Bilateral Femoral Fracture in a Young Female Filipina with Autoimmune Polyendocrine Syndrome Type 4 and Probable Turner's Syndrome: A Case Report

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Introduction. Autoimmune polyendocrine syndrome (APS) type 4 is a clustering of at least 2 or more organ-specific autoimmune diseases in a single patient, which do not fall into other categories of APS, in combination with at least one more endocrine or non-endocrine organs. The multitude of autoimmune comorbidities and their associated treatment may contribute to osteoporosis and fracture.

Case description. A 35-year-old female with bilateral distal femoral pathologic fracture from an inch fall underwent bilateral, minimally invasive plate osteosynthesis. Pathologic fracture from secondary osteoporosis resulted from rheumatoid arthritis, chronic steroid use from rheumatoid arthritis (prednisone 10 mg for 24 months), premature ovarian failure since 20 years old without hormone replacement therapy, and possible Turner syndrome. She had persistently elevated thyroid-stimulating hormone in spite of high levothyroxine (4.25 µg/kg/day) dose; hence, gastric malabsorption from possible atrophic gastritis was likewise considered. Benefits and risks associated with treatment were reviewed to manage the patient holistically.

Conclusion. APS is a rare complex syndrome which may lead to various complications. Presence of hypogonadism, rheumatoid arthritis, and chronic steroid use further predisposes the development of secondary osteoporosis. Early screening and treatment of osteoporosis would have decreased the risk of development of fracture.

Keywords. *Autoimmune polyendocrine syndrome, Pathologic fracture, Premature ovarian failure, Secondary osteoporosis, Rheumatoid arthritis, Iatrogenic Cushing's syndrome, Case report*

Introduction

Autoimmune polyendocrine syndrome (APS) is a clustering of at least two or more endocrine diseases in a single patient.[1-3] It occurs in discrete patterns in subjects with immune dysregulation, and that permits treatment and anticipation of associated systemic or hormonal deficiencies.[4]

APS can be classified into four types. APS type 4 encompasses two or more organ-specific autoimmune diseases which do not fall into type 1, 2, or 3; it is considered a diagnosis of exclusion.[2,5,6] APS type 4 (ORPHA:227990) includes all the different clinical combinations of autoimmune diseases not included in the previous groups and affecting an endocrine organ (with the exception of Addison's disease, thyroid diseases, or hypoparathyroidism) in combination with at least one more endocrine or non-endocrine organ. Clinical manifestations of APS type 4 include type 1 diabetes mellitus or latent autoimmune diabetes in adults, premature ovarian failure, celiac disease, atrophic gastritis, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjogren syndrome, mixed connective tissue disease, vasculitis, anti-phospholipid syndrome, primary biliary cirrhosis, autoimmune hepatitis, alopecia areata, autoimmune urticaria, myasthenia gravis, multiple sclerosis, pernicious anemia, immune

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thrombocytopenia, vitiligo, seronegative arthritis, ankylosing spondylitis, psoriasis, and pemphigoid.[7-9]

The approximate prevalence of APS type 1 is 1:100,000 in the United States, and it has been studied far more thoroughly than the other types, whereas APS types 2, 3, and 4 have an approximate prevalence of 1:20,000. However, the precise prevalence and incidence of APS in different countries and ethnic groups around the world remains unknown.[6] In Philippine literature, only one case of APS type 1 has been published as a case report, and this is the first case report on APS type 4.

There are several endocrine and non-endocrine disorders that may be associated with APS type 4. Little is known regarding its inheritance, but HLA haplotypes HLA-DRB1*03:01-DQA1*05:01-DQB1*02:01 have been reported to be present in this type. It is also linked with single nucleotide polymorphisms, PTPN2211858 C/T (rs2476601), CTLA-4 C/T60 (rs3087243), Bsm I (rs1544410), Aps I (rs7975232), Taq I (rs731236), IL2-Ra CD25 (rs10795791), TNF-a -308 (rs1800629), and autoantigens to 17-OH, CaSr, TSH-R, TPO, Tg, GAD, insulin, IA-2, islet cell, and ZnT8.[6,8]

Case Presentation

We report a case of APS type 4. A 35-year-old female missionary, hypertensive, and non-diabetic, came in with a chief complaint of bilateral lower extremity pain. While walking up to the restroom, the patient was not able to see the extra step going up, tripped on a ledge, and fell hip first. Both knees landed on the floor and the patient was unable to move. She then started to experience continuous bilateral lower extremity pain graded 5/10, described as cramping and heavy in character. Hip and bilateral lower extremity X-ray were requested, showing bilateral fracture, distal femur. She was advised to have surgery.

