Iatrogenic Osteomalacia: Report of Two Cases

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Abstract: Case 1: An 80-year-old man presented at our hospital with pain in both knees. He had received continuous intravenous administration of saccharated ferric oxide (SFO) over a period of five years following a diagnosis of iron-deficiency anemia. Blood tests revealed hypophosphatemia (1.4 mg/dl) and high circulating levels of fibroblast growth factor 23 (FGF23) at 248.8 mg/dl. These findings led to the diagnosis of FGF23-related osteomalacia due to SFO administration. Accordingly, the treatment plan was first to discontinue SFO, which led to a decrease in pain and normalization of phosphorus and FGF23 after 1 month. Case 2: A 63-year-old woman presented at our hospital with leg pain. She had undergone total gastrectomy for gastric cancer at 36 years of age. Blood tests revealed hypocalcemia (8.3 mg/dl) and hypophosphatemia (2.2 mg/dl), and 25(OH)D at no more than 5 pg/ml. Bone X-rays showed significantly diminished bone shadowing. These findings led to a diagnosis of vitamin D-deficient osteomalacia due to impaired absorption following total gastrectomy. For therapy, she was treated with 1 μg/day oral alfacalcidol. Two months after initiating treatment, the pain improved. Conclusion: When a patient is diagnosed with unexplained pain, it is important to pay attention to the possibility of an iatrogenic etiology.

Key words: osteomalacia, saccharated ferric oxide, fibroblast growth factor 23, gastrectomy.

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Introduction

Osteomalacia is a disease in which defective bone calcification leads to a decrease in bone strength, which subsequently causes pain and fractures [1]. It has multiple causes, some of which are iatrogenic; others include various diseases that result in vitamin D deficiency or chronic hypophosphatemia. Previous reports have noted cases of osteomalacia occurring after long-term administration of saccharated ferric oxide (SFO) or after gastrectomy [2–4]. However, the majority of these cases cannot be noticed and diagnosed before bone fractures and related symptoms appear. We here report two cases of iatrogenic osteomalacia experienced at our hospital and discuss the importance of avoiding it.

Case Reports

Case 1

The first patient was an 80-year-old man who presented at a hospital with pain in both knees. He was referred to our hospital for further examination after a diagnosis of hypophosphatemia. At 12 years of age, a part of his small intestine was resected because of perforated peritonitis (surgical technique unknown). At 75 years of age, he received continuous intravenous
administration of SFO (3,840 mg/year) following a diagnosis of iron-deficiency anemia. On admission, blood tests revealed hypocalcemia (8.1 mg/dl) and hypophosphatemia (1.4 mg/dl), and a tubular maximum for phosphate corrected for glomerular filtration rate (TmP/GFR) of 1.3 mg/dl with impaired tubular resorption of phosphorus (Table 1). His blood levels of 1,25-dihydroxyvitamin D [1,25(OH)₂D] were low at 16 pg/ml, and intact parathyroid hormone (i-PTH) at 77 pg/ml indicated secondary hyperparathyroidism. Bone metabolism markers such as bone alkaline phosphatase (BAP; 87.5 IU/l) and urinary collagen type 1 cross-linked N-telopeptide [u-NTx; 41.7 mmol bone collagen equivalent (BCE)/mmolCre] showed high bone turnover. His lumbar spine bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA) was 0.953 g/cm², and the T-score was -0.7, indicating preservation of bone mass. A bone X-ray showed compression fractures in the thoracolumbar region, and bone scintigraphy showed abnormal accumulations in the bilateral knee and ankle joints and in multiple ribs (Fig.1A).

The patient had a history of SFO intake and showed high circulating levels of fibroblast growth factor 23 (FGF23) at 248.8 mg/dl. These findings led to the diagnosis of FGF23-related osteomalacia due to SFO administration. Accordingly, the treatment plan was first to discontinue SFO, which led to a decrease in pain and normalization of calcium (8.5 mg/dl), phosphorus (2.8 mg/dl), 1,25(OH)₂D (68 pg/ml), and FGF23 (26.2 mg/dl) after 1 month. The impaired tubular resorption of phosphorus was also reversible. The bone metabolism markers BAP (77.8 IU/l) and u-NTx (44.8 mmolBCE/mmolCre) still indicated high bone turnover. In addition, intravenous iron for treating the iron-deficient anemia was changed to siderferron, after which the hypophosphatemia improved to the point of disappearing.

