was unlikely, as the child had been on continuous monitored enteral feeding for the preceding 3 months. However, on laboratory assessment, the serum vitamin C level was found to be significantly reduced at 6 mmol/L (normal range: 15–90 mmol/L). Supplemental vitamin C was added to his enteral feed, but symptoms failed to resolve over a 3-week period. The serum vitamin C level dropped further to 4 mmol/L. The possibility of underlying malabsorption was considered, and the child underwent endoscopy. There was very extensive ulceration present throughout the oesophagus, stomach and duodenum, with a stricture at the pylorus. Histology showed an extensive necrotising gastritis/enteritis, with necrosis of the mucosal layer of the stomach, and significant bacterial overgrowth of the

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resulting membrane. Total parenteral nutrition was commenced, with intravenous vitamin C supplementation, and continued for 84 days. Within 2 weeks, the bone pain had significantly reduced, and 2 months later the serum vitamin C levels had returned to normal.

The child subsequently went on to have a matched unrelated bone marrow transplant with complete recovery of his bone marrow. A follow-up radiograph 3 months later (Fig. 3) showed significant improvement in appearances. He remains in complete remission with no evidence of recurrent neuroblastoma 7 years following diagnosis.

## Discussion

Scurvy is now an extremely rare condition in the developed world. However, it is still seen in certain adult populations with poor nutrition, including elderly persons, those living in poverty, institutionalised or chronically ill patients, and alcoholics [1]. Scurvy is detected even less frequently in the paediatric population. Those most at risk include children with underlying malabsorption and nutritional disorders. In the literature, there are a number of case reports of scurvy occurring in children with a restricted diet [2] or with psychiatric or developmental disorders, and in infants who are fed with evaporated or boiled milk [3]. More recently, it has been reported to occur in patients with chronic graft versus host disease involving mucous membranes [4].

Scurvy results from a deficiency of the water-soluble vitamin C (ascorbic acid), a necessary cofactor in collagen biosynthesis. This deficiency results in the failure of normal collagen synthesis, which in turn results in impaired wound healing and deficient osteoblast and fibroblast function. Vitamin C functions as a cofactor, enzyme complement and strong antioxidant in a variety of reactions and metabolic processes [5]. These important antioxidant capabilities stabilize a number of other compounds, which include vitamin E and folic acid [6]. It plays a role in prostaglandin metabolism [7], and can consequently influence the inflammatory response.

Absorbed in the small intestine through an energy-dependent process, vitamin C has a biological half-life of approximately 30 min. As humans are unable to synthesize ascorbic acid, an exogenous source is required—daily requirements are obtained from natural sources, particularly citrus fruits and vegetables. The usual dietary doses (up to 100 mg/day) are almost completely absorbed. The clinical manifestations of hypovitaminosis C can become apparent within 8 to 12 weeks of inadequate intake, or when the body pool falls below 350 mg [1].

The first clinical manifestations are usually preceded by a prodromal asymptomatic period of 1–2 months. Early signs include pallor, muscle and bone pain, irritability, poor weight gain, easy bruising, petechiae, mood changes, and the more commonly known manifestations of poor wound healing and gingival disease. In the rarely encountered advanced stages of scurvy, infants may assume an immobilized posture due to pain associated with subperiosteal haemorrhage, with legs

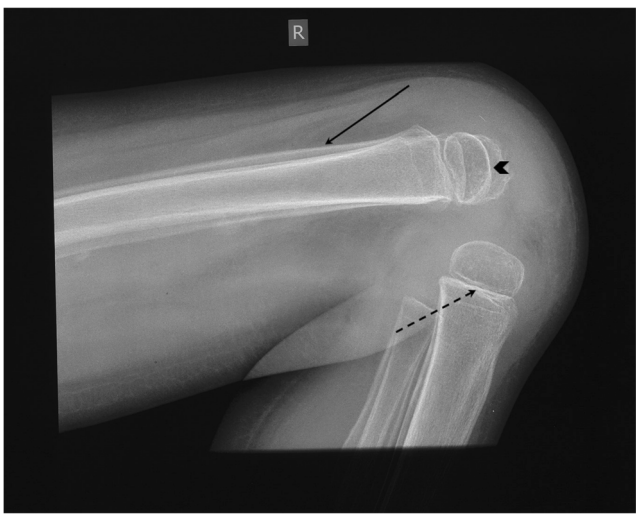


**Fig. 1** Lateral view of the right knee. Elevation of the periosteum with early calcification (*solid arrow*). Reduced density at the growing ends of long bones with adjacent white line of Fraenkel (*dotted arrow*). Wimberger's ring sign is also seen at the distal femoral epiphysis (*arrowhead*)