In her medical history, she had been diagnosed with hypothyroidism secondary to Hashimoto's thyroiditis in 2003 (20 years prior), presenting as weight gain, increased appetite, and irregular menstruation. She claimed to have been compliant with prescribed levothyroxine 150 µg/tab 1 tab on Tuesdays to Sundays, levothyroxine 225 µg on Mondays (4.25 µg/kg/day). She was also a known case of premature ovarian failure since 2007 (16 years prior), presenting as irregular menstruation, with menses only three times since birth, and transvaginal sonography findings of absent ovary on the right and atrophic ovary on the left, for which she had not been given any hormonal replacement therapy ever since. Furthermore, she had iatrogenic Cushing syndrome secondary to chronic intake of steroids for rheumatoid arthritis (RA). She had been on prednisone at 10 mg/day since 2021. She had already been diagnosed with osteoporosis more than 5 years ago; unfortunately, no treatment had been given. She had no hypoparathyroidism, candidiasis, nor type 1 diabetes, alopecia, vitiligo, systemic lupus erythematosus, or idiopathic thrombocytopenic purpura.

She was a non-smoker and not an alcohol beverage drinker, with no history of illicit drug use. Family history revealed hypertension in both parents and type 2 diabetes mellitus in father. Of note is that there was no other history of hereditary disease, especially endocrinologic or autoimmune, within their family.

On admission, she had stable vital signs with weight of 53 kg, height of 129.54 cm, and BMI of 31.5, classified as obese II based on World Health Organization Asia-Pacific Classification. Pertinent physical exam was unremarkable except for presence of moon facies, buffalo hump, truncal obesity, hirsutism, and slightly pale palpebral conjunctiva.

Pertinent laboratory showed significantly elevated thyroid-stimulating hormone, 87.84 (0.35–4.94); low free triiodothyronine, 1.50 (1.58–3.91); low free thyroxine, 0.46 (0.70–1.48); and mild microcytic, hypochromic anemia at 102. She had normal fasting blood sugar, calcium, creatinine, and liver function test. Thyroid ultrasound showed a small thyroid gland and an unremarkable parathyroid gland. Ultrasound of the whole abdomen showed an atrophic uterus.

Assessment: bilateral fracture, distal femur, autoimmune polyendocrine syndrome (premature ovarian failure, rheumatoid arthritis and possible atrophic gastritis), Hashimoto's thyroiditis, Iatrogenic Cushing syndrome, hypertension, probable Turner syndrome.

Patient underwent open reduction internal fixation plating, bilateral femur, uneventfully. To prevent recurrence of fracture, she was started on subcutaneous denosumab 60 mg every 6 months, calcium carbonate 50 mg tab once a day, vitamin D 5,000 IU capsule once a day, and zoledronic acid 4 mg intravenous to run for 15 minutes once a month. Multivitamin tablet once a day and folic acid tablet 3x/day were prescribed with instructions to take the vitamins 4 hours apart from levothyroxine. Levothyroxine was increased to 200 µg/day (100 mg/tab, two tablets once a day) to be taken at least 60 minutes before breakfast. For deep vein thrombosis prophylaxis, apixaban 2.5 mg tablet once a day for 40 days was continued until able to mobilize. And lastly, to address her elevated blood pressure, she was given losartan 50 mg tablet once a day and bisoprolol 2.5 mg tablet once a day. Patient was eventually discharged stable, tolerated treatment, and was able to come back to her country of employment, where regular follow-up is to be done.

