CASE REPORT

Neurofibromatosis and fibrous dysplasia manifesting in the same patient: a rare case report

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Abstract

Neurofibromatosis and fibrous dysplasia show the presence of café-au-lait spots, bone lesions, and endocrinopathies. There has been speculation whether neurofibromatosis and fibrous dysplasia are different manifestations of the same disease or if these conditions are in some way related. We provide a case of whether neurofibromatosis and fibrous dysplasia complicated by hyperparathyroidism and osteoporosis.

Case report

A 45-year-old female patient reported to the department of Oral Medicine and Radiology at our institution with a complaint of swelling on the right body of the mandible that had persisted for 6 months. The swelling was initially small, and gradually increased to the present size of 3 × 4 cm. On inspection, the swelling was oval in shape. It extended superiorly from the line joining the angle of the mouth to the pinna of the ear, inferiorly, approximately 1.5 cm below the lower border of the mandible, and anteroposteriorly extended from the corner of the mouth to approximately 1 cm from the angle of the mandible (Figure 1). On palpation, the swelling was of normal temperature on touch, tender and firm in consistency, and the skin over the swelling was pinchable. Past dental history revealed surgery for a similar swelling at the same site, and extractions of the lower right first and second molars during her second decade of life. Intraoral examination revealed no obliteration of the vestibule in relation to the extraoral swelling. Previous histopathological reports of the swelling were suggestive of fibrous dysplasia (FD).

The patient's medical history revealed the presence of neurofibromatosis (NF)1 for 20 years, with neurofibromas all over the body and café au lait spots present on the thigh and back with regular borders (resembling the "coast of California" in contrast to McCune–Albright syndrome where the café-au-lait spots have irregular borders resembling the "Coast of Maine"). The patient reported that a history of NF1 ran in the family, and complained of generalized weakness, headache, fatigue, and pain in the lower limbs, joints, and back, which caused difficulty in walking. The patient was also a known hypertensive since 5 years of age, and was on medication. She had attained menarche at the age of 15 years. Based on her medical history and the clinical examination, a provisional diagnosis of (recurrent) FD was given. Central ossifying fibroma, McCune–Albright syndrome (MAS), and intraosseous lesions of NF-1 were considered under the differential diagnosis.

Panoramic radiograph demonstrated a well-defined mixed radio-opaque and radiolucent lesion on the right body of the mandible, with ballooning of the inferior border. A computed tomography scan of the right body of the mandible showed an expansile mixed lesion (hypodense

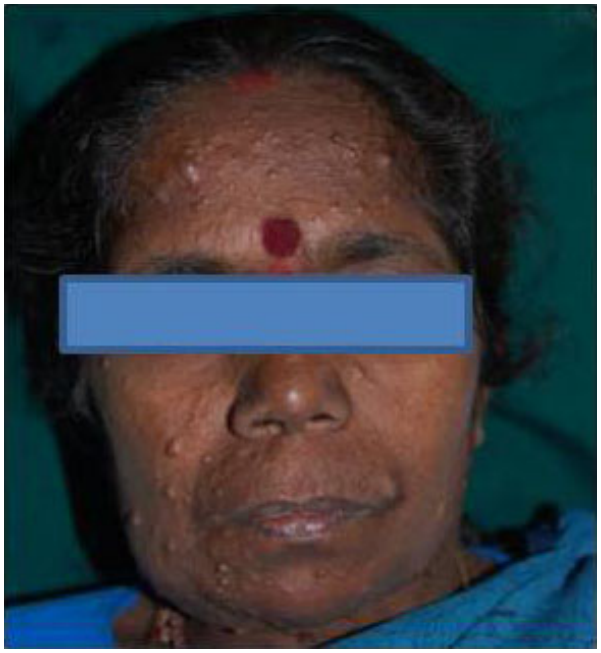

Figure 1. Diffuse swelling on the right lower half of the face with multiple nodules.

and hyperdense), with thinning of cortices and areas of hard and soft tissue attenuation, with densities ranging from 60 to 150 HU, suggestive of FD (Figure 2). The anteroposterior (AP) and lateral view of the spine showed the presence of scoliosis (Figure 2), and the lateral view showed thinning of the ribs. The AP and lateral view of the lower limbs showed an ill-defined mixed lytic-sclerotic lesion in the lower end of the right fibula with cortical thickening, suggestive of FD.

A bone scan revealed an increased uptake of pertechtenate in the right body of the mandible and the lower end of the right fibula, suggestive of polyostotic FD. Dual-energy X-ray absorptiometry scan showed decreased bone mineral density (BMD), with a T score of −2.7, suggestive of osteoporosis.