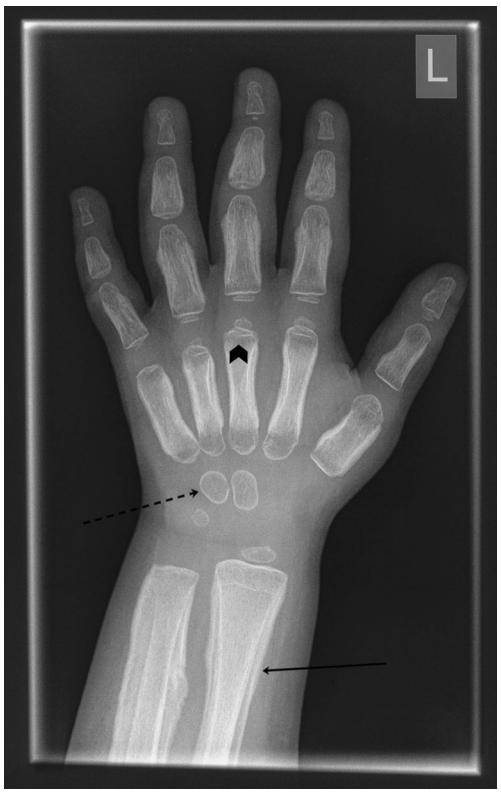


**Fig. 2** Postero-anterior view of the left hand. Similar findings of periosteal elevation (*solid arrow*), Wimberger's ring sign (*dotted arrow*) and reduced bone density at the Trümmerfeld zone of lucency (*arrowhead*)

**Table 1** Differential diagnosis of extensive periosteal reaction on paediatric X-rays

| Cause | Reason for exclusion |
|---|---|
| Bony metastases | The distribution and radiographic features were not typical of metastatic neuroblastoma, and the urinary catecholamines were not elevated |
| Scurvy | Possible, despite absence of classic radiographic features |
| Infantile cortical hyperostosis (Caffey disease) | Incorrect age profile |
| Hypertrophic osteoarthropathy | No underlying cause |
| Hyperphosphataemia | Normal serum calcium and phosphate |
| Vitamin A intoxication | Not administered |
| Idiopathic periostieal hyperostosis with dysproteinaemia (Goldbloom's syndrome) | Normal immunoglobulins |
| Prostaglandin E therapy | Not administered |

held in flexion [7] (pseudoparalysis). Late manifestations include generalised oedema, severe jaundice, fever, seizures, acute spontaneous bleeding and death.

The earliest radiographic changes appear at the metaphyses and are most apparent at the sites of most rapid growth, which include the distal femur, proximal tibia and distal radius and ulna [8]. The basic skeletal changes are due to the suppression of normal cellular activity in the growing bones, leading to generalised atrophy of the cortex and spongiosa [9]. At the zone of provisional calcification, mineral deposition continues in the cartilaginous matrix on the epiphyseal side. This results in a thickened zone of provisional calcification radiographically, the white line of Fraenkel [8], which may project peripherally beyond the shaft, forming the classical "Pelken's spurs" [7] of scurvy. Despite its thickening, this zone is fragile, and is consequently often the site of subepiphyseal corner fractures.

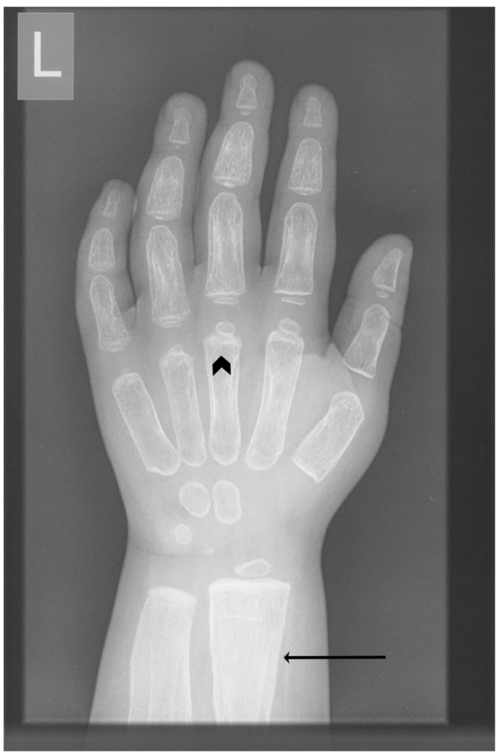


**Fig. 3** Postero-anterior view of the left hand 3 months later. Resolving metaphyseal radiolucency (*arrowhead*), with the calcified periosteum becoming new cortex (*arrow*)