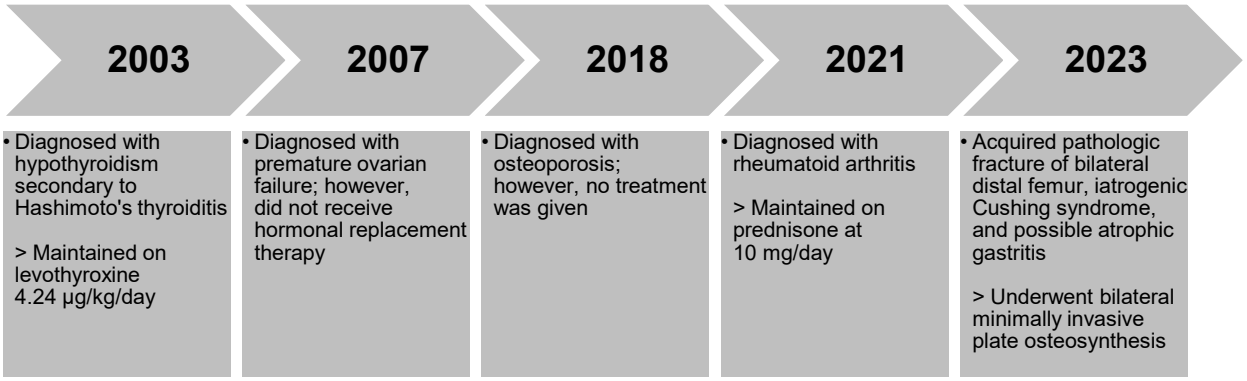

Figure 1: Historical timeline

Discussion

We presented a case of APS type 4 (premature ovarian failure, rheumatoid arthritis, and possible atrophic gastritis) with Hashimoto's thyroiditis, iatrogenic Cushing syndrome, and probable Turner syndrome leading to secondary osteoporosis.

Premature ovarian failure (POF) is a primary ovarian defect characterized by absent menarche (primary amenorrhea) or premature depletion of ovarian follicles or arrested folliculogenesis before the age of 40 years (secondary amenorrhea). It affects 1% of young women. Its incidence is estimated to be as great as 1 in 100 by the age of 40 and 1 in 1,000 by the age of 20 years.[10] Our patient has no known genetic disorders, no prior history of chemotherapy radiotherapy, no prior exposure to infections such as varicella, mumps, cytomegalovirus, tuberculosis, malaria, shigella, or environmental factors (cigarette) that might cause her POF; hence we hypothesized that patient's POF was autoimmune in origin, which is seen in 4–30% of POF cases.[11,12] The evidence for an autoimmune etiology are presence of lymphocytic oophoritis,[13-15] demonstration of ovarian autoantibodies,[14,15] and associated autoimmune disorders.[16] Unfortunately, in our country, we have no available test to check for the presence of ovarian autoantibodies and there is no value in ovarian biopsy. Instead, thorough screening for associated autoimmune disorder and cytogenetic analysis should be performed as a part of the diagnostic work-up. Hypothyroidism is the most common autoimmune disorder associated with POF, which was present in our patient. Karyotyping would be requested, especially if our patient were presented with short stature; Turner syndrome has to be ruled out. Since POF causes low estrogen levels, it increases the risk for osteoporosis. Looking back, our patient should have been prescribed hormone replacement therapy 16 years ago, calcium and vitamin D supplementation should have been started early on, regular physical exercise and resistance exercise and maintenance of healthy weight should have been emphasized.[17]

RA is a systemic autoimmune disease characterized by inflammatory arthritis and extra-articular involvement.17 Literature reveals that steroids significantly improve RA symptoms such as pain and stiffness and decrease joint swelling and tenderness. Steroids are generally effective especially in treating RA that severely limits a person's ability to function normally.[9,10] However, long-term steroid use, especially at a high dose of prednisone more than 7.5 mg/day or its equivalent, causes iatrogenic Cushing syndrome. Our patient had been on prednisone 10 mg/day for 2 years; hence she developed signs and symptoms of Cushing syndrome. Osteopenia and osteoporosis are complications of the disease itself and can also be associated with drug therapies (glucocorticoids). Compared to the general population, patients with RA have a 60% to 100% increased risk of fracture.[18-21]

