Neurofibromatosis Type 1 (NF1), also termed von Recklinghausen disease, is a rare autosomal dominant genetic disorder accompanied by several osseous and skeletal manifestations. In NF, hypophosphatemia linked to secondary hyperparathyroidism due to Vitamin D deficiency and low calcium intake has been reported as a risk factor for low bone mass density (BMD), but reports of NF1 associated oncogenic hypophosphatemic osteomalacia (HO) are extremely rare.

Case Report: We report a patient with NF1 associated with intracranial low-grade gliomas and congenital renal agenesis suffering from HO. Bone defects and deformities such as generalized bone pains located in feet, ankles and lower limbs, thoracic scoliosis, mild bowing of long bones of lower limbs, stress fractures, and old fractures as well as with altered bone metabolic serum markers were present. After 8 weeks of follow-up, it was observed that the combination of oral administration of phosphate and Vitamin D improved her medical symptoms without significant changes in phosphate levels or BMD.

Conclusion: Although renal agenesis is not correlated with hypophosphatemia, the coexistence of NF1, renal congenital deformities, and low-grade gliomas may contribute to disease severity. Conventional treatment with high doses of oral calcitriol associated with phosphate is efficient to improve the clinical and laboratory symptoms of the disease.

Keywords: Bone pains, scoliosis, bone mass density, stress fractures, vitamin D.

Introduction

Neurofibromatosis Type 1 (NF1), also termed von Recklinghausen disease, is a rare autosomal dominant genetic disorder with a worldwide incidence of 1/2500–3000 individuals [1, 2]. NF1 is caused by loss-of-function mutations in the NF1 gene that is located on chromosome 17q11.2 encoding an intracellular protein called neurofibromin (NF), which is responsible for the disease [3]. NF is a cytoplasmic protein consisted of 2818 amino acids and is expressed in the central and peripheral nervous system [4] being involved in the regulation of cellular growth and differentiation through two major pathways: First, NF acts as a Ras-GTPase activating protein regulating negatively the Ras downstream signaling and second, NF functions as an activator of the intracellular levels of cyclic adenosine monophosphate (cAMP), resulting in the inhibition of cell proliferation, differentiation, and survival [5]. Therefore, NF
Despite the fact that NF1 is an autosomal dominant disorder with 100% penetrance, there is a great variance in clinical presentation with relatively minor contribution of the nature of the NF1 mutation to disease expression. Diagnostic algorithm is based on the criteria of USA National Institute of Health (NIH) \[8\] and/or the mutation analysis of NF1 gene. Clinically, it is characterized by the presence of café-au-lait spots, intertriginous freckling, Lisch nodules, neurofibromas, optic pathway gliomas, and distinctive bony lesions. Other features include malignant peripheral nerve sheath tumors, neurocognitive defects, epilepsy, and cardiovascular abnormalities \[9\]. NF1 is also accompanied by several osseous and skeletal manifestations, including macrocephaly, short stature, sphenoid wing dysplasia, scoliosis, congenital pseudoarthrosis of the long bones \[10, 11\], and increased fracture risk \[12\]. Furthermore, various research studies reported that 20–50% of pediatric and adult patients with NF1 presented with reduced bone mineral density (BMD) or osteoporosis \[13, 14, 15\]. Reduced levels of Vitamin D and increased concentrations of parathyroid hormone (PTH), calcium, and bone turnover markers, like tartrate resistant acid phosphatase, were detected in the serum of NF patients with low BMD \[16, 17\]. Histological examinations of bone samples that were received from NF patients with low BMD, revealed reduced volume of trabecular volume, increased osteoid volume and raised number of non-differentiated osteoblastic and osteoclastic cells \[18\].

Hypophosphatemia linked to secondary hyperparathyroidism due to Vitamin D deficiency and low calcium intake has been reported as a risk factor for low BMD in NF patients \[13\]. However, reports of NF1 associated oncogenic hypophosphatemic osteomalacia (HO) are extremely rare \[13\]. This article describes a NF1 patient diagnosed with HO associated with intracranial gliomas and congenital renal agenesis.

Case Report

Figure 1: (a) Anteroposterior view of tibias and fibulas demonstrates the distal tip of the intramedullary nail applied for the treatment of old fracture of the right femur and a small stress fracture on the periosteum and cortex of the lower third of the right fibula medially (yellow arrows). (b) Lateral view of the right tibia and fibula with signs of peristeal reaction and cortical thickening of the posterior right tibia (red arrow) after a recent stress fracture (c). Lateral view of the left tibia and fibula with signs of cortical thickening of the proximal posterior left tibia consistent with healed stress fracture (red arrow). Small stress fractures on the periosteum and cortex of the lower third of left fibula were also observed (yellow arrows). Lateral and anteroposterior views of tibias and fibulas suggesting generalized demineralization of long bones. Also, note mild bowing of the tibiae and fibulas bilaterally (a, b, and c).

