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Case Report

Noonan Syndrome and Osteoporosis: A Comprehensive Case Study and Literature Review

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ABSTRACT

Noonan syndrome (NS) is a genetic disorder caused by mutations in the RAS/MAPK signaling pathway, typically characterized by unique physical features, congenital heart defects, and short stature. Osteoporosis (OP), although uncommon in NS, can significantly impact patients' quality of life. We report the case of a 60s-year-old male with NS who experienced progressive osteoporosis over seven years. Dual-energy X-ray absorptiometry (DEXA) scans revealed a marked decline in bone mineral density (BMD) accompanied by multiple fractures. Despite normal vitamin D and parathyroid hormone intact levels, the patient's BMD continued to deteriorate, leading to vertebral compression fractures that necessitated surgical intervention. This case highlights the importance of early osteoporosis screening and prompt management in NS patients to prevent severe complications. Further research is warranted to explore the mechanisms underlying bone fragility in NS and to develop targeted therapeutic strategies.

1. Introduction

Noonan syndrome (NS) is a genetic condition that presents unique physical features and medical complications. It affects approximately 1 in 1,000 to 2,500 individuals worldwide and results from mutations in the RAS/MAPK signaling pathway, including genes like PTPN11, SOS1, RAF1, and others [1, 2]. NS arises from de novo mutations, which are not inherited from the parents, or mutations in RAS/MAPK pathway genes, with PTPN11 being the most frequently affected. This pathway regulates cell growth, differentiation, and survival, and disruptions lead to the characteristic features of NS [3].

NS often includes congenital heart defects, such as pulmonary valve stenosis, and distinctive facial traits, such as a webbed neck, hypertelorism (wide-set eyes), and low-set ears. Other frequent features include short stature, intellectual and developmental delays, gonadal dysfunction, hearing loss, and an increased cancer risk [1, 2].

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Osteoporosis weakens bones by reducing bone mass and deteriorating bone tissue, typically affecting older adults and postmenopausal women [4]. Researchers are increasingly exploring the link between NS and osteoporosis. Genetic mutations associated with NS, particularly in the PTPN11 gene, directly impact bone development and contribute to abnormal bone growth [5]. Additionally, mobility limitations in individuals with NS reduce weight-bearing activity, which increases their risk of osteoporosis. This report documents a detailed case of NS associated with decade-long progression from osteopenia to osteoporosis, despite extensive treatment regimens including bisphosphonates, teriparatide, and Denosumab. It provides a detailed longitudinal follow-up through serial DEXA scans, offering novel insights into the challenges of managing osteoporosis in NS and underscoring the need for early screening and intervention research.

2. Case Presentation

A male patient in his 60s presented for evaluation and management of ongoing osteoporosis and associated symptoms. He has a medical history of NS, osteoporosis, vitamin D deficiency, hypocalciuria, hypogonadism, migraines, cervical arthritis, mild intermittent asthma controlled with an Albuterol inhaler, and a spontaneous lumbar fracture at age late 50s. He denies smoking, alcohol use, and substance use. His family history reveals significant osteoporosis affecting his mother, sister, and daughter, along with a history of stroke in his father. He reports no systemic symptoms, including fever, chills, headaches, blurry vision, oral ulcers, abdominal pain, nausea, vomiting, diarrhea, chest pain, or shortness of breath.

He takes calcium carbonate 1200 mg daily, vitamin D3 1000 IU daily, Fioricet (Butalbital/Acetaminophen/Caffeine) as needed, sumatriptan 6 mg subcutaneous as needed, oxycodone-acetaminophen 10 mg-325 mg every six hours as needed, and an Albuterol inhaler as needed.

During the physical examination, the patient appeared comfortable with stable vital data and showed no signs of distress. Examination findings included normal conjunctiva, intact extraocular movements, normal ear structure and hearing, clear lungs bilaterally, regular heart sounds, normal gait and range of motion, and an oriented mental status with average mood and affect. His body mass index (BMI) was 20.99 kg/m². Laboratory evaluations previously showed a vitamin D level of 25 ng/mL (reference range 30–100 ng/mL) and negative results for Antinuclear Antibody (ANA), celiac testing, Serum Protein Electrophoresis (SPEP), Urine Protein Electrophoresis (UPEP), and parathyroid hormone (PTH) levels within the normal range. Imaging studies revealed progressive bone density loss. Ten years before presentation to the clinic Dual-energy X-ray absorptiometry (DEXA) scan showed lumbar spine bone mineral density (BMD) of 0.96 g/cm² (T-score -2.4) and hip BMD of 0.78 g/cm² (T-score -2.4). Two years later, lumbar spine BMD declined to 0.84 g/cm² (T-score -3.3) and hip BMD to 0.73 g/cm² (T-score -2.8). After 4 and 6 years after the initial DEXA scan further decreases, with lumbar spine BMD at 0.80 g/cm² (T-score -3.5) and 0.798 g/cm² (T-score -3.5), and hip BMD at 0.66 g/cm² (T-score -3.3) and 0.707 g/cm² (T-score -2.9), respectively. FRACTURES score of 17.3% 10-year probability of major osteoporotic fracture, 7.7% 10-year probability of hip fracture (Table 1).