Atrophic gastritis is frequently associated with autoimmune thyroid disorders.[22] It has a prevalence of 0.5–5% (51%). It is a histopathologic entity characterized by chronic inflammation of the gastric mucosa with loss of the gastric glandular cells and replacement by intestinal type epithelium, pyloric-type glands, and fibrous tissue. It manifests as achlorhydria, hence affecting the dissolution of thyroxine from the solid form to aqueous solution, leading to increased levothyroxine requirement. Three main features may lead to suspicion of a gastric disorder: clinical symptoms, malabsorption of drugs and micronutrients, and the presence of chronic unexplained anemia.[23] Atrophic gastritis is a prevalent silent disease that progresses from a mild chronic gastric inflammation to an advanced stage of atrophy and metaplasia.[24] Anemia follows this worsening, proceeding from iron deficiency microcytic phenotype to vitamin B12-deficiency-associated macrocytic anemia (pernicious anemia).[25,26] This latter is a consequence of vitamin B12 malabsorption, in turn due to intrinsic factor deficiency,[26] whereas the reduced gastric acid secretion lowers iron absorption leading to iron deficiency anemia.[25] Our patient had mild iron deficiency microcytic phenotype. If atrophic gastritis were to be confirmed, the patient may benefit from novel formulations of levothyroxine such as the soft gel capsule and the liquid solution.[27] In the soft gel capsules, levothyroxine is dissolved in glycerin and surrounded by a gelatin shell, while in the liquid solution, the hormone is dissolved in

95% ethanol and 86% glycerol. The presence of *Helicobacter pylori* infection has also to be ruled out, since it can also increase the need for levothyroxine dose.

Hashimoto's thyroiditis affects roughly 4 out of 1,000 women and 1 out of 1,000 men in each year. Overall, 10–12% of the general population will develop Hashimoto's at some time in their life. It is treated with levothyroxine replacement at 1.6 µg/kg/day. If untreated, it can lead to reproductive alterations and lead to higher risk of premature ovarian insufficiency.[28] Furthermore, inadequately treated hypothyroidism predisposes the development of secondary osteoporosis. Our patient claimed to be compliant with her levothyroxine, taken at 30–60 minutes on an empty stomach and without any vitamins such as calcium, iron, or multivitamins taken within 4 hours, nor intake of proton pump inhibitors, papaya, soya, coffee, or fibers. She was also taking the same brand of levothyroxine (the innovator brand) and buying it in a reputable drug store. With her high dose of levothyroxine computed at 4.6 µg/kg/day, thyroid-stimulating hormone was still surprisingly high, hence the presence of atrophic gastritis was considered, for which the patient was advised to have a gastroenterology evaluation.

Osteoporosis is a global public health problem, with fractures contributing to significant morbidity and mortality. Secondary osteoporosis accounts for 40% of cases. The identification of secondary causes of osteoporosis is critical as the treatment of such patients is dependent on the underlying condition. The response of secondary osteoporosis to conventional anti-osteoporosis therapy may be incomplete if the underlying condition remains unrecognized and untreated. A box listing causes and a framework for diagnostic evaluation and management of secondary osteoporosis is summarized in Figure 2.[29]

