Abstract

Objective: Nowadays, the occurrence of brown tumor lesions or osteitis fibrosa cystica caused by long-lasting primary hyperparathyroidism are very rare, since measuring serum calcium became available routinely in the mid-1970s. It is a tumor-like lesion that may affect the entire skeleton, often presenting with diffuse focal bone pain or by pathological fracture.

Methods: We describe our experience of brown tumor lesions at different skeletal sites that were treated at our trauma centre within the last two years. This included surgical therapy for the indications (i) pain at the pelvis, (ii) increased risk for pathological fracture at the tibia and (iii) acute radicular symptoms at the lumbar spine. The literature was reviewed for the current understanding of the pathophysiology as well as therapy of brown tumor lesions in primary hyperparathyroidism.

Results: Curettage of a left-sided iliac crest brown tumor terminated focal pain. A less invasive stabilisation system and bone cement decreased both patient pain and the fracture risk of brown tumor lesion sites of the shinbone; and internal fixator including laminectomy at the lumbar spine ended radicular symptoms.

Conclusion: Patients with refractory primary hyperparathyroidism should be monitored closely by endocrinologists and the patient's serum calcium became available routinely in the 1970s [7-9]. Thus, primary hyperparathyroidism is increasingly being diagnosed during the asymptomatic phase [7, 8]. About 75% of patients with diagnosis of primary hyperparathyroidism do not have disease-related symptoms, whereas 25% demonstrate disease progression over a follow-up period of 10 years [10]. Thus, patients were followed closely and there may be no indication for parathyroid surgery if the patient does not meet the National Institutes of Health guidelines criteria for parathyroidectomy [7, 8, 10]. These guidelines are based on, among other criteria, the patient's compliance and age, serum calcium levels, renal function and cortical bone mineral density, as well as the patient's own request. Thus, a bone mineral density of ≥ 2 standard deviations below the mean for age-matched control subjects (Z-score) constitutes a recommendation for parathyroid surgery [4]. In experienced hands, bilateral parathyroidectomy has a success rate of about 95% [11]. There is evidence that, following surgery and normalisation of calcium homeostasis, bone mineral density at the lumbar spine or femoral neck improves significantly [4, 12-14]. Therefore, a formerly found bone involvement of 10-23% decreased to 1-2% in patients at diagnosis of primary hyperparathyroidism [10, 16, 17]. Thus, full-blown osteitis fibrosa cystica with the so-called brown tumor lesions has become a rarity as well as the characteristic plan radiographic changes seen e.g. in the patients hand. An increased risk for disease progression may be assessed for younger patients at diagnosis or in women entering the menopause [4, 15]. Meanwhile osteitis fibrosa cystica is seen predominantly in individuals suffering from parathyroid carcinoma, parathyreomatisos, undiscovered primary hyperparathyroidism, or hyperparathyroidism secondary to terminal renal fail-

1. INTRODUCTION

Primary hyperparathyroidism is the result of an excessive and inappropriate secretion of the parathyroid hormone, clearly recognized by von Recklinghausen al-most 115 years ago [1]. It is caused by a solitary parathyroid adenoma in 80-85% of cases and by hyperplasia or multiple adenomas of the parathyroid glands in 15-20%, whereas carcinomas are rare < 1% [2, 3]. Primary hyperparathyroidism has an incidence in western countries of 1,4/1000 individuals [2, 4-6]. The diagnosis is made in most individuals above the age of 40 years [2]. The clinical appearance of this disease, previously characterized by severe hypercalcaemia, recurrent nephrolithiasis and bone loss, has changed since hypercalcaemia became easily detectable by automated analyser systems in the 1970s [7-9]. Thus, primary hyperparathyroidism is increasingly being diagnosed during the asymptomatic phase [7, 8]. About 75% of patients with diagnosis of primary hyperparathyroidism do not have disease-related symptoms, whereas 25% demonstrate disease progression over a follow-up period of 10 years [10]. Thus, patients were followed closely and there may be no indication for parathyroid surgery if the patient does not meet the National Institutes of Health guidelines criteria for parathyroidectomy [7, 8, 10]. These guidelines are based on, among other criteria, the patient's compliance and age, serum calcium levels, renal function and cortical bone mineral density, as well as the patient’s own request. Thus, a bone mineral density of ≥ 2 standard deviations below the mean for age-matched control subjects (Z-score) constitutes a recommendation for parathyroid surgery [4]. In experienced hands, bilateral parathyroidectomy has a success rate of about 95% [11]. There is evidence that, following surgery and normalisation of calcium homeostasis, bone mineral density at the lumbar spine or femoral neck improves significantly [4, 12-14]. Therefore, a formerly found bone involvement of 10-23% decreased to 1-2% in patients at diagnosis of primary hyperparathyroidism [10, 16, 17]. Thus, full-blown osteitis fibrosa cystica with the so-called brown tumor lesions has become a rarity as well as the characteristic plan radiographic changes seen e.g. in the patients hand. An increased risk for disease progression may be assessed for younger patients at diagnosis or in women entering the menopause [4, 15]. Meanwhile osteitis fibrosa cystica is seen predominantly in individuals suffering from parathyroid carcinoma, parathyreomatisos, undiscovered primary hyperparathyroidism, or hyperparathyroidism secondary to terminal renal fail-