The metaphyseal trabeculae, just deep to the Fraenkel line, are not arranged in a normal longitudinal pattern but in a random pattern, which also predisposes to fractures, resulting in epiphyseal displacement and separation. This sparsity of trabeculae results in a transverse zone of diminished density, known as the lucent scurvy line (or Trümmerfeld zone) [7], between the sclerotic provisional zone on the diaphyseal side and the heavier spongiosa in the shaft. In the epiphyses and ossification centres, the contrast between the atrophic spongiosa and the thickened peripheral shell of calcified cartilage can be very conspicuous, and gives the classic Wimberger's ring sign [9]. Within the diaphyses, the radiographic findings of scurvy include diffuse "ground-glass" osteopaenia, a non-specific finding due to atrophy of the spongiosa. Lack of intercellular cement substance leads to extensive subperiosteal haemorrhage, which frequently affects the large tubular bones such as the femur and humerus. The resolution of the metaphyseal abnormalities after vitamin C supplementation is consistent with radiographic findings of the healing stage of scurvy.

With healing, the cortex becomes thicker and the spongiosa more clearly defined. The lucent Trümmerfeld zone regains normal bone density and disappears. As healing continues, the thickened provisional zone of calcification becomes incorporated into the shaft as a dense transverse line. In those cases where subperiosteal haemorrhage has occurred, the raised periosteum at the periphery of the haematoma begins to grow a new shell of subperiosteal bone. As the haematoma is gradually resorbed, this new thickened layer of bone amalgamates with the shaft to become the new cortex. Evidence of healing as cortical thickening has been reported to persist for many years after treatment [9]. In the healing epiphyseal ossification centres, a central area of rarefaction may persist for many years. Despite initial shortening, a complete catch-up of growth is seen in almost all children.

Because of the extremely rare occurrence of scurvy in modern society, the MRI findings are not well known. A recent review [10] described the most common features: diffuse multifocal decreased signal within bone marrow on T1-weighted images and increased signal on T2-weighted images, with varying degrees of periosteal and adjacent soft-tissue signal abnormalities. Other findings include periosteal elevation, subperiosteal haematomas and enhancing bone marrow. These MRI findings are nonspecific and may resemble other more common conditions such as osteomyelitis, subperiosteal abscess, or leukaemia.

A low vitamin C level in the plasma is specific for the diagnosis of scurvy; however, this is not always reliable because plasma levels may be normal if there has been recent ingestion of ascorbic acid. Measuring vitamin C levels in the buffy coat of leukocytes is a more accurate reflection of body stores; although this method is technically more difficult [5]. The best evidence to support the diagnosis of scurvy is the resolution of the manifestations of the disease after treatment with ascorbic acid. Spontaneous bleeding usually ceases within 24 h, muscle and bone pains subside quickly and gum healing begins within 2 to 3 days. Even large bruises and hematomas resolve in 10 to 12 days. Complete recovery usually occurs after 3 months of adequate supplementation. The dose and duration of treatment are patient-specific [3].

Few case reports exist in the literature of the occurrence of scurvy in patients on enteral nutrition. Gorman et al. [11] reported a case of scurvy in a child on long-term (38 months) enteral nutrition via a gastrostomy. Several causative factors were considered for the development of scurvy—apart from liquid feed, no other nutrition was ingested and therefore the child had no alternative source of vitamin C. Bulk preparation and storage of the feed, and the addition of iron to the feed have been found to reduce the active vitamin C content of enteral feed. Other case reports have recognized drug-nutrient interactions that include vitamin C and phenobarbital, and the decreasing bioavailability of some agents with enteral feeding [12].

## Conclusion

Our patient's course of treatment for his neuroblastoma was prolonged and complex, and he suffered many complications related to drug toxicity. He had required supplemental nasogastric feeding due to dysphagia caused by Candida-related oesophageal strictures. When he first complained of intermittent leg pain, the initial consideration was that it might relate to bony metastatic disease. When this pain became persistent 4 weeks later, and he was totally bed-bound, the relevant X-rays were performed. At that stage, some of the classical radiographic features of scurvy, such as Pelken's spurs, were absent. The mild calcification around the sub-periosteal haemorrhage would suggest early healing, presumably related to the supplemental nasogastric feeding. However, as his pseudomembranous gastritis and enteritis progressed, he was evidently unable to absorb the enteral vitamin C supplements. This report illustrates that even when all nutritional requirements are carefully calculated and provided for, deficiency may still occur.

Although rare, scurvy is still encountered in the paediatric population, especially among certain groups with underlying malabsorption and nutritional disorders. A heightened awareness is needed by clinicians and radiologists to avoid unnecessary delay in diagnosing and treating this potentially fatal but easily curable disease.

## Compliance with ethical standards

**Conflicts of interest** The authors declare that they have no conflicts of interest. No funding was received for this article.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** Informed consent to publish this article was obtained from the patient's mother.

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