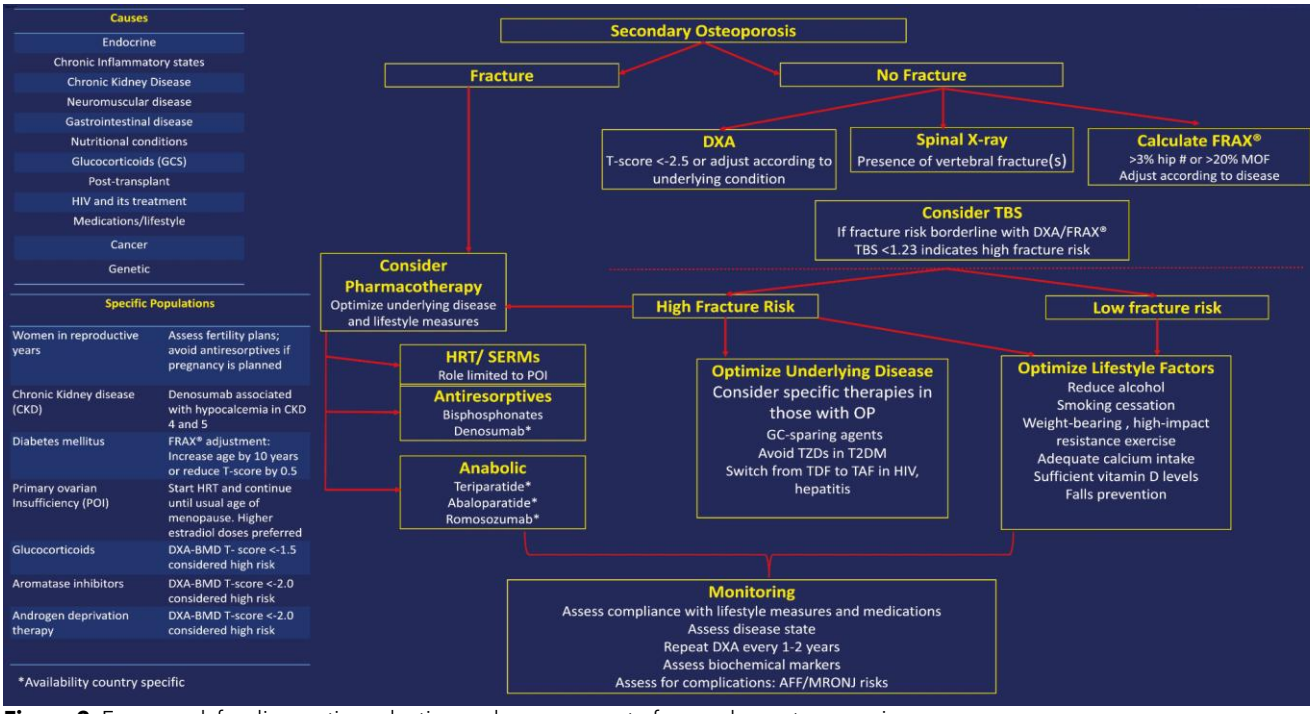

Figure 2. Framework for diagnostic evaluation and management of secondary osteoporosis

Cushing syndrome–glucocorticoid-induced osteoporosis

Glucocorticoid-induced osteoporosis (GIO) is the most common form of secondary osteoporosis. Adverse effects of glucocorticoids on bone are cumulative and dependent on dose, duration, and the underlying disease.[30] Excess glucocorticoid exposure results in reduced bone mineral density (BMD) and fragility fracture. The decline in BMD occurs rapidly; fracture risk increases with 3 months of supraphysiological glucocorticoid exposure, and fractures occur at a higher BMD compared with post-menopausal osteoporosis.[31,32] Glucocorticoids exert their effect on bone cells through a complex molecular mechanism.[29]

The optimal management of GIO requires the use of the lowest and least potent glucocorticoid for the shortest duration of time possible. As for our patient, prednisone had to be tapered down gradually to avoid precipitation of adrenal crisis, and shift to other anti-rheumatic agents is recommended.