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In these patients, normalisation of calcium homeostasis may fail and severe bone involvement often occurs after years of disease.

Here, we focus on patients with refractory primary hyperparathyroidism due to parathyreomatosis and severe bone involvement, also called brown tumor lesions, being referred to our University Medical Centre for surgical evaluation within the last two years. We describe each lesion operated on as well as the surgical course, and we address the issues with regard to pathophysiology, nature and fracture risk by reviewing the current literature.

2. METHODS

The surgical database at our institution was searched for all surgical treatments in conjunction with brown tumor lesions in primary hyperparathyroidism within the last two years and patients’ records, including operative procedures and processed radiographic diagnostics, were reviewed. In addition to that, we searched the PubMed database for reports dealing with primary hyperparathyroidism in conjunction with bone, fracture, brown tumor, osteitis fibrosa cystica, and von Recklinghausen’s disease.

3. RESULTS

We identified a total of four surgical procedures performed for brown tumor lesions in one patient suffering from refractory primary hyperparathyroidism at our institution between 2005 and 2006. Table 1 summarizes the single lesion, endocrine diagnosis, indication for operation, operative procedure and clinical outcome.

### Table 1. Admissions for brown tumor lesions between 2005 and 2006.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Predominant symptoms</th>
<th>Main localisation of the brown tumor</th>
<th>Indication for operation</th>
<th>Performed surgical therapy</th>
<th>Outcome (Follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>refractory primary hyperparathyroidism</td>
<td>diffuse left sided iliac crest pain</td>
<td>Left pelvis</td>
<td>pain</td>
<td>curettage + Bone cement</td>
<td>pain freeness</td>
</tr>
<tr>
<td></td>
<td>diffuse right proximal tibia bone pain</td>
<td>proximal right tibial bone</td>
<td>pain + fracture risk</td>
<td>curettage + Bone cement</td>
<td>pain reduction</td>
</tr>
<tr>
<td></td>
<td>diffuse recurrent tibia shaft pain</td>
<td>right tibia shaft</td>
<td>pain + fracture risk</td>
<td>curettage + bone cement + osteosynthesis</td>
<td>pain freeness</td>
</tr>
<tr>
<td>radicular lumbar spine symptomatic</td>
<td>lumbar spine (vertebra No. 2)</td>
<td>neurology</td>
<td>curettage + hemilaminectomy + Bone cement + internal fixator</td>
<td>pain reduction + complete peripheral neurological recovery</td>
<td></td>
</tr>
</tbody>
</table>
parison with the initial radiography showed a significant increase in the extent of the lesion at the ventral cortical site of the tibial middle-third. Additionally, a radiographic progression was noted at the proximal right tibia around the Palacos® plombage, as illustrated by Figure 2. The patient was scheduled for surgery, and curettage of the tumor as well as a Palacos® plombage was performed. Additionally, an osteosynthesis of the tibia was performed, using a less invasive stabilisation system due to the worsening of the tibial stability with increased fracture risk, as can be seen in Figure 2.

The fourth brown tumor lesion operated on at our institution within the last 2 years was localised in the spine. The patient presented at our surgical emergency department with acute radicular symptoms and known diagnosis of refractory primary hyperparathyroidism. The laboratory tests revealed excessive levels of calcium and parathormone. An emergency computer tomography of the lumbar spine was done, which showed disastrous brown tumor invasion and destruction of the second lumbar vertebra, including a crush of the front edge, a brown tumor mass lesion reaching the spinal canal at the right-sided pedicular level of second vertebra (Fig. 3). Urgent surgery was done and a tumor curettage, a right-sided laminectomy, a Palacos® plombage as well as a dorsal 3D-navigated stabilisation using an internal fixator was performed without complication (Fig. 3). The patient is doing well, and is without pain or any neurological sign after recovery and further medical endocrine optimization.

