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CASE REPORT

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Hypophosphatemic Osteomalacia associated with Neurofibromatosis 1 Type-1: A case report and literature review

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Abstract

Introduction: *Skeleton abnormalities are not uncommon in neurofibromatosis type-1 (NF1), which usually manifest as congenital malformations, such as scoliosis and sphenoid wing dysplasia. However, rare cases of NF1 have been associated with hypophosphatemic osteomalacia (HO), which is characterized with later onset in adulthood, severe hypophosphatemia and disorder of the mineralization of organic bone matrix.*

Patient Concerns: *Here we reported a rare case of a 29-year-old woman presented with weakness and pain in lower limbs for 18 months and aggravated for half a year. On physical examination, her lower limbs' myodynamia reduced and tenderness in multiple bone areas was detected. Light brown patches and scattered nodules could be seen on her skin, and a soft subcutaneous mass was found in the low back. Laboratory evaluation showed hypophosphatemia. Bone ECT suggested multiple abnormal bone metabolism and MRI scan of lumbosacral spine revealed numerous fractures. Neuroimaging indicated the neurofibromas, and then the biopsy of the subcutaneous lump confirmed neurofibromatosis.*

Diagnosis: *HO associated withNF1 was diagnosed, based on the presence of café-au-lait spots and the results of bone ECT scan and biopsy.*

Interventions: *The patient was treated with oral calcitriol, calcium carbonate d3and phosphorus, as well as intramuscular carbocalcitonin.*

Outcomes: *During hospitalization, her serum phosphorus level increased and symptoms improved.*

Conclusion: *The case reported here calls attention to that when NF1 patients manifested with weakness and neurology diseases have been excluded, HO should be taken into consideration*

Keywords: hypophosphatemia; osteomalacia; neurofibromatosis; NF1; FGF23

Abbreviations: NF1: Neurofibromatosis Type-1; HO: Hypophosphatemic Osteomalacia; ALP: Alkaline Phosphatase; PTH: Parathyroid Hormone; EMG: Electromyogram; MM: Multiple Myeloma; TIO: Tumor-Induced Osteomalacia; FGF23: Fibroblast Growth Factor23; FGFR: Fibroblast Growth Factor Receptor

Introduction

Neurofibromatosis type 1(NF-1) is a dominant autosomal genetic neurocutaneous syndrome, with an incidence of 1 in 3,000 persons. [1] Its clinical manifestations varied, mainly includes 'café-au-lait' macules and multiple neurofibromas [2]. Skeleton abnormalities are not uncommon in NF1, with incidence been reported as high as 51% [3]. However, the relation between hypophosphatemic osteomalacia (HO) and NF1 is rarely mentioned.

Case report

A 29-year-old woman, presenting with weakness in lower limbs and difficulty in climbing stairs for 18 months, developed bilateral groin pain and found her walking unstable one month after the attack. About 6 months prior to the visit, she felt traction pain in the right thigh, which gradually developed to the lumbar vertebrae and thorax, and would aggravate with exercise and cough. Besides, she denied a history of injuries.

Physical examination revealed that her lower limbs' myodynamia reduced and tenderness presented in the regions of her spine, shoulder joints, bilateral hip bones and thighs. Different sizes of light brown patches could be seen on her skin (Figure 1). In addition, several scattered nodules with size of green beans were found on her trunk and a soft subcutaneous mass was found in the low back (Figure 1).

The laboratory data in our institute is showed in table 1. The patient was characterized by hypophosphatemia, namely low phosphate in the serum, with increased alkaline phosphatase (ALP) and serum calcium normality. Her serum parathyroid hormone (PTH) elevated. Other laboratory test results including ENA and ANCA were within normal range, which excluded autoimmune diseases.

MRI of lumbosacral spine showed multiple lesions around nerve, which neuroimaging indicated neurofibromas, and multiple fractures. What's more, her bone scan showed generalized abnormal bone metabolism (Figure 2). Besides, no signs of other tumors were detected in 18F-PET-CT. Then, subcutaneous mass biopsy was performed, and the results confirmed neurofibromatosis (Figure 3). Meanwhile, her electromyogram (EMG) was normal, which rule out diseases of the peripheral nerves, and negative