Figure 2: Anteroposterior view of total spine in standing position shows a right thoracic curve of 11 degrees between 5th and 10th thoracic vertebrae without any signs of dystrophic deformities.

Figure 3: Brain magnetic resonance imaging demonstrates two low-grade gliomas on the right to putamen and globus pallidus.

Figure 4: Renal ultrasound (U/S) imaging demonstrates solitary kidney with the left renal agenesis (a, b, and c). Note physiological compensatory hypertrophy of the right kidney (c).
A 29-year-old active Caucasian female with multiple facial cutaneous nodules was diagnosed with NF1 according to the clinical criteria of NIH [8]. She presented in the outpatient’s department of our institute complaining about progressive bone aches of the feet and ankles, lower limbs, and low-back pain for the past 5 years that were accompanied by muscle weakness, unstable gait, inability to weight bear, and frequent falls. She had also experienced right femoral shaft fracture before 1 ½ years treated with intramedullary nailing (Fig. 1a). She did not suffer from any visual or hearing impairment and her medical history did not reveal renal, liver, gastrointestinal, or constitutional symptoms associated with malignancies. In addition, focal or generalized neurological symptoms were not present. Family history affirmed that her mother was diagnosed with NF1 without evidence of bone metabolic and systematic clinical diseases.

Physical examination displayed a female with short stature (1.52 m with body mass index of 19.8 cm/kg2) with small facial neurofibromas located in the temporal, orbital and cheek areas. Few neurofibromas were also observed over her trunk associated with axillary freckles and numerous café-au-lait macules over her back. Neuromuscular and skeletal examinations were unremarkable. Bilateral multiple Lisch nodules were, also, found during oculom examination.

Skeletal survey with plain radiographs demonstrated generalized demineralization of bilateral lower limb bones (Fig. 1a, b, c) as well as signs of moderate periosteal and endosteal reactions with cortical thickening at the posterior proximal metadiaphyseal region of both tibias (Fig. 1a, b, c), consistent with recent healed stress fractures [19]. Stress fractures were also detected in the lower third of the fibula bilaterally (Fig. 1a, b, c). Despite the fact that feet and ankle aches were prominent symptoms, radiographic examination did not show fracture defects. Full spine X-ray in standing position revealed a right thoracic curve of 11 degrees between T5 and T10 vertebrae without any dystrophic signs (Fig. 2). Bone densitometry measures by DEXA showed low BMD. Spinal sBMD was 914 mg/cm2, while lumbar spinal and hip T and Z-scores were −2 and −2.2, respectively. Cranial magnetic resonance imaging (MRI) detected two low-grade gliotic lesions on the right to putamen and globus pallidus without signs of calcification and ossification or ventricle displacement (Fig. 3). CT-scan and ultrasonography (U/S) of the abdomen were normal, while renal U/S revealed solitary kidney with the left renal agenesis (Fig. 4). Application of quantitative renal scintigraphy with technetium-99m dimercaptosuccinic acid (99mTc-DMSA) did not detect any disturbances in the structural and functional renal integrity.

Laboratory findings were as follows: Serum calcium was 8.9 mg/dL (reference range between 8.5 and 10.5 mg/dL), serum phosphorous was 1.8 mg/dL (normal: 2.5 and 4.5 mg/dL), serum 25-(OH) Vitamin D, and 1,25-(OH)2 Vitamin D3 were 30.2 ng/ml (normal: 30 and 80 ng/ml) and 55 pg/ml (normal: 16 and 56 pg/ml), respectively, serum alkaline phosphatase and plasma osteocalcin were elevated to the level of 480 iu/L (normal: 35 and 150 iu/L) and 110 ng/ml (normal: 11 and 43 iu/L), respectively. Daily urinary excretion of calcium and phosphorous was 80 mg/24 h (normal range: 0–300 mg/24 h) and 400 nmol/24 h (normal range: 10–40 nmol/24 h), while serum levels PTH, urea, and creatinine were measured within normal limits.