Case 2

The next patient was a 63-year-old woman who presented at a hospital with gait disturbance due to leg pain. She was referred to our hospital for further examination following a diagnosis of hypocalcemia. At 36 years of age, she had undergone total gastrectomy and combined distal pancreatectomy and splenectomy for gastric cancer and pancreatic metastases. Her body weight at that time was 48 kg; however, she had persistent postoperative diarrhea and gradually lost weight. She reached menopause at 53 years of age. By around the age of 58, she began experiencing leg pain and lumbar back pain with no apparent provo-

<table>
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<th>Clinical variables</th>
<th>Reference ranges</th>
<th>Case 1</th>
<th>Case 2</th>
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<td>T-Score</td>
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Two Cases of Iatrogenic Osteomalacia

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cation, which gradually impaired her ability to walk. On admission, her height was 155.6 cm, her weight was 29.2 kg, and her BMI was 12.1 kg/m²; she was remarkably thin. Blood tests revealed hypocalcemia (8.3 mg/dl) and hypophosphatemia (2.2 mg/dl), and her i-PTH was 340 pg/ml, indicating secondary hyperparathyroidism. She was also remarkably vitamin D-deficient, with 25(OH)D at no more than 5 ng/ml. The bone metabolism markers BAP (221.0 IU/l) and u-NTx (208.1 mmolBCE/mmolCre) indicated high bone turnover. Bone X-rays showed significantly diminished bone shadowing and pseudo-fractures, and bone scintigraphy showed indications of multiple abnormal accumulations (Fig.1B). DXA in the lumbar spine showed significantly decreased bone mass, with BMD at 0.349 g/cm² and a T-score of -6.0.

These findings led to the diagnosis of vitamin D-deficient osteomalacia due to impaired absorption following total gastrectomy. For therapy, she was treated with 1 μg/day oral alfacalcidol. Two months after initiating treatment, the pain improved and she was able to walk using a cane. Her serum calcium level (10.0 mg/dl) and phosphorus level (3.5 mg/dl) were also normalized. By 12 months after initiation of treatment, her i-PTH also normalized to 14 pg/ml. However, her bone metabolism marker levels were still high, with alkaline phosphatase (ALP) at 426 IU/l and u-NTx at 164.3 mmolBCE/mmolCre. DXA in the lumbar spine showed slightly improved bone density, with a BMD of 0.405 g/cm² and a T-score of ~5.5. We are considering bisphosphonate administration as further treatment.

Discussion

Osteomalacia is a disease in which vitamin D deficiency or chronic hypophosphatemia impairs bone calcification and leads to an increase in noncalcified bone matrix (osteoid). Loss of bone strength can lead to fractures or pain [1]. Known causes of osteomalacia include inadequate dietary intake of vitamin D, impaired vitamin D action, neoplastic osteomalacia, and renal tubular damage (e.g., Fanconi syndrome). However, the etiology may be iatrogenic [1]. Iatrogenic osteomalacia is a preventable condition; in previous cases of patients on maintenance hemodialysis who developed osteomalacia due to aluminum accumulation, improving the dialysate reduced the condition frequency. On the other hand, some drugs such as phenytoin and rifampicin can cause osteomalacia by impairing active vitamin D metabolism. There have been some prior reports [2–4] similar to the cases presented.

Fig. 1. Bone scintigraphy. A: case 1, B: case 2.
here, relating to osteopathy secondary to intravenously administered SFO (case 1) and postgastrectomy osteopathy (case 2). Osteomalacia cases are sometimes first discovered after the appearance of symptoms such as fractures, as in the cases presented above. We believe that reporting these cases will increase the understanding of the pathology of osteomalacia and raise awareness regarding its prevention.

The occurrence of chronic hypophosphatemia and the onset of osteomalacia due to long-term administration of SFO or iron polymaltose have been reported previously [2, 3, 5], but the mechanism has long been unclear. A novel mechanism acting through FGF23 was reported recently [6]. FGF23 is a peptide secreted by osteocytes and comprises 227 amino acids that suppress phosphorus resorption by decreasing the expression of type IIa and IIc Na-P cotransporter in the renal proximal tubules [7]. FGF23 also decreases the 1,25(OH)₂D in the blood, thus decreasing phosphorus absorption in the bowels. This decrease is the result of a decrease in the expression of 25(OH)D-1α-hydroxylase, a metabolic enzyme of vitamin D, in the renal tubules and promotion of 25(OH)D-24-hydroxylase expression [7]. Accordingly, excessive FGF23 over a long term has been found to cause hypophosphatemic osteomalacia (FGF23-related osteomalacia) [8]. Intravenously administered SFO has actually been found to elevate circulating FGF23 levels, and osteomalacia caused by SFO administration is now implicated in FGF23-related osteomalacia [6]. However, the mechanism by which SFO elevates circulating FGF23 levels is unknown, and since cideferron or chondroitin sulfate iron colloid, which are intravenous iron drugs, do not cause hypophosphatemia [9], iron itself might not promote FGF23 secretion. Case 1 had an inappropriate amount of FGF23 secretion following intravenously administered SFO, but the FGF23 levels in the blood were rapidly normalized after SFO was discontinued; subjective symptoms and the hypophosphatemia itself improved. FGF23-related osteomalacia caused by SFO appears to be reversible. Therefore, despite frequent use of SFO to treat iron-deficiency anemia, we believe that care must be taken to avoid unnecessary administration, considering the effects on bone health. In cases where long-term administration cannot be avoided, it is important to use the minimum required dosage over the minimum period of time and to periodically check circulating phosphorus levels to preemptively avoid osteomalacia.