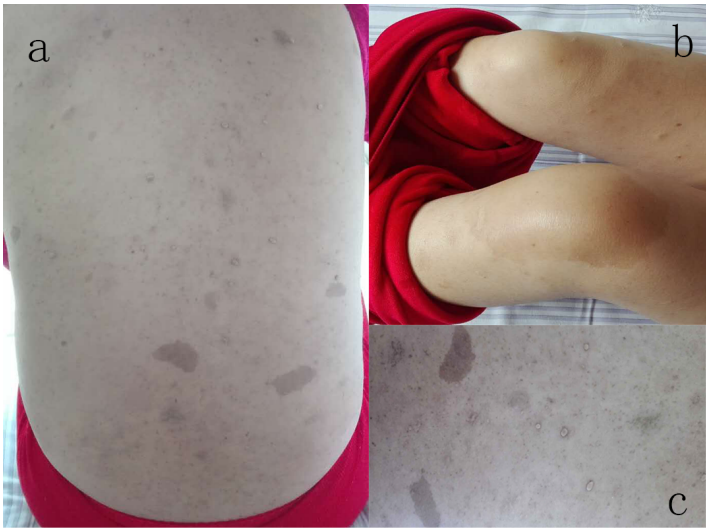

Figure 1.*The visual examination of the patient's skin: (b) the biggest café au lait macule on the left knee; (a) & (c) several café au lait macules on the back.*

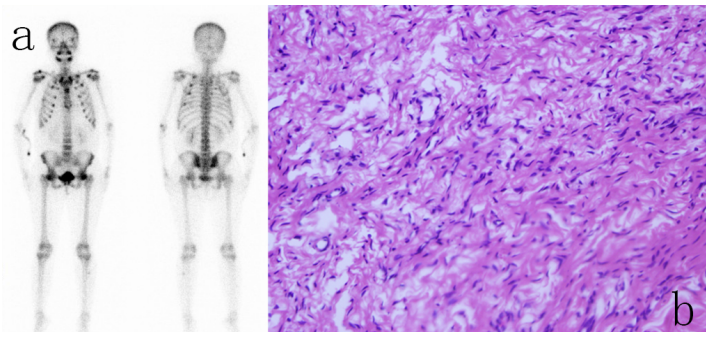

Figure 2.*The ECT images shows abnormal metabolism in multiple skeletons*

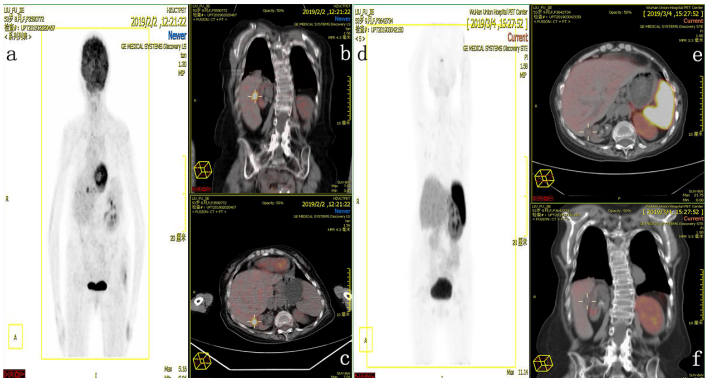

Figure 3.*The biopsy of the lump indicates neurofibromas: (a)HE 40x ; (b) HE 400x*

Table 1.*Important laboratory data of the case*

Clinical variables	Reference range	Prime	Review
Blood:			
Calcium(mg/dl)	2.03	2.54 2.24	2.53
Phosphorus(mg/dl)	0.96	1.62 0.48	0.81
Potassium (mg/dl)	3.5	5.2 3.67	4.97
Sodium(mmol/L)	136	145 139.3	140.3
Chloride(mmol/L)	96	106 105.2	105.2
Alkaline phosphatase			
(ALP;IU/l)	20-150	236	not performed
PTH (pg/ml)	15	68.3 102.7	115.2
Calcium(mg/dl)	2.03	2.54 2.24	2.53
24 hour Urine:			
Calcium(mg/dl)	2.5-7.5	3.69	not performed
Phosphorus(mg/dl)	22-48	18.73	
Sodium(mmol/L)	130-260	289.2	
Chloride(mmol/L)	140-250	297.3	

BJP as well as normal result of bone marrow puncture excluded Multiple Myeloma (MM). The last but not the least; ultrasound thyroid indicated nothing unusual, which eliminated the possibility of hyperparathyroidism.

Hence, the diagnosis of NF1 was confirmed, based on typical manifestation as 'café-au-lait' macules and multiple neurofibromas. We had consulted the Endocrinology and made a consensus that the patient also suffered hypophosphatemic osteomalacia which might associate with NF1, on the basis of the radiological and laboratory findings.