We next reviewed the literature for the current understanding of the pathophysiology of primary hyperparathyroidism with respect to its effect on bone, including the fracture risk.

3.2. Pathophysiology of the Primary Hyperparathyroidism and its Effect on Bone

Primary hyperparathyroidism is defined by hypercalcemia and slightly elevated levels of the parathyroid hormone in the serum. In general, parathormone restores any tendency to extracellular hypocalcemia by an increase of calcium reabsorption in the kidney. Parathormone stimulates hydroxylation of 25-hydroxy-vitamin D in the kidney, and increases bone resorption by stimulating different osteoclast-activating factors even for a slightly decreased level of serum calcium. On the other hand, parathormone binds calcium in the parathyroid glands and the kidney to inhibit both the secretion of parathyroid hormone in parathyroid cells and the 1-hydroxylation of 25-hydroxy-vitamin D, respectively. Moreover, it affects the thyroid C cells, stimulating calcitonin release via the G protein-linked activation of the calcium-sensing receptors, and at the bone site it may regulate bone resorption.

Although the full-blown skeletal manifestation, osteitis fibrosa cystica, is distinctly unusual in patients with primary hyperparathyroidism in western countries, this does not imply that the bone is unaffected in individuals with asymptomatic disease. However, skeletal radiographs are not performed or recommended routinely [25]. In recent years it has become clear that the skeleton is involved in even mild primary hyperparathyroidism. The most common sites to see evidence for skeletal effects are the distal third of the radius and the radial aspects of the middle phalanges, sites of cortical bone with typical subperiostal resorption. Additional sites may include the distal phalanges, distal tapering of the clavicle, and the salt-and-pepper appearance of the skull [2, 25, 26]. Bilezikian and co-workers provided evidence that mainly cancellous

Fig. 1. Brown tumor lesion at the left iliacal crest in refractory primary hyperparathyroidism. Preoperative plan radiographic survey of the pelvis (A) measuring about 4.0 x 3.0 cm, bony distension and interruption of the cortical substance (arrow). Please note a small asymptomatic brown tumor lesion at the right sided femoral neck. Plan radiography of the left sided pelvis after complete curettage of the brown tumor lesion (B).
Fig. 2. Brown tumor lesion of the right proximal tibia with later disease progression in refractory primary hyperparathyroidism. Magnet resonance tomography of the right tibia, sagittal (A), coronar (B) and trasversal (C) view of the proximal tibial lesion. The arrow indicates the typical bone deformity. The corresponding plan radiographic survey of the right tibia is given in D and E. F and G showing the later disease progression of the same leg after curettage of the brown tumor and Palacos® plom- bage leading to an osteosynthesis of the tibia by a less invasive stabilization system and curettage of an addition tumor lesion and pallagos plombage distal to the first lesion as indicated by arrow (H and I).
bones, like the lumbar spine, are affected only minimally. The hip region, containing an equal mixture of cortical and cancellous elements, shows a bone density intermediate between cortical (distal radius) and cancellous sites (spine) when compared to age and gender-mixed control values [15]. These results obtained by densitometry were supported by quantitative bone histomorphometric analyses, which indicates that a reduced cortical bone mineral density is seen regularly in mild primary hyperparathyroidism, and that the cancellous bone is relatively well preserved [4, 27, 28]. Therefore, the parathyroid hormone appears to be largely catabolic at cortical sites and anabolic at cancellous sites [4]. Thus, known markers of bone formation like osteocalcin or the bone-specific alkaline phosphatase are present in primary hyperparathyroidism as well as markers of bone resorption, like deoxypyridinoline and N-telopeptide [29, 32, 34, 35]. Khosla et al., among others, showed in a population-based study that the vast majority of distal forearm fractures were Colles’ fractures, which occur at a site containing predominantly cancellous bone, and hypothesized that this may be due, in part, to the fact that primary hyperparathyroidism is associated with increased bone turn-over [36]. Evidence indicates that this turn-over may represent an independent risk factor for bone fracture, caused by perforative resorption of trabeculae and loss of structural elements, or a reduction in bone strength [37-40]. Destructive bone lesions, such as brown tumours, however, occur only in the more advanced stages of hyperthyroid bone disease and can involve the whole skeleton [31].