The combination of normal levels of 25-hydroxyvitamin D, PTH, serum calcium, and the concomitant presence of low serum and increased urine secretion of phosphates, as well as the association with bone defects, led us to the diagnosis of oncogenic HO. Patient was treated with oral phosphorous supplementation (2.0 g/day) and calcitriol (1 mg/day). Although during the assessment of the patient 8 weeks after initiation of the treatment, radiological findings were not altered significantly, clinical symptoms, such as foot and lower limb aches or weakness, were markedly improved. Laboratory findings, also, demonstrated elevation in the serum calcium (9.6 mg/dL) but slight improvement in the levels of serum phosphorus (2.0 mg/dL), while the plasma levels of osteocalcin and alkaline phosphatase were not significantly altered.

Discussion

We presented a case of HO in NF1 accompanied by systematic computer-based literature review search with predefined criteria that were performed in the following databases: PubMed (1947 to present) and Web of Science (1900 to present) using MeSH. The research methodology used a combination of the following terms: “Neurofibromatosis and/or von Recklinghausen (All Fields)”, “hypophosphatemia (All Fields)”, and “oncogenic osteomalacia (All Fields)”. Only full-text articles were eligible for inclusion. Articles written in English, case series, and case reports, case-based reviews were, also, selected for the study. Studies written in a language other than English were excluded from the study.

HO secondary to tumors of mesenchymal origin is a rare paraneoplastic syndrome, which is characterized by remarkable low levels of serum and increased concentrations of urine phosphate leading to abnormal bone mineralization [20]. Multiple myelomas, hemangiopericytomas, osteosarcomas, chondroblastomas, chondromyxoid fibromyxomas, malignant fibrous histiocytomas, giant cell tumors, and prostatic cancers are entities that were associated with adult-onset HO [20, 21]. NF1 has been implicated with HO very rarely (Table 1) [22, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33]. Despite the fact, that the association between NF1 and HO was described by Gould in 1918, <50 cases have been referred in the international literature [28]. Moreover, to the best of our knowledge, this is the first report in which HO secondary to NF1 is implicated with low-grade brain gliomas and unilateral renal congenital agenesis.

The combination of clinical manifestations, radiographic, and
laboratory examinations contributed in the diagnosis of oncogenic HO. Metabolic data in oncogenic osteomalacia included hypophosphatemia, hyperphosphaturia secondary to reduced proximal renal tubular phosphate reabsorption and low or inappropriate normal levels of serum Vitamin D. Moreover, serum concentrations of calcium and parathormone (PTH) were in normal levels while calcium levels in urine were low [20]. It has been reported that NF1 patients display several skeletal manifestations and deformities [10]. Bone pains, located on the feet and lower limbs as well as muscle weakness, bowing of long bones, pseudofractures, fractures, kyphoscoliosis, and triadate pelvis, were the most common described defects (Table 1) in NF1 patients with HO [22, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33]. In our case, generalized bone pains, weakness of the proximal muscles, thoracic scoliosis, mild bowing of long bones of lower limbs, stress fractures, and old healed fractures accompanied by altered bone remodeling serum markers were observed. Interestingly, stress fractures of the distal tibia and fibula were clinically presented with feet and ankles pain, tenderness, and inability to weight bear. Similarly, NF1 patients with HO (Table 1) had low BMD suffering from diffuse osteopenia [27, 30] or osteoporosis [25, 28, 33] and bone demineralization [29, 33]. In our report, plain radiographic figures revealed generalized demineralization of the long bones of the lower limbs. In general, the BMD of the patient was low indicating osteopenic defects. This finding was in consistence with the studies of Heerva [13, 15] and Lammert [14], in which decreased BMD occurred among patients with NF1 [14] and was accompanied by low bone quality and persistent osteopenia in young patients [15] resulting in generalized bone alteration and osseous dysplasias [14]. Similarly, Jalabert et al. [13] reported that low BMD in NF1 patients was 3.3 times more frequent compared to general population. In the same study, hypophosphatemia was detected in 12 women with NF1 but it was correlated with secondary hyperparathyroidism, and not to oncogenic HO, as it was linked to low calcium intake and Vitamin D deficiency [13].

Recently, the implication of fibroblast growth factor 23 or FGF-23 in the pathogenesis of NF1 bone defects with HO was proposed. Specifically, it was suggested that the elevated secretion of FGF-23 from neurofibromin-deficient osteocytes resulted in mineral defects and an osteomalacia – like bone phenotype [33]. Indeed, in conditional knockout for neurofibromin mice model, it was observed that primary osteocytes showed remarkable increase in the expression of FGF-23 in the serum and in the femur [32]. This was linked to abnormal calcium-phosphorus metabolism and to reduced bone formation and mineral apposition rate [34]. In the same study, micro-ct examination, also, demonstrated thinner and porous cortical bones with disorganized osteocyte dendrites that exhibited reduced strength in mechanical forces leading to spontaneous fractures [34]. This was supported by the clinical findings of increased circulating levels of FGF-23 in two patients with NF1 that appeared severe HO [23, 25]. A possible explanation was that the increased serum concentration of FGF-23 inhibited renal reabsorption of phosphorus and decreased the production of 1,25-dihydroxyvitamin D leading to increased phosphate wasting and lower levels of phosphorus in the serum [34].

