Association of Paget's Disease of Bone and Graves':A series of two Cases

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ABSTRACT

Introduction: Hyperthyroidism is related with increased bone remodelling, decreased bone density, osteoporosis and increased risk of bone fractures. But the relation between hyperthyroidism and metabolic disorders of bone like Paget's disease is unclear. **Case report series:** We diagnosed Paget's disease associated with Graves' in our two patients. In literature, we found only one case published about this association to date. The first patient was 68 years old female who admitted to our outpatient clinic with weight loss, low back pain and fatigue. The other patient was 61 years old male suffering from fatigue and palpitation whose Paget's disease was diagnosed 3 years ago. Both patients had elevated levels of serum alchaline phosphatase, decreased thyroid stimulating hormone levels associated with elevated levels of triiodothyronine and thyroxine. Their Tc99m thyroid scintigraphy revealed homogeneously increased activity and marked hyperplasia in thyroid glands indicating Graves' disease. And Tc 99 MDP labelled whole body bone scan was consistent with Paget's disease in both patients. **Conclusion:** Hyperthyroidism is related with bone resorbtion. But different effects of thyroid hormones by their receptors on osteoclast and osteoblasts may be the case. Therefore we suggest that the relation between thyroid hormones and metabolic bone disorders must be researched widely.

Keywords: Etiopathogenesis, hyperthyroidism, Paget's disease of bone

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INTRODUCTION

In 1877, Paget's Disease of Bone (PDB) was first named as 'osteitis deformans' by Sir James Paget [1]. Paget's disease of bone is a common disorder characterized by focal areas of increased and disorganized bone remodeling affecting one or more bones throughout the skeleton. Preferably it trends to the axial skeleton, frequently affects the pelvis (70%), femur (55%), lomber spine (53%, skull (42%) and tibia (32%) [2]. Hyperthyroidism is related with bone resorbtion according to the resembling publications. But different effects of thyroid hormones by their receptors on osteoclast and osteoblasts may be the case. In literature, we found only one case published about this association to date. In this report, we describe two cases in association Paget's disease of bone and hyperthyroidism due to Graves' disease.

CASE SERIES

CASE REPORT 1

A 68 years old female patient admitted to our outpatient clinic with fatigue, low back pain and weight loss. Physical examination revealed bilateral exopthalmos, incision scar on lower anterior neck and soft thyroid gland with nearly 4 cm palpable nodule on the left lobe of the gland. Her skin was warm, moist and there was tremor on hands. Her resting heart rate was 100 per minute, blood pressure 120/80 mmHg and body temperature 36,7 ^{0}C. In her past medical history she had thyroidectomy operation before 21 years.

In laboratory investigations; free T3 (triiodothyronine) and free T4 (thyroxine) were 4,08 (normal range 1,71-3,71 pg/ml) and 2,7 (normal range 1-1,7 ng/dl) respectively and thyroid stimulating hormone (TSH) was 0,02 (normal range 0,27-4,2 µIU/ml). Serum alchaline phosphatase (ALP) was 650 (normal range 40-150 U/L). The electrolytes, creatinine, other liver enzymes and complete blood count were all normal. Thyroid ultrasonography revealed a large nodule nearly covering whole of the left lobe with a diameter of 40x24x17 mm and a smaller nodule on the right wing of the gland, all with benign ultrasonographic characters.

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Tc 99m thyroid scintigraphy revealed, homogeneously increased activity in bilateral enlarged gland with hypoactive nodules (Figure 1).

Figure 1: Tc 99m thyroid scintigraphy showing, homogeneously increased activity in bilateral enlarged gland with hypoactive nodules

Tc 99 MDP labelled whole body bone scan was consistent with Paget's disease of lumbosacral region. She was given metimazole 10 mg twice a day for hyperthyroidism and zoledronic acite 5 mg by intravenous infusion for Paget's disease. Fine needle aspiration biopsy of thyroid nodules was carried out and she was discharged with a plan of control.

CASE REPORT 2

A 61 years old male patient admitted to our clinic with fatigue and palpitation. On his physical examination thyroid gland was soft and diffuse enlarged. His resting heart rate was regular with tachycardia and 108 beats per minute. In his past medical history he admitted with pain and cambering on the right leg, thereby Paget's disease was diagnosed 3 years ago. He used calcitonin salmon 200mcg/day for two years but changed it to alendronate 70 mg per week on last one year for the lack of regression of his complaints.

In his laboratory investigations free T3 and free T4 were 5,17 pg/ml and 4,3 ng/dl respectively and TSH was 0,005 µIU/ml . Serum ALP was 844 U/L. The electrolytes, creatinine, other liver enzymes and complete blood count were all normal. In thyroid ultrasonography there was a diffuse enlarged and pseudo-nodular view of the gland. Tc99m thyroid scintigraphy revealed homogeneously increased activity and marked hyperplasia on the right lobe of the gland.

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Tec ^{99} MDP labelled whole body bone scan revealed increased osteoblastic activity on nearly whole of pelvis, on the region from right knee joint to the middle of tibia and on the upper part of femur, all consistent with Paget's disease (Figure 2). He was given METIMAZOLE 15 mg twice a day for Graves' and zoledronic acite 5 mg by intravenous infusion for Paget's disease.