3.3. Brown Tumor Lesions in Primary Hyperparathyroidism

Brown tumors are tumor-like lesions without signs of neoplasm, but changes similar to them with regard to their appearance, symptoms and radiographic signs without having any autonomous growth [13]. The osteoclastic activity, and therefore bone breakdown, are increased by elevated secretion of the parathyroid hormone [13, 23]. Thus, osteolytic cavities occur in the spongiosal bone in which secondary haemorrhage and proliferation of soft tissue result in a red-brown shining elastic mass completely filling the bone defect, giving the name osteitis fibrosa cystica for this tumor-like lesion [32, 33]. Therefore, the histopathological features of the osteitis fibrosa cystica are the osteoclastic resorption of the bone with increased numbers of os-

Fig. 3. Brown tumor lesion of the lumbar spine presenting with radicular symptoms in refractory primary hyperparathyroidism. The computed tomography shows the second lumbar vertebra before (A and B) and after (C and D) curettage, hemilaminectomy and stabilization using an internal fixator.
teoclasts and osteoblasts, irregularly thickened woven trabecular bone surrounded by loose fibrous tissue, areas of tissue granulation, giant cells, inflammatory cells and deposition of hemosiderin. A histological example of a typical brown tumor after curettage from the right tibia bone of a male patient is shown in Figure 4.

In recent years, brown tumor lesions have become rare due to the ready availability of measuring serum calcium, allowing early diagnosis of primary hyperparathyroidism and subsequent surgical therapy by parathyroidectomy if necessary [2]. Therefore, radiographic bone involvement of 23% of all patients with primary hyperparathyroidism seen between 1930 and 1965 has decreased to 2%, making brown tumor lesions a rarity [10, 16]. Thus, especially younger physicians may not be familiar with the advanced stage of this disease [13]. Apart from the typical bone changes, like the cortical accented osteopenia seen in primary hyperparathyroidism, brown tumors appear radiographically as destructive osteolytic lesions [22]. Patients with brown tumor lesions often present with diffuse focal bone pain, including pathological fractures [13, 22, 32]. The whole skeleton can be infested; however, the bones of the stem skeleton, like the lumbar spine, seem to be less affected [31]. Evidence has been provided that in patients with primary hyperparathyroidism, even destructive bone lesions tend to heal spontaneously after parathyroid surgery and normalization of the calcium homeostasis [12, 22]. Even a complete recovery of spinal cord compression has been reported following parathyroidectomy [41]. However, in refractory disease, surgery to the bone is almost always the only way to decrease the risk for spontaneous fracture and to eliminate focal bone pain.

3.4. PRIMARY HYPERPARATHYROIDISM AND THE RISK OF BONE FRACTURE

Over the past few years, several studies have addressed the fracture risk in patients with primary hyperparathyroidism and provided evidence that these patients sustain more fractures before diagnosis. However, once the diagnosis is made and adequate therapy established to protect from further bone loss, the fracture risk is brought into line with that of a normal population [10, 36, 42-44].

Brown tumor lesions, at the severe end of the spectrum of bone involvement, are known to increase in size over time without adequate therapy [45]. There are no data available in the literature estimating the specific fracture risk in patients with parathyromatosis and brown tumor lesion. However, surgical curettage, bone grafting, or prophylactic stabilization are recommended in patients with persistent symptomatic bone lesions, persistent osteolytic lesions in high-stress locations and pathologic fractures [2, 13]. Thus, the individual fracture risk and therefore indication for prophylactic surgical stabilization of a specific brown tumor lesion can be derived from the scoring system for diagnosing impending pathological fractures, introduced by Mirels, which includes localization, type of lesion, grade of pain, and size of lesion [46].

Bilezikian and Potts estimated the relative fracture risk in primary hyperparathyroidism as being increased by up to 3 times, and recommended bone mineral densitometry at three sites, lumbar spine, femur neck and distal radius [47]. Khosla and Melton estimated the fracture rates in patients with primary hyperparathyroidism to be up to 1.5-fold greater than those of the general population [48]. In a retrospective analysis, Kebebew et al. followed 18 patients with parathyroid carcinoma from 1966 to 1999 and found one pathologic fracture in four patients with substantial bone involvement [3]. Khosla et al. reviewed 407 patients in a population-based study with primary hyperparathyroidism over a period of 28 years and found an overall increased fracture risk for individuals within this population. There were increases in vertebral, distal forearm, rib and pelvic fractures seen at individual sites [36].
4. Discussion

The present paper represents, to our knowledge, the first analysis of surgical therapy for brown tumor lesions at different bone sites in refractory primary hyperparathyroidism.