In our report, low-grade gliomatic lesions were also present. Although, association of low-grade gliomas with HO has not been reported in the international literature, we must underline the fact that several angiogenetic growth factors were expressed during gliomas development [35]. The FGF growth factor family played a key role in glioma survivorship. It was reported that increased expression of FGFs (including FGF-23) induced the proliferation, differentiation, and migration of endothelial cells in vitro and the angiogenetic process in vivo [35]. As gliomas showed increased expression of FGF-23, we can speculate that the coexistence of NF1 and low-grade gliomas may enhance the possibility for the development of HO. Unfortunately, our patient did not approve the examination for serum or tissue FGF-23 levels using immunological techniques. However, the above assumption was supported by our finding that 7 years ago, when visible evidences of the gliomatic tumors were not detected, laboratory examinations of the patient were within normal levels, indicating a recent tumor-induced overproduction of FGF23. It must be noted that recent experimental and human immunochimical data suggested that in NF patients, bones and/or concomitant malignancies of mesenchymal origin and not neurofibromas were the primary source of FGF23 overproduction [25].

In our case, NF1 was associated with unilateral renal agenesis that was considered as benign condition. Although it was linked to metabolic abnormalities such as hypercalcuria or hypocitraturia, no correlation between renal agenesis and increased urine loss of phosphorous was observed [36]. However, in animal rat model, renal agenesis was accompanied by increased expression of FGF-23 and, therefore, the contribution of renal agenesis in the HO development cannot be excluded from the study [37]. With a given agenesis of the left kidney, differential diagnosis of conditions of renal phosphate wasting, such as Fanconi syndrome, was deemed necessary. In this report, clinical or laboratory results specifying Fanconi syndrome were not observed. The diagnosis of Fanconi syndrome was based on typical findings of glycosuria (with normal plasma glucose), proteinuria, and phosphaturia along with hypophosphatemia and non-anion gap hyperchloremic metabolic acidosis due to increased renal secretion of bicarbonate. Early serum and urine laboratory examination may reveal the presence of Fanconi syndrome [38]. Although, in our report, NF1 was implicated with intracranial low-grade gliomas and congenital renal disorder, the current therapeutic approach with administration of high doses of oral calcitriol combined with phosphate was efficient and improved
the clinical symptoms of the patient. We must highlight the fact that clinical improvement was usually observed during the first 8 weeks of the treatment [22, 24, 26, 27, 28, 29, 30], whereas marked increase in the calcified components of the bone with complete fractures healing and restoration of BMD as well as normalization of the serum markers of bone remodeling such as osteocalcin, alkaline phosphatase, and C-terminal telopeptides were detected after 10–12 months of the treatment [25, 27, 32]. Similarly, persistent hyperphosphaturia and gradual increase of serum phosphorus were also reported [39]. The role of serum calcium, phosphate, and PTH in regulating FGF23 levels is not clear. In-vitro experimental studies have shown Vitamin D dependent regulation of FGF23 promoter activity, but have failed to identify effects of calcium or phosphate on FGF23 promoter [40]. Moreover, calcitriol was an important modulator of FGF23 production in osteoblasts, potentially regulating FGF23 levels indirectly [40]. Careful monitoring of renal function and possible complications such as hypercalciuria or nephrolithiasis must be considered. However, surgical resection of the tumors or large neurofibromas could be the treatment of choice.

