OSTEOPOROSIS IN PATIENTS WITH SYSTEMIC MASTOCYTOSIS

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Abstract
Mastocytosis is a disease characterized by abnormal proliferation and accumulation of clonal mast cells. One of the systems that may be affected in patients with mastocytosis is the skeletal system. Osteolysis, osteopenia, osteoporosis and osteosclerosis may occur as a result of skeletal system involvement. Osteoporosis is seen in more than 1/5 of these patients and the disease may even present with multiple fractures. Underlying factors of the deterioration of bone health in systemic mastocytosis include mast cell infiltration and systemic release of mast cell mediators, increased number of osteoclasts, and overproduction of proinflammatory cytokines. Taking preventive measures for bone health disorders in patients with systemic mastocytosis, implementing screening protocols and treating osteoporosis appropriately if it develops are extremely important in preventing fragility fractures. The aim of this review is to provide an insight to the changes in bone tissue in patients with mastocytosis.

Keywords: Bone, Bone and bone tissue, Osteoporosis, Mastocytosis


INTRODUCTION
Mastocytosis is a condition with an estimated prevalence of 1 in 10,000 persons. The pathophysiological background involves the abnormal proliferation of clonal mast cells. This abnormal accumulation of mast cells is followed by increased release of mediators. The response to the excessive amount of cells and mediators is responsible for the clinical features of mastocytosis. The disease is classified as cutaneous and systemic mastocytosis according to the clinical manifestations and the presence of organ involvement [1]. Skeletal system is one of the systems that can be affected in systemic mastocytosis. Skeletal abnormalities of systemic mastocytosis include osteopenia, osteolysis, osteoporosis, and osteosclerosis [2]. Osteolysis may lead to osteoporosis and pathologic fractures [1,3]. According to the reports in the literature, more than 1/5 of the patients with systemic mastocytosis experience osteoporosis [4,5]. Multiple fractures can even be the first manifestation in patients with systemic mastocytosis [6].

Herein, we aimed to provide an insight to the changes in bone tissue in patients with mastocytosis.

SEARCH METHODOLOGY
A search was performed through Scopus, PubMed and WoS. Articles written in English were included. The search strategy was adopted from recommendations for
writing biomedical narrative reviews [7]. Congress abstracts and unpublished data were excluded. Articles published during the last 5 years were given preference. Each included article’s reference list was also evaluated for further relevant articles.

Epidemiology of osteoporosis in mastocytosis

Skin lesions, anaphylaxis, osteoporosis, gastrointestinal disorders, and organomegaly are a few of the many signs, symptoms, and concurrent illnesses that can accompany mastocytosis [8]. Mastocytosis might be regarded as a risk factor for bone mineral density loss, osteoporosis and low-energy pelvic fracture. Systemic mastocytosis, which is an uncommon condition, can be complicated by osteoporosis and fractures. The prevalence of osteopenia and osteoporosis in systemic mastocytosis is 39% and 24%, respectively. Yet, there are reports with higher frequencies. Zanotti et al. found that osteoporosis was present in 35% of cases, even in young adults and particularly males [9]. Additionally, fragility fractures are also observed commonly in patients with systemic mastocytosis [10,11]. On the other hand, the prevalence of mast cell-related disorders in severe osteoporosis was found to be 3.0%, accounting for 7.4% of the secondary reasons of osteoporosis [12].

Mechanisms related to osteoporosis in mastocytosis

Depending on which organ the active mast cells are located in, mast cell activation in systemic mastocytosis causes symptoms from that organ, such as flushing, palpitations, anaphylactic reactions, and bone health issues including osteoporosis [13]. The causes underlying deteriorated bone health in systemic mastocytosis are poorly understood [14]. Underlying factors include mast cell infiltration and systemic release of mast cell mediators [15]. Mast cells may have a role in the development of osteoporosis since people with age-related or postmenopausal osteoporosis have more mast cells in their bone marrow [16]. Increased number of osteoclasts related to the presence of mast cells has been detected in histomorphometric studies on systemic mastocytosis [17]. Extracellular vesicles (EVs) released by mast cells carry and distribute miRNAs that may disrupt with bone formation epigenetically which in turn lead to bone mass loss [14].

Bone loss in systemic mastocytosis has been linked with an increased proinflammatory cytokine profile in plasma. Rama et al. conducted a study on 120 adult patients with systemic mastocytosis. Patients were divided in three groups: those with i) significant bone loss, ii) diffuse bone sclerosis, and iii) healthy bone. Patients with bone loss revealed significantly higher tryptase, interferon (IFN)-γ, interleukin (IL)-1β, and IL-6, level compared to patients with healthy bone [18]. Systemic inflammation is an important factor in bone health impairment in several other diseases such as multiple sclerosis and autoimmune inflammatory rheumatic conditions [19, 20].