Hypercalcemia represents an incidental finding in about one-third of patients with primary hyperparathyroidism [23]. Thus, the clinical occurrence of primary hyperparathyroidism has changed towards an asymptomatic disease with fewer untreated long-lasting courses [15]. Brown tumor lesions have been reported as secondary to chronic renal failure in individuals with severe hyperparathyroidism. However, its occurrence rate in secondary hyperparathyroidism is assumed to be lower compared to primary hyperparathyroidism [20]. Evidence has been provided that in refractory osteitis fibrosa secondary to chronic renal failure, the long-term intermittent intravenous infusion of calcitriol is effective in ameliorating osteitis fibrosa [49]. It has been shown that even manifest brown tumor lesions due to long-lasting primary hyperparathyroidism or caused by poor alimentation can improve with regard to bone mineral density as well as its symptoms following parathyroidectomy and calcitriol substitution, respectively [12]. However, one should consider surgery in high-stress locations when an increased risk for pathological fracture is present or in those patients with persistent focal bone pain.

The diagnosis of primary hyperparathyroidism is made, in general, on the basis of laboratory tests, including measurement of the levels of calcium, phosphate and parathormone in the serum. The radiographic and histological findings may be difficult to interpret without knowledge of the clinical findings. Brown tumors have no specific radiological findings, and the same histological findings can be present in giant cell tumors [23].

The series of osteitis fibrosa cystica lesions being operated on at our department within the last two years is large with respect to its natural frequency and reports in the literature. In our series, diffuse focal bone pain has been the predominant complaint in each lesion, and radiographic investigation in conjunction with the known patient’s medical history established diagnosis beyond doubt. In fact, skeletal changes caused by brown tumors most commonly present as focal pain; however, pathologic fractures and skeletal deformities are not infrequent complications [22]. It has been reported that pathological fracture and pain may be the first signs of a brown tumor lesion that may include the spine [22, 23, 35]. It is important to mention that parathyroidomatosis, and therefore refractory primary hyperparathyroidism, was the endocrine background to every tumor-like lesion of the patient reported here. Thus, endocrine surgery was not an option, after multiple endocrine surgical attempts, and medical therapy was focussed on pharmacological reduction of serum calcium.

The first brown tumor lesion of the right-sided pelvis we report here was considered for surgery due to increasing persistent focal pain; and indeed the patient is free of local pain one year after curettage of the brown tumor. When reviewing the literature, we found brown tumor lesions involving the pelvis being reported in hyperparathyroid crises, chronic renal failure and tertiary hyperparathyroidism, but surgery to the bone was not performed in any of these cases [50-52]. No similar case of a brown tumor of the iliac crest being successfully operated by curettage of the tumor-like mass for persistent pain has been reported.

Substantially more reports were found in the literature for the occurrence of brown tumor involvement of the lower extremities in primary hyperparathyroidism in large follow-up trials, as well as in the case reports of patients with parathyroid carcinoma, and primary and tertiary hyperparathyroidism [36, 42, 51, 53-56]. However, neither the diagnosis of parathyromatosis nor the surgical therapy with regard to the brown tumor lesion was suggested. A similar case of brown tumor lesion at the proximal tibial bone, however, in a patient with multiple endocrine neoplasia type II, was reported by Schaser et al. in 2002 [57]. However, a pathological fracture had occurred already in this patient, in contrast to our patient, where surgery was performed due to an increased fracture risk. Schaser used an autologous spongiosa instead of bone cement to fill the osteolytic defect, but the tibia was osteosynthetised using a less invasive stabilization system (LISS), too [57].

The invasion of the thoracic spine is a rare occurrence among brown tumor lesions of the bone. Mustonen et al. searched Medline from 1966 to 2004 for brown tumor of the thoracic spine in primary hyperparathyroidism and found six cases in this context [23]. The lumbar spine is involved not more frequently. When brown tumors affect the vertebra, they have a slow progression of symptoms, including back pain and weakness of the legs [23]. However, an acute course with paraplegia due to a pathological fracture and spinal cord compression has been documented in the literature [22, 58-61]. In our patient, a rapid progression with radicular symptoms was seen. Evidence has been provided that symptoms of radicular or spinal cord compression can be resolved in primary as well as in secondary hyperparathyroidism after parathyroidectomy without local surgery of the brown tumor [23, 62]. In our patient, several attempts, including three sternotomies, have failed to localize and remove all ectopic mediastinal endocrine foci. Refractory primary hyperparathyroidism due to parathyromatosis is found to be the reason for persistent or recurrent primary hyperparathyroidism in about 1-2% of patients [63-65].

In conclusion, we have presented a report describing brown tumor lesions in refractory primary hyperparathyroidism at different bone sites, its predominant symptoms, and indication for surgical therapy and outcome. Moreover, we have provided extended information on the current understanding of the pathophysiology of primary hyperparathyroidism and its effects on the bone, including the severe end of the spectrum presenting as osteitis fibrosa cystica.

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