Table 1: Progressive Bone Mineral Density Decline in a Noonan Syndrome Patient: A 6-Year DEXA Scan Overview.

Year Since First DEXA	Lumbar Spine BMD (g/cm²)	Lumbar Spine T-score	Hip BMD (g/cm²)	Hip T-score
Initial	0.96	-2.4	0.78	-2.4
2 Years	0.84	-3.3	0.73	-2.8
4 Years	0.8	-3.5	0.66	-3.3
6 Years	0.798	-3.5	0.707	-2.9

DEXA: Dual-energy X-ray Absorptiometry; BMD: Bone Mineral Density; g/cm²: grams per square centimeter; T-score: A measure used in medicine to describe bone density

The patient sustained multiple fractures, including an L1 fracture (Figure 1) and a left wrist fracture at earls 60s, which were treated with kyphoplasty and wrist fixation. A year later, he underwent cervical spine surgery for chronic neck pain and used a bone growth stimulator. After another year, his DEXA scan showed L1-L4 with a T-score of -3.0 and a Z score of -1.8. This represents a 7% improvement compared to the prior study. Bilateral hip with a mean T score of -3.0 and a Z score of -1.7. This is a 1.3% decline from the prior study. Additionally, he received an intra-articular corticosteroid knee injection for a suspected meniscus tear, which provided minimal relief of knee pain. He manages vitamin D deficiency with supplements and previously managed hypogonadism with testosterone cypionate injection, which was discontinued due to elevated PSA levels. He has declined to resume testosterone therapy.

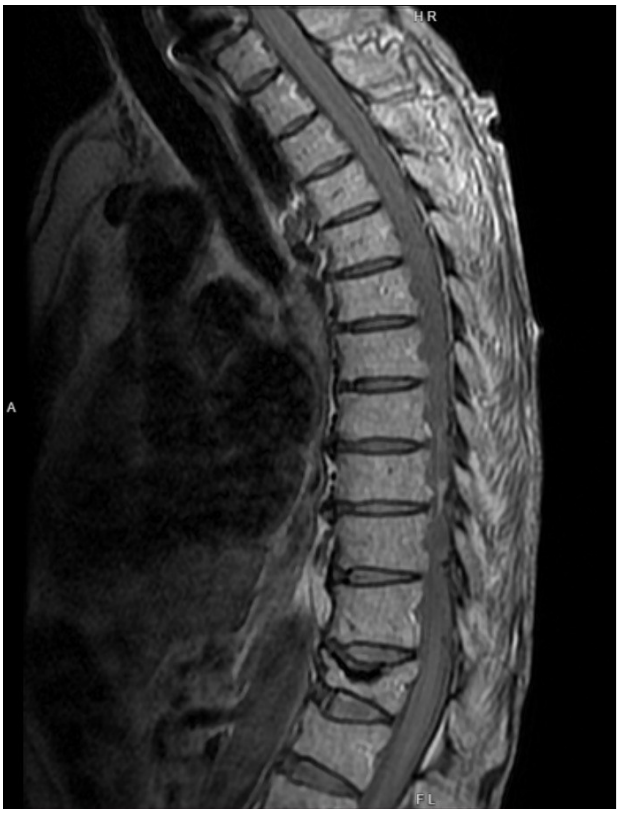

Figure 1: This MRI image shows post-kyphoplasty changes at T12 with no evidence of acute complications and a stable mild chronic compression fracture of the L1 superior endplate.

His treatment for osteoporosis began at his mid-40s with a five-year course of Alendronate 70 mg oral weekly. After that in the setting of worsening BMD and fracture; he completed a two-year course of teriparatide 20 mcg SUBQ daily. At age 53, he received a single dose of zoledronic acid IV, followed by another two-year course of teriparatide 20 mcg SUBQ daily. Currently patient on Denosumab injection every 6 months for the last 6 years. He adhered to his medication regimen and reported no side effects.

3. Discussion

"RASopathies" refers to a group of phenotypically similar congenital disorders caused by gene mutations within the RAS/MAPK signaling pathway, a critical molecular cascade for cell division and differentiation [6]. NS is the most prevalent RASopathy, while cardiofaciocutaneous syndrome (CFC) and Costello syndrome (CS) are extremely rare, with only a few hundred cases documented worldwide [6]. Mutations in the PTPN11 gene account for about half of the genetic causes of NS [7]. Baldassare et al. found that approximately 15% of the 35% of patients with NS had compromised bone quality, as assessed by phalangeal quantitative ultrasound (QUS) [8]. Furthermore, a recent retrospective analysis of 35 individuals with NS revealed reduced axial and appendicular bone mass compared to the general population [4]. However, data on adult patients with NS remains limited.