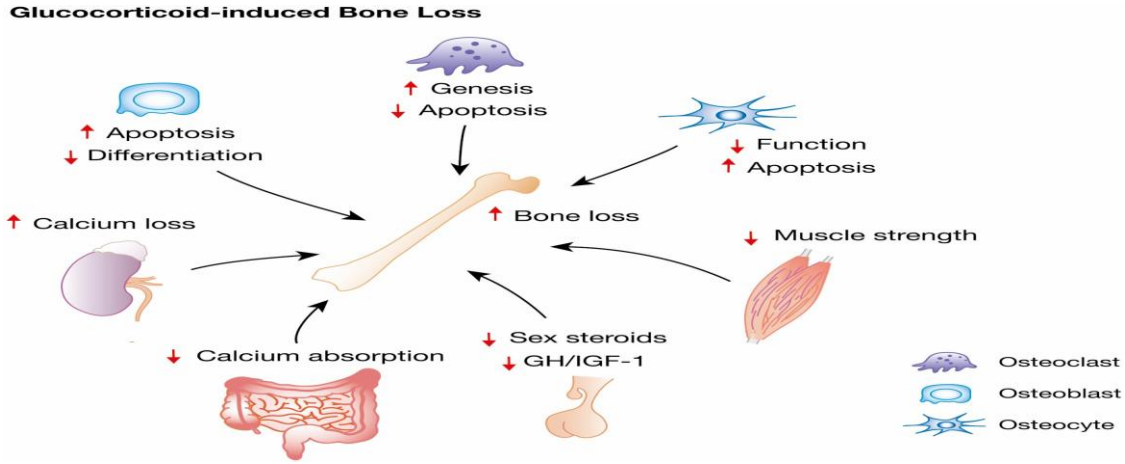

Figure 3: Mechanism of glucocorticoid-induced bone loss

Treatment of GIOs are either bisphosphonates, denosumab, or teriparatide. Bisphosphonates are widely used in the prevention and treatment of GIO. It increases the lumbar spine and hip BMD in GIO. The duration of therapy should be as long as glucocorticoid therapy is prescribed. Denosumab in three randomized controlled trials was found to be superior to alendronate and risedronate in increasing BMD at the spine and total hip.[33-35] GIO is a disease of reduced bone formation, and therefore, the use of teriparatide is particularly attractive. Teriparatide increases osteoblast formation and reduces osteoblast apoptosis.[36] When compared with alendronates, teriparatide treatment for 3 years resulted in a superior increase in spine BMD, fewer incident vertebral fractures, but a similar incidence of nonvertebral fractures.[37] In a 24-month study comparing denosumab with teriparatide in GIO patients with prior bisphosphonate exposure, teriparatide increased lumbar spine and femoral neck BMD, whereas denosumab increased lumbar spine BMD only.[38]

Premature ovarian failure (POF)

Osteoporosis is a key concern for women with POF,[39,40] with estimated prevalence rates ranging from 8% to 27%. They have lower lumbar and femoral neck BMD compared with age-matched premenopausal women.[41-44] Underlying mechanisms for low bone mass include insufficient peak bone mass accrual, increased bone resorption associated with estrogen deficiency, presence of comorbidities that increase the risk of osteoporosis, and factors specific to the cause of POF, such as Turner syndrome.[45]