The patient was subjected to various investigations to assess the cause of generalized body weakness and bone pain (serum calcium, 8.4 mg/dL; serum alkaline phosphatase, 151 u/L; serum parathormone [PTH], 105 mg/mL; 1,25-dihydroxyvitamin D3, 18 pg/mL).These levels were found to be suggestive of secondary hyperparathyroidism due to vitamin D deficiency. Investigations for hypothyroidism, gigantism, and Cushing syndrome were performed to exclude MAS. Serum and urinary levels of calcium, phosphorous, and creatinine were assessed and were suggestive of hypophosphatemia (Serum phosphorous, 2 mg/dL). These levels were also used to evaluate the ratio of the renal tubular maximum reabsorption rate

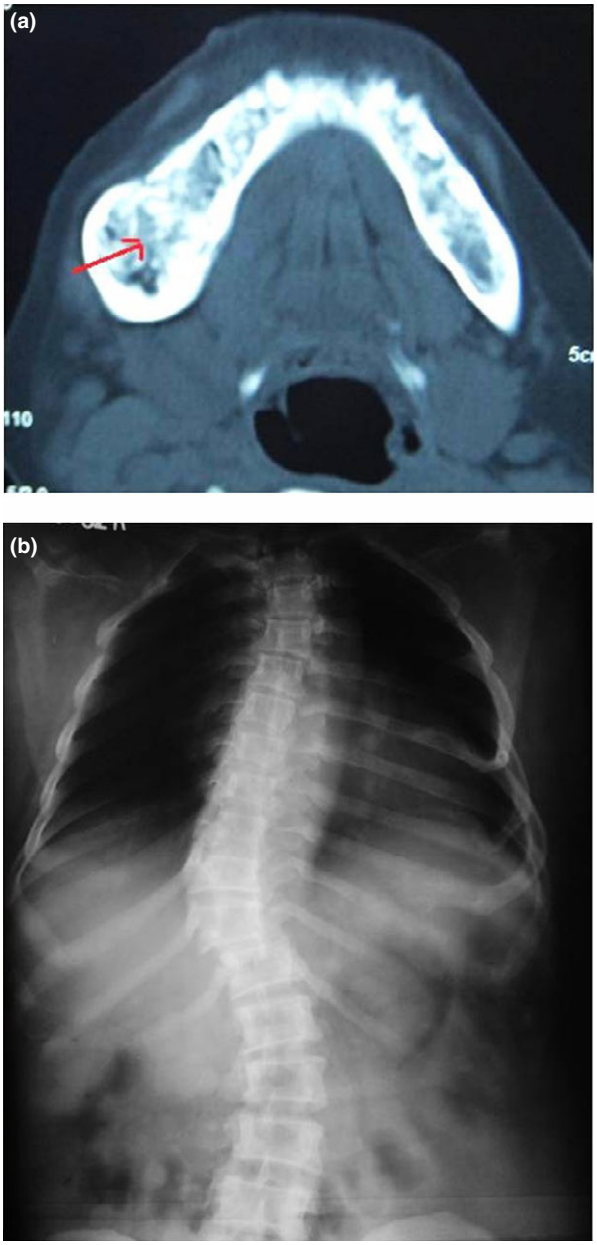

Figure 2. Axial computed tomography scan showing ground glass appearance (a), and anteroposterior view of spine showing scoliosis (b).

of phosphate to the glomerular filtration rate (TmP/GFR), and the levels were found to be reduced (TmP/GFR, 0.08 mmol/L).

Through an intraoral approach, curettage of the lesion was performed, followed by histopathological examination, which revealed trabeculae of woven bone with osteoblastic and osteoclastic activity without rimming of osteoblasts, suggestive of FD.

A final diagnosis of NF1, polyostotic FD associated with osteoporosis, and secondary hyperparathyroidism

due to vitamin D deficiency was established. The patient was prescribed vitamin D and calcium supplements. Follow up of the patient after 3 and 6 months showed remission in her symptoms.

Discussion

Neurofibromatosis has been linked with FD of bone by various physicians, notably Aegerter, who emphasized the various expressions of NF, such as skin nodules, pigmented spots, and endocrine manifestations, which are often seen in FD.[1] Rosenberg *et al.* indicated that some relationship exists between the two, although it certainly cannot be interpreted to mean that these conditions are different manifestations of the same disease. He also pointed out that only more severe states of FD, such as polyostotic FD, are likely to be associated with evidence of NF, as seen in our case. The onset of FD is most often seen in the first decade of life, and usually ceases its progressive course at skeletal maturation, whereas NF does not manifest before the second decade.[2] In the present case, both NF1 and polyostotic FD manifested almost at the same time, at approximately the second decade of the patient's life. Rosenberg *et al.* reported a case series in which FD and NF were present in a family of nine, and Schotland reported concurrent occurrence of NF and FD in a family of four; in the father and three children.[2,3] It has been speculated that this is more than a chance occurrence. During embryogenesis, a regulator gene mutation with variable penetrance was responsible for both these diseases.

The overlapping clinical signs and symptoms and the similarity in cell morphology and pattern strongly suggest that these conditions are in some way related.[3] This proposition can be substantiated in the present case. Additionally, the secondary manifestations of NF and FD, such as osteoporosis, hyperparathyroidism, and osteomalacia, are investigated in the present case, which has not been conversed in the literature to date. The ongoing discussion will shed light on the implications of NF and FD in causing these secondary manifestations.