Studies have consistently shown that BMD used as a marker of bone health in NS, is reduced. DEXA scans, commonly employed in such evaluations, have confirmed significantly lower BMD in NS patients

compared to matched controls, even when bone mineralization markers appear normal [5]. In this case, DEXA scans revealed a progression from osteopenia in 2013 to osteoporosis in subsequent years. The patient has reduced BMD correlated with low physical activity, low muscle mass, diminished quality of life, low IGF-1 levels, pain, and bone fragility. Although Siano et al.'s case series reported elevated parathyroid hormone (PTH) levels and reduced calcitonin and vitamin D in NS patients, this case demonstrated normal PTH and vitamin D levels[9]. While PTH and vitamin D are crucial for bone metabolism and mineralization, they are not specific markers for diagnosing osteoporosis. This case aligns with previous reports of osteoporosis in three adult NS patients [10, 11].

RAS/ERK hyperactivation in RASopathies, including NS, disrupts the balance between osteoclast and osteoblast activity, contributing to bone metabolic disorders [5]. Evidence suggests that mesenchymal progenitor cell differentiation, regulated by the Ras/MAPK pathway, plays a key role in osteoblast proliferation during skeletal muscle development [12]. The Ras family of GTPases (H-ras, K-ras, and N-ras) regulates this pathway by transmitting signals from the cell surface to the interior. Mutations in any component of this pathway increase MAPK activity, disrupting normal cell proliferation regulation. Hyperactivation of the RAS/MAPK/ERK pathway enhances osteoclast activity, resulting in greater bone resorption and loss. Studies in mouse models suggest that early postnatal inactivation of ERK in osteoprogenitors contributes to bone loss [13].

The PTPN11 gene encodes SHP2, a protein tyrosine phosphatase involved in regulating the proliferation, differentiation, and mobilization of mesenchymal stem cells (MSCs) and neural crest cells (NCCs) via the MAPK pathway [14]. SHP2 also plays a developmental role in chondrogenesis, mineral homeostasis, and chondrocyte transdifferentiation. Tajan et al. demonstrated that SHP2 deficiency significantly reduces osteoblast numbers necessary for bone maturation [15]. Another pathogenic variant, the KRAS gene, has also been implicated in NS. Yang et al. recently described KRAS's role in osteogenesis, showing that small GTPase coordination in stem cells modulates autophagy, contributing to extracellular matrix accumulation [16].

Bone homeostasis involves more than the Ras/MAPK/ERK pathway. It synergizes with other signaling cascades, such as Wnt-frizzled/β-catenin, BMP/SMAD/Runx2, and PI3K/AKT, which are essential for maintaining bone health. The BMP-signaling pathway enhances osteoblast differentiation through SMAD1/5/8, Runx2, and osterix activation [17]. However, SMAD3 hyperactivation interferes with osteogenic differentiation, reducing alkaline phosphatase (ALP) activity and impairing mineralization. These effects are compounded by MAPK/ERK pathway overactivity [18]. The interactions between the Ras/MAPK pathway and other cascades, like Wnt/β-catenin and PI3K/AKT, remain unclear but are likely critical for bone remodeling [19].

Additional factors contributing to increased bone resorption markers in RASopathies include reduced physical activity, low serum vitamin D, and limited sun exposure, as observed in patients with neurofibromatosis type 1 (NF1) [20]. Collectively, the RAS/MAPK pathway, reduced activity, and inflammatory cytokines disrupt bone metabolism in RASopathy patients. Differential diagnosis includes Osteomalacia, Osteogenesis Imperfecta (Mild Form), hypogonadism, Glucocorticoid-Induced Osteoporosis, and Neurofibromatosis type 1.

This case is unique due to the early onset of OP in a patient with NS and the progressive worsening of BMD despite treatment with calcium and vitamin D supplementation. It underscores the importance of early detection and proactive management of osteoporosis in individuals with NS.

4. Conclusion

This case illustrates the link between Noonan syndrome and osteoporosis, highlighting the role of dysregulated RAS/MAPK signaling in bone metabolism. The progressive decline in BMD and recurrent fractures emphasize the importance of early screening and proactive osteoporosis management in NS patients. Future research should focus on developing precise genetic screening protocols to identify Noonan syndrome patients at risk for osteoporosis early in life. Additionally, investigating targeted therapeutic strategies that modulate the RAS/MAPK pathway could offer new avenues for managing and potentially reversing bone density loss in this patient population.

Conflicts of Interest:

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Data Availability Statement:

The data underlying this case report are not publicly available due to privacy or ethical restrictions. The clinical data that support the findings of this case are contained within the patient's medical record, which is confidential. Specific data excerpts that do not compromise the patient's anonymity can be made available from the corresponding author upon reasonable and ethical request.

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