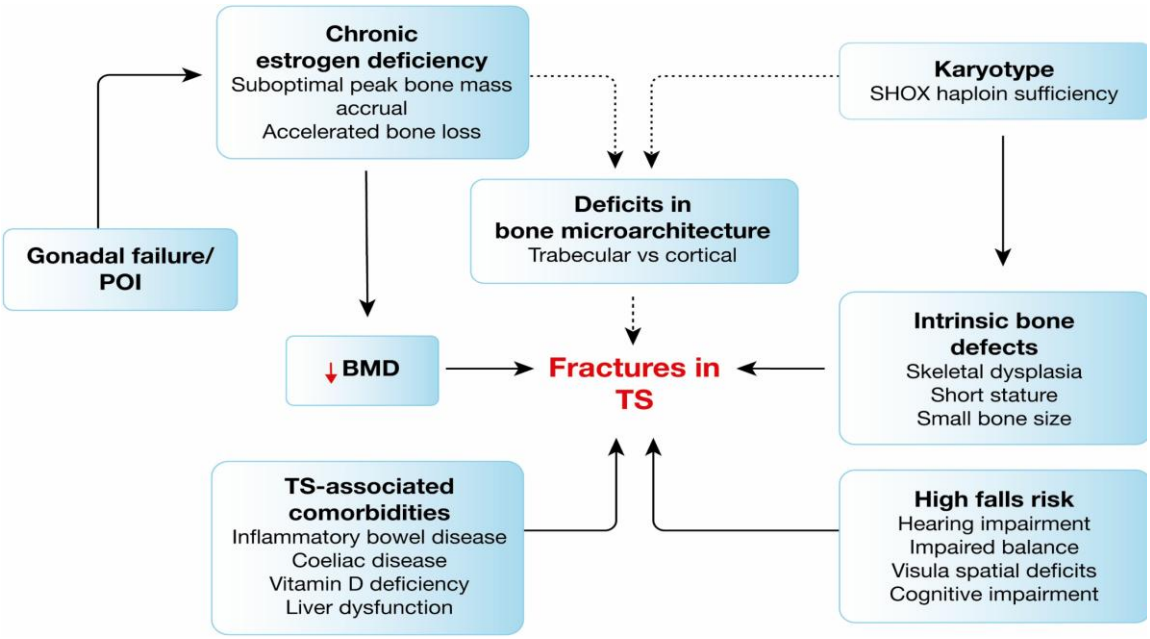

Figure 4. Proposed mechanisms for skeletal fragility in Turner syndrome

In women with spontaneous normal karyotype, identified risk factors for low BMD include age <20 years at onset of irregular menses, >1 year delay in diagnosis, African-American or Asian ethnicity, low serum 25 hydroxyvitamin D concentrations, low dietary calcium, non-adherence to estrogen therapy, and lack of exercise.[46,47]

All guidelines agreed that estrogen therapy (with added progestogen, as appropriate) should be initiated and continued until at least the age of usual menopause at 52–53 years old.
Turner syndrome is the most common genetic cause of POF, affecting 1 in 2,000 live female births.[48] The cardinal features are short stature (height <150 cm) and hypergonadotropic hypogonadism, with exogenous growth hormone therapy and hormone replacement therapy being standard therapy. Our patient's height was only 124 cm; hence, Turner syndrome was considered as well. Plan was to do karyotyping.

Rheumatoid arthritis

The mechanism for osteoporosis in RA is multifactorial. There are likely direct effects of inflammation on bone, with the course of osteoporosis correlated with underlying disease activity, longer duration of disease, and anti-citrullinated protein antibody titer. Autoantibodies stimulate pro-inflammatory cytokines leading to increased bone resorption via upregulation of the receptor activator of NF-κB ligand/osteoprotegerin pathway[49] and suppression of bone formation.[50]

The management of RA-related osteoporosis includes general lifestyle measures, RA-related factors, and osteoporosis-specific therapies. Modifiable RA factors include sustained remission or low disease activity, using the lowest dose of glucocorticoids possible, and steroid-sparing agents such as disease-modifying anti-rheumatic drugs. However, methotrexate may suppress bone formation and increase the risk of stress fractures.

Bisphosphonates have been shown to reduce vertebral fractures in GIO and increase spine and hip BMD.[51,52] Zoledronic acid in combination with methotrexate for treatment of RA-related osteoporosis showed greater BMD gains after 12 months of therapy than treatment with zoledronate or methotrexate alone.[53] Teriparatide therapy has been associated with increases in BMD and reductions in vertebral and non-vertebral fractures in the RA population[54,55] and may be superior to bisphosphonate and denosumab.[56] Denosumab use in the RA population may prevent periarticular bone erosions as well as treat osteoporosis.[57,58]

Since the patient was a missionary and working in different countries and just had an acute fracture, denosumab was our choice of treatment, plus calcium and vitamin D supplementation, as well as iron supplementation, with instructions to take the vitamins 4 hours away from levothyroxine. Levothyroxine was further increased to 200 µg/day, to be taken at least 60 minutes before breakfast.

The multitude of comorbidities present in the patient and their associated treatment have contributed to the challenges of therapeutic intervention and consequent complications, primarily osteoporosis. Osteoporosis with the consequent fragility fractures constitutes one of the most underdiagnosed and undertreated medical conditions. It remains a silent disease until the occurrence of fragility fracture. After the first osteoporotic fragility fracture, the risk of subsequent fracture increases further. Therefore, it is of utmost importance that once osteoporosis has been diagnosed, medication should be initiated immediately to prevent future fractures and also to reduce morbidity and mortality.[59] The importance of a holistic approach and early screening for osteoporosis in a patient with multiple comorbidities should be emphasized. Weighing risks and benefits of each treatment, as well as emphasis on regular follow-up, are important in order to streamline medical/surgical management.

Conclusion

APS is a rare complex syndrome which may lead to various complications. Multiple comorbidities, including presence of Hashimoto's thyroiditis, hypogonadism, rheumatoid arthritis, chronic steroid use, and their associated treatment, further predispose the development of secondary osteoporosis. Early screening and treatment would have decreased the risk of development of fracture.

Disclosure

The authors have no conflict of interest to disclose.

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