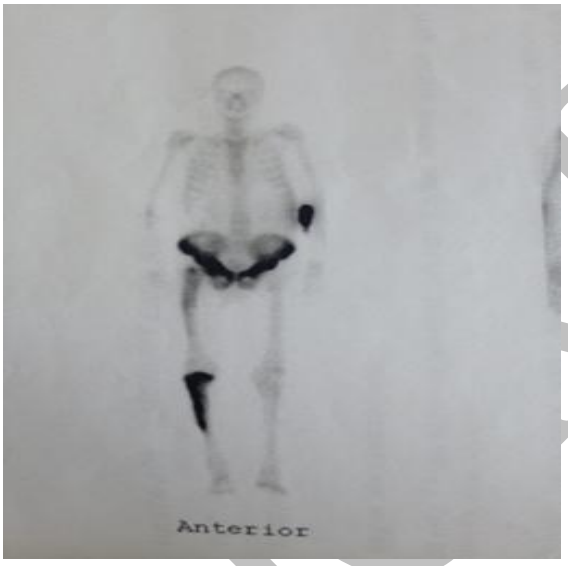

Figure 2: Tec ^{99} MDP labelled whole body bone scan showing increased osteoblastic activity on nearly whole of pelvis, on the region from right knee joint to the middle of tibia and on the upper part of femur

DISCUSSION

PDB is characterized by disorganized or increased bone turnover in different sites of the skeleton. After osteoporosis, PDB is the most common seen bone disease [2]. The prevalence of of PDB is variable between geographical areas. It is frequently seen Western Europe, America and Australia, but rarely reported in Asia and Africa. The course of the disease became less severe and the prevalence reduced over the last decade, with an unexplained reason [3]. PDB frequently seen in adults, dominantly in men, over the age of 55 years. The prevalence increases therafter [4].

Pagetic bone lesions show evidence of increased osteoclastic bone resorption, which is accompanied by other abnormalities such as marrow fibrosis, increased vascularity of bone, and increased but disorganised bone formation. Osteoclasts are increased in number and

size in Pagetic bone lesions and contain many more nuclei than is normal [5].

The precise cause of PDB has not been fully defined, yet. Environmental factors and genetic predisposition plays role in the aetiology of PDB. CSF1, TNFRSF11A, TNFRSF11B, TM7SF4, SQSTM1, VCP, and OPTN are important genes acting in osteoclastic differentiation and function. Mutations and various polymorphisms in these noteworthy genes have been associated with PDB. The important one of these is SQSTM1 (sequestosome1, also known as p62) mutation. SQSTM1 is an intracellular protein contributing in ubiquitination and NF-kappa-B signaling. The mutations on SQSTM1 gene, have been identified with strong susceptibility for PDB in sporadic and familial cases [6,7].

Thyrotoxicosis is a hypermetabolic situation in which serum levels of triiodothyronine (T3) and/or thyroxine (T4) are elevated. Hyperthyroidism is the excessively synthesis and secretion of thyroid hormone. In young and middle aged adults, the most common cause of hyperthyroidism is Graves' disease. In the course of exogenous thyroid hormone intake and thyroiditis, thyrotoxicosis may exist without hyperthyroidism. This hypermetabolic condition in thyrotoxicosis affects several organ systems. The adverse effects on skeleton were well known before the manifestation of hyperthyroidism treatment. In 1891, von Recklinghausen first reported 'worneaten' view of long bones of a young women with hyperthyroidism [8]. In organ culture studies, it has seen that thyroid hormone stimulates the bone resorbtion. Triiodothyronine (T3) receptor has been found in human and rat osteoblast cell lines and in osteoclasts of osteoclastoma. From this reason, bone resorbtion of thyroid hormone may be mediated via nuclear triiodothyronine receptors [9-11]. It is suggested that, in mice models lacking both TR-alpha and TR-beta receptors, bone loss is mediated via Thyroid Receptors. And in these mice models bone loss was found unrelated with the Thyroid stimulating hormone (TSH) levels [12]. By the TSH receptors localized on osteoblast and osteoclast precursors, TSH also plays a role on bone formation and resorption [13].

In thyroid hormone related bone loss, increased levels of serum interleukin-6 (IL-6) also plays an important role. IL-6 may contribute to the stimulation osteoclast activity and may activate parathyroid hormone on bones [14]. The

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history of hyperthyroidism is an obvious risk factor for hip fractures in elderly [15,16]. The association of PDB with hyperthyroidism may contribute he fracture risk in adults.

CONCLUSION

Hyperthyroidism is related with bone resorbtion according to the resembling publications. But different effects of thyroid hormones by their receptors on osteoclast and osteoblasts may be the case. To date, there is only one case reported about hyperthyroidism associated with Paget's disease [17]. In our two cases Graves was associated with Paget's disease. Therefore we suggest that the relation between thyroid hormones and metabolic bone disorders must be researched widely.

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