Patients with NF1 are shorter than expected, and often have low BMD. Our patient was of short stature at 127 cm, with decreased BMD, suggestive of osteoporosis. Various studies have found high serum PTH concentrations and lower serum 1,25-hydroxy vitamin D3 concentrations to be associated with lower BMD among NF1 patients. Individuals with NF1 have increased osteoclastic activity that leads to increased bone breakdown and increased frequency of fractures, indicating a generalized abnormality of bone metabolism. Further studies are needed to elucidate the precise nature of this abnormality.[4]

Renal phosphate wasting and hypophosphatemia are also commonly observed among polyostotic FD patients.[5] Fibroblastic growth factor-23 (normal levels: 18–108 RU/mL) can be elevated in patients with FD.[6] It decreases phosphate tubular reabsorption, thus lowering serum phosphate and 1,25-dihydroxy vitamin D3, which contributes to the worsening of lesional osteomalacia that is observed in FD.[7] Compared to unaffected bone, lesional FD bone is very sensitive to the effects of PTH and renal phosphate wasting, which bring about hyperparathyroid or osteomalacic changes.[8] The TmP/GFR, which is regulated by PTH, is an index used to assess the sensitivity of renal threshold for phosphorous, and it can be decreased in many conditions, including secondary hyperparathyroidism and NF. PTH, which is elevated in secondary hyperparathyroidism due to vitamin D deficiency, decreases the TmP/GFR by reducing renal tubular reabsorption of phosphorous, and increases its excretion, as seen in our patient (Table 1).[9] All of the abovementioned mechanisms could lead to the occurrence of secondary hyperparathyroidism, as seen in our case.

McCune–Albright syndrome, central ossifying fibroma, and intraoral lesions of NF were considered under a differential diagnosis. MAS,[10] which is considered the most severe form of FD, was ruled out, as her menstrual history was normal and other endocrine investigations were within normal limits. In NF1, café-au-lait macules (CALM) are uniformly hyperpigmented, with smooth borders resembling the "coast of California" in contrast to MAS, in which they tend to be very large and unilateral, with irregular and ragged borders resembling the "coast of Maine". They have a tendency to follow the developmental lines of Blashko. In our case, more than

Table 1. Biochemical investigations

Laboratory values	Normal levels	Observed levels
Serum calcium (mg/dL)	9.00–10.40	8.40
Serum alkaline phosphatase (u/L)	40.00–136.00	151.00
Serum parathormone (mg/mL)	10.00–60.00	105.00
Serum phosphorous (mg/dL)	3.00–4.50	2.00
Serum creatinine (mg/dL)	0.60–1.20	0.60
Urinary phosphorous (mmol/L)	0.60–1.40	1.48
Urinary creatinine (mmol/L)	0.60–1.20	0.88
TmP/GFR (mmol/L)	0.15–0.24	0.08
1,25-dihydroxyvitamin D3 (pg/mL)	25.00–40.00	18.00
Thyroid stimulating hormone (Mu/L)	0.30–0.40	0.32
Thyroxin, total T4 (μg/dL)	4.50–10.90	8.50
Triiodothyronine, total T3 (ng/dL)	60.00–181.00	102.00
Growth hormone (ng/mL)	0.50–1.70	1.20
Cortisol, free (μg/24 h)	20.00–70.00	34.00

TmP/GFR, ratio of the renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate.

six CALM were present on the thigh and back, with regular borders and of varying size (1.5–2.5 cm), further emphasizing that these are manifestation of NF1.[11] The central ossifying fibroma was excluded, as it is radiographically well defined with varying degrees of calcification, but rarely radiopaque. It has a symmetric growth pattern, which is equal in all directions, and occasionally has a soft tissue capsule, unlike FD, which blends with surrounding bone.[12] Intraosseous lesions of NF1 were ruled out, as these lesions exhibit either radiopacity due to bone hypertrophy or radiolucency due to pressure from overlying tumors or central bone tumors, unlike the mixed radiolucent–radiopaque appearance of FD.[13]

Treatment with bisphosphonates is found to be beneficial in FD, resulting in rapid pain relief and normalization of bone turnover.[14] Calcium and vitamin D supplements in patients with vitamin D deficiency are necessary to limit osteomalacia and hyperparathyroidism.[7] The management of NF1 is currently focused on genetic counseling and esthetic treatment of specific lesions, usually through surgery.[15]

A possible relationship between NF, FD, hyperparathyroidism, and osteoporosis was found through a literature search, and has been substantiated in our case. An understanding of this relationship would be more than just academic importance, and might be of therapeutic value. If this is so, all NF patients should be routinely reviewed for the above associated diseases, which could be rewarded with an early diagnosis and better prognosis, thus preventing the risk of fractures in these individuals. The benefit of exercise might be especially important in improving BMD in NF1 patients.

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