On the other hand, anemia caused by vitamin B12 deficiency and gastric dumping syndrome are well-known postgastrectomy complications [10]. Osteopathy is easily overlooked unless there are fractures, pain, or related symptoms. It has been reported that 18% of gastrectomies are complicated by osteopathy; this number increases to 24–62% in studies that include measures of bone metabolism or other biomarkers [4]. Impaired calcium and vitamin D absorption is thought to be one cause of postgastrectomy osteopathy [11]. Calcium absorption takes place in the duodenum and upper small intestine mediated by gastric acid; thus, decreased postgastrectomy secretion of gastric acid makes calcium insoluble, impairing calcium absorption [12]. Impaired calcium absorption also involves insufficient vitamin D (described later) and calcium intake caused by a decrease in intake and the curtailed transit time for food in the absorption sites. On the other hand, the absorption of vitamin D, which is fat-soluble, is impaired as decreased bile secretion decreases fat absorption [12]. Based on this mechanism, the patient enters a secondary hyperparathyroidism condition, suffering from increased bone resorption and loss of bone density, which ultimately leads to severe osteoporosis or osteomalacia [11]. In addition to dietary therapy and sunlight exposure, treatment for postgastrectomy bone metabolism disorder empirically involves vitamin D, vitamin K, and calcium supplements for malabsorption, but the effects in humans are unclear [13, 14]. On the other hand, the American Gastroenterological Association recommends starting postgastrectomy patients on bisphosphonates if the bone density measured by DXA has a T-score less than −2.5 or if steroids are being administered with a T-score between −2.5 and −1.0 [15, 16]. Similarly, a multicenter study in Japan reported results showing the effectiveness of alendronate in patients who have undergone gastrectomy [17]. The most important point is to prevent bone loss as early as possible.

At present, the underlying illness in the majority of patients requiring gastrectomy is gastric cancer, and osteopathy is expected to occur even more frequently as the postoperative survival rate continues to increase.
It is important to prevent postoperative fractures in patients through regular bone density measurements and aggressive pharmaceutical therapy, where needed. The risk of postgastrectomy osteopathy in terms of different surgical procedures is highest for total gastrectomy, followed by Billroth II and Billroth I. Accordingly, patients who have undergone total gastrectomy, as in the present case, Case 2, are at high risk and thus require particularly careful attention [18]. Treatment of obesity (“bariatric surgery”) by gastrectomy has been on the rise recently, and excessive weight loss, in addition to insufficient calcium and vitamin D, has been reported to cause osteopathy. This indicates that long-term follow-up is essential [19–21].

We here report two cases of iatrogenic osteomalacia experienced at our hospital. When a patient is diagnosed with unexplained pain or osteoporosis, it is important to pay attention to the possibility of an iatrogenic etiology and to diagnose and treat the disorder as early as possible.

References


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医原性骨軟化症の2例

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要 旨：症例1は80歳男性。鉄欠乏性貧血に対し約5年間にわたり含糖酸化鉄を静脈内投与され、両膝痛が出
現した。低リン血症(1.4 mg/dl), fibroblast growth factor 23(FGF23) 248.8 mg/dlと高値より、FGF23関連骨软化症と診
断した。含糖酸化鉄の投与中止のみで、1ヶ月後には症状は改善し、血中リンやFGF 23も正常化した。症例2は63
歳女性。36歳時に胃癌に対し胃切除術を施行された。下肢痛が出現し、低カルシウム血症(8.3 mg/dl)および低リン
血症(2.2 mg/dl), レントゲンで著明な骨陰影減弱を認め、骨軟化症と診断した。25(OH)D 5 pg/ml以下と低値であり、
Alfacalcidol 1μg/日の内服により、2ヶ月後には症状は改善した。これらの症例により原因不明の疼痛患者を診た際
に、医原性の骨軟化症も鑑別にあたる必要がある。

キーワード：骨軟化症, 含糖酸化鉄, fibroblast growth factor 23, 胃切除術。