Because of the innumerable neurofibromas, surgical resection was not performed. During hospitalization, she was firstly prescribed with mecobalamin intravenous drip (1mg once a day) and oral pregabalin (75mg twice a day), which showed no effect. Treatment with oral gabapentin (0.3g three times a day) provided remission on the tenderness to some extent. Then she was prescribed with oral calcitriol capsules (0.25ug once a day), calcium carbonate d3 tablets (Calci, 0.6g once a day) and neutral phosphorus solution (dibasic sodium phosphate 29g and potassium dihydrogen phosphate 6.4g diluted in 1000ml ddH2O, 10ml per 6 hours) as well as intramuscular carbocalcitonin (5ml once a day). During this period, serum phosphorus level increased and her 100 clinical symptoms improved to some degree, with no complications appeared.

Discussion

We have reported an unusual case of a 29-year-old woman presented with weakness and pain in lower limbs for 18 months and aggravated for half a year. Skelton imagine showed multiple abnormal bone metabolism and fractures. However, she denied a history of injuries. Through retrospective analysis, we found that the patient had neurofibromas at an early age but did not develop bone

symptoms until the age of 29. Typically, skeleton abnormalities in NF1 usually manifest as congenital malformations, such as scoliosis and sphenoid wing dysplasia [4]. These are thought to be the result of mesoderm dysplasia, not associated with disturbances in calcium and phosphate metabolism, and appear early in life [5]. In contrast, the patient was characterized with low serum phosphate and increased alkaline phosphatase (ALP), and she responded well to our treatment. Taken the presence of multiple pseudo fractures, high ALP, hypophosphatemia and generalized demineralization of bones into consideration, this was likely a case of HO secondary to NF1, an infrequent class of TIO.

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome and the most common type of acquired HO in adult. [5,6]. It is characterized by abnormal bone mineralization and hypophosphatemia. And patients will gradually develop muscle weakness, bone pain and fractures as the disease progresses [5,7]. As its initial clinical presentations are not specific, it may be mistaken for muscular dystrophy or neurological disorder in some cases [8]. The biochemical profile of hypophosphatemia and the patients' responding adequately to oral neutral phosphorus solution therapy help doctors take osteomalacia into consideration. Overwhelming majority of TIO is caused by tumors of mesenchymal origin, with hemangiopericytoma most common described [7]; however, very rare cases of TIO have been associated with carcinomas and syndromes such as NF1.

The pathogenesis of TIO is considered relating to overproduction of FGF23, a phosphaturic hormone ordinarily secreted by osteocytes. FGF23 can bind to the FGF receptors (FGFR) and acts on proximal renal tubular epithelial cells to control renal phosphorus reabsorption [7] and inhibits renal 25 (OH) -1-hydroxylase activities, leading to decreased calcitriol synthesis [9]. Neurofibrin is the product of NF1gene, which is not only mainly expressed in the nervous system cells but also expressed in separated bone cells where neurofibrin can regulate the expression of FGF23 via PI3K pathway [9,10]. There has been one case0020with NF1 reported had elevated FGF23. with NF1 reported had elevated FGF23 [7]. For NF1 patients with osteomalacia, in detail, lacking NF1genein osteocytes leads to a drastically up-regulationofFGF23, which then causes a mineralization insufficiency through the change of calcium-phosphorus metabolism [9].

Removal of the tumor is the only effective treatment identified for TIO [11]. As in patient who suffered with neurofibromatosis with osteomalacia, complete resection of the tumor is hardly achieved, but surgical removal of the largest ones or those with recent growth is recommended [5], and supplement of calcitriol and oral phosphate salts helps to increase serum level of phosphate and to improve clinical symptoms to some extent. The last but not the least, patients who take long-term such treatment need to regularly monitor biochemical indicators such as serum calcium phosphorus and PTH, and adjust the dose to avoid tertiary hyperparathyroidism [12].

Conclusion

Here we reported a case of neurofibromatosis type-1 (NF1) with hypophosphatemic osteomalacia (HO). Osteomalacia in NF1is a quite rare instance and differentiates from other much more common skeleton abnormalities of the syndrome, characterized with later onset in adult and disturbances in calcium-phosphate metabolism. Typically, patient with osteomalacia in NF1 manifest as hypophosphatemia and multiple fractures. Removal of neurofibromas is the best choice of therapy but hard to achieve. Then supplement of calcitriol and oral phosphate may help a lot.

Ethics statement

The case report was conducted in accordance with the ethical standards set out in the Helsinki Declaration of 1964. Written informed consents were obtained from the patient for the participation and publication of this case report.

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Author contributions

All the authors were involved in patients' management and made patient treatment decisions. Xiaoman Yang conceived the idea, drafted the manuscript, and revised all the literatures. Weiqi Zeng collected the clinical data and images. Yan Xu participated in the revision of the manuscript. The manuscript has been read and approved by all the namedauthors.164

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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