### Table 1: PubMed Literature review (1985–2022) on cases and treatment

<table>
<thead>
<tr>
<th>References</th>
<th>N</th>
<th>Age (in years)</th>
<th>Sex</th>
<th>Serum phosphate (in mg/dl)</th>
<th>Serum 25OH-Vitamin D (in ng/dl)</th>
<th>Skeletal symptoms and bone defects</th>
<th>Clinical response to vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makhlouf et al., 2020, [22], Tunisia</td>
<td>1</td>
<td>67</td>
<td>Male</td>
<td>0.51 mmol/lit</td>
<td>Not Applicable</td>
<td>Limitation of hips abduction and internal rotation, biconcave vertebrae, fuzzy structure of pelvis, Looser’s zone of upper femoral shafts</td>
<td>Yes</td>
</tr>
<tr>
<td>Obo et al., 2020 [23], Japan</td>
<td>1</td>
<td>65</td>
<td>Female</td>
<td>1.9</td>
<td>14</td>
<td>Spinal compression fractures and multiple rib fractures</td>
<td>Yes</td>
</tr>
<tr>
<td>Nagaratnam et al., 2020 [24], Malaysia</td>
<td>1</td>
<td>44</td>
<td>Female</td>
<td>0.31–0.56</td>
<td>25</td>
<td>Thoracolumbar kyphoscoliosis and L1 vertebral compressive fracture</td>
<td>Yes</td>
</tr>
<tr>
<td>Sahoo et al., 2019 [25], India</td>
<td>1</td>
<td>34</td>
<td>Female</td>
<td>1.6</td>
<td>30</td>
<td>Pseudofractures, bowing of long bones, and kyphoscoliosis triradiate pelvis diffuse osteoporosis</td>
<td>Yes</td>
</tr>
<tr>
<td>Gupta et al., 2015 [26], India</td>
<td>1</td>
<td>43</td>
<td>Female</td>
<td>1.5</td>
<td>Normal</td>
<td>Bone pain, proximal muscle weakness, pseudofractures, triradiate pelvis, and fractures</td>
<td>Yes</td>
</tr>
<tr>
<td>Chadha et al., 2009 [27], India</td>
<td>1</td>
<td>46</td>
<td>Female</td>
<td>1.7</td>
<td>Not Applicable</td>
<td>Bone aches, supracondylar femoral fracture, pseudofractures, triradiate pelvis, coarse trabeculae, and osteopenia</td>
<td>Yes</td>
</tr>
<tr>
<td>Soved 2003 [28] Iran</td>
<td>1</td>
<td>34</td>
<td>Male</td>
<td>1.2–1.4</td>
<td>35</td>
<td>Bone pain, proximal muscle weakness, pseudofractures, and osteoporosis</td>
<td>Yes</td>
</tr>
<tr>
<td>Konishi et al., 1991 [29], Japan</td>
<td>1</td>
<td>40</td>
<td>Female</td>
<td>1.02</td>
<td>37.3</td>
<td>Pseudofractures, demineralization, and triradiate pelvis deformation</td>
<td>Yes</td>
</tr>
<tr>
<td>Weinstein et al., 1990 [30], USA</td>
<td>1</td>
<td>61</td>
<td>Female</td>
<td>1.3–2.3</td>
<td>25.5</td>
<td>Bone pain, proximal muscle weakness, mild kyphosis, and diffuse osteopenia</td>
<td>Yes</td>
</tr>
<tr>
<td>Suda, 1989 [31] Japan</td>
<td>1</td>
<td>56</td>
<td>Male</td>
<td>1.6</td>
<td>27</td>
<td>Bone pain, pseudofractures, bone atrophy, and coarse trabecula</td>
<td>Yes</td>
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<tr>
<td>Hogan et al., 1986 [32], Canada</td>
<td>1</td>
<td>62</td>
<td>Male</td>
<td>2.05</td>
<td>64</td>
<td>Bone pain, pseudofractures, and fractures</td>
<td>Yes</td>
</tr>
<tr>
<td>Wattiaux et al., 1985 [33], France</td>
<td>2</td>
<td>49, 42</td>
<td>Male</td>
<td>2.1</td>
<td>20</td>
<td>Bone pain, kyphoscoliosis, vertebral osteoporosis, and demineralization</td>
<td>Yes</td>
</tr>
</tbody>
</table>

We report a patient with NF1 associated with intracranial low-grade gliomas and congenital renal agenesis suffering from HO. Bone defects and deformities such as generalized bone pains, thoracic scoliosis, mild bowing of long bones of the lower limbs, stress fractures, and old fractures were present. Despite the fact that renal agenesis was not associated with HO, the concomitant presence of NF1 and low-grade gliomas may enhance the possibility of the development of HO. Further studies are deemed necessary to elucidate the exact role of these pathologies in the signaling pathways that result in HO.

### Clinical Message

Association of Neurofibromatosis 1 with tumors of the central nervous system and/or congenital renal deformities may enhance the possibility of osteopenia and skeletal abnormalities due to hypophosphatemia in young ages. However, conventional treatment with high doses of oral calcitriol combined with phosphate is efficient to improve the clinical and laboratory symptoms of the disease.
References