Management of systemic mastocytosis in terms of osteoporosis

The establishment of systemic mastocytosis subtypes in accordance with the International Consensus Classification [21]/World Health Organization classification systems [22] is a critical initial step. Patients have either indolent/smoldering systemic mastocytosis or advanced systemic mastocytosis, which includes aggressive systemic mastocytosis, systemic mastocytosis with associated myeloid neoplasm, and mast cell leukemia [23]. Riffel et al. concluded that osteoporosis was as a common feature in indolent systemic mastocytosis but not in advanced systemic mastocytosis. On the other hand, an increased bone mineral density was common in advanced systemic mastocytosis but not as frequent in indolent systemic mastocytosis [24]. Yet, Franco et al. evaluated bone microarchitecture in 21 patients with systemic mastocytosis. Patients revealed significantly lower total volumetric bone mineral density, cortical thickness, and cortical volumetric bone mineral density at the radius, when compared to controls. Furthermore, when compared to those with indolent systemic mastocytosis, patients with aggressive systemic mastocytosis exhibited substantially reduced trabecular number and estimated failure load at the tibia [25]. Patients with indolent systemic mastocytosis have a significantly better prognosis compared to those with aggressive systemic mastocytosis. Since complications affect survival, osteoporosis and related fractures stand as an important topic for this group [26]. In a cohort of individulas with osteoporosis, indolent systemic mastocytosis was found in 0.5% and 3.1% (men 5.8%) of the patients who had bone biopsies. Thus, in men and premenopausal women presenting with vertebral fractures, indolent systemic mastocytosis should be considered even if urticaria pigmentosa is absent [27]. As a relevant term, bone marrow mastocytosis, represents a provisional, indolent subvariant of systemic mastocytosis, characterized by bone marrow involvement and the absence of mastocytosis skin lesions. In bone marrow mastocytosis, even the only presentation could be osteoporosis. Bone marrow mastocytosis is an underestimated condition since tryptase levels are not frequently evaluated in
cases with unexplained osteoporosis or anaphylaxis [28]. Carosi et al. evaluated the medical data of 232 individuals with osteoporosis. The results revealed the role of hypertryptasemia as all osteoporotic individuals with hypertryptasemia suffered at least 1 vertebral fracture, which was accompanied by a severe impairment in lumbar bone mineral density [12]. Proximal femoral and lumbar spine dual-energy X-ray absorptiometry (DXA) is recommended given the increased frequency of osteoporosis in patients with systemic mastocytosis [29]. The results derived by DXA are related to bone marrow biopsy parameters and clinical variables in systemic mastocytosis [2]. Makavoz et al. provided an interactive calculator created using a prediction model based on a North American cohort, which was proposed to be utilized for better screening for fracture risk [30].

There are reports regarding the management of osteoporosis in patients with mastocytosis [31-35]. Bisphosphonates are recommended as first-line treatment in osteoporotic patients with systemic mastocytosis [33]. Bisphosphonates can significantly increase bone mineral density and decrease serum cross-linked C-telopeptide of type I collagen in patients with indolent systemic mastocytosis [36]. Wang and Seibel reported a case treated with denosumab with favourable response in bone mineral density over the following 5 years [34]. Denosumab, which is a receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitor, inhibits resorption of the bone in patients with osteoporosis [37].

CONCLUSIONS
Osteoporosis and fragility fractures can be observed in systemic mastocytosis. It is of utmost importance to be aware of the risk of bone impairment, particularly in those with systemic mastocytosis. Taking preventative measures for bone health impairment, screening protocols and proper treatment of osteoporosis when diagnosed would be of great value to prevent fragility fractures.

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None

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References

Figure 1. Potential mechanisms underlying osteoporosis in patients with mastocytosis. miRNA: micro-ribonucleic acid, EVs: extracellular vesicles, IFN-γ: interferon gamma, IL: interleukin
Мастоцитоз — заболевание, характеризующееся аномальной пролиферацией и накоплением клональных тучных клеток. Одной из систем, которая может поражаться у больных mastoцитозом, является костная система. В результате поражения костной системы могут возникать остеолиз, остеопения, остеопороз и остеосклероз. Остеопороз наблюдается более чем у 1/5 этих пациентов, и заболевание может даже проявляться множественными переломами. К основным факторам ухудшения здоровья костей при системном mastoцитозе относятся инфильтрация тучных клеток и системное высвобождение тучных клеток, увеличение количества остеокластов и перепроизводство противовоспалительных цитокинов. Профилактика нарушений здоровья костей у пациентов с системным mastoцитозом, внедрение протоколов скрининга и соответствующее лечение остеопороза в случае его развития чрезвычайно важны для предотвращения хрупких переломов. Цель данного обзора — дать представление об изменениях костной ткани у больных mastoцитозом.

Ключевые слова: кость, кость и костная ткань, остеопороз, mastoцитоз.