The Gorham-Stout syndrome (Gorham’s massive osteolysis)

A REPORT OF SIX CASES WITH HISTOPATHOLOGICAL FINDINGS

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The Gorham-Stout syndrome (Gorham’s massive osteolysis) is a rare condition in which spontaneous, progressive resorption of bone occurs. The aetiology is poorly understood. We report six cases of the condition and present evidence that osteolysis is due to an increased number of stimulated osteoclasts. This suggests that early potent antiresorptive therapy such as with calcitonin or bisphosphonates may prevent local progressive osteolysis.

Osteolysis, a localised resorption of bone, is a common radiological observation. Usually the destruction is associated with some underlying disease. From these so-called secondary osteolyses the rare entity of idiopathic osteolysis or disappearing bone disease can be differentiated.

Idiopathic osteolysis was first described in 1838 and again in 1872 by Jackson who reported a case of a ‘boneless arm’. The humerus of an 18-year-old man disappeared completely in the course of 11 years, during which he twice sustained a spontaneous fracture of the bone. In spite of the disease he was able to do manual labour until his death at the age of 70 years. In 1955, Gorham and Stout defined a specific disease entity and reviewed 24 cases from the literature. The Gorham-Stout syndrome presents as progressive idiopathic osteolysis of one bone or contiguous bones around one focus, without respect for joint boundaries. It may affect any part of the skeleton, but most commonly involves the skull, shoulder and pelvic girdle.3-6 Spontaneous fractures are common.

Regeneration of bone does not occur even when the osteolysis ceases to progress. In no case was there a family history of a similar condition. The phenomenon commences with intramedullary and subcortical radiolucent foci resembling “patchy osteoporosis”. It makes slow, irregular, local progress with a concentric shrinkage of the shaft of bones, tapering the involved end and giving the appearance of ‘sucked candy’.5,8 The affected bone disappears more or less completely unless spontaneous remission occurs.8 Bone scans usually show decreased uptake in the affected areas. Associated pathological fractures rarely heal and the osteolytic process continues through the fragments.5,10,11 The Gorham-Stout syndrome is not accompanied by general symptoms. During the acute phase, localised pain, swelling, progressive deformity and contractures are the common features. Despite this, the function of the limb remains remarkably good. No case has been reported in which a second osteolytic lesion developed in another bone after a quiescent period. Often, there is a history of trauma. Biochemical and haematological tests are usually normal and helpful only to exclude other diagnoses. Alkaline phosphatase may be elevated in a patient with associated fracture.11 While contiguous bony involvement is usual, ‘skip lesions’, multiple foci or metasteses do not occur.8

A total of 175 cases, including two from our own centre,1-7 described variously as massive osteolysis,1 dis-appearing or vanishing bone disease,1 Gorham’s disease,4 acute spontaneous absorption of bone,1 and phantom bone1 has been reviewed recently.8 The disease can occur at any age, but is common in adolescents and young adults. There is no gender or racial predilection.

The Gorham-Stout syndrome is a rare skeletal disorder of which the aetiology and pathogenesis remain unknown. The diagnosis is, essentially, one of exclusion and must be based on combined clinical, radiological and histopathological findings. Deaths from the disease have occurred in patients in whom the process was localised to the rib, mandible, or vertebral bodies leading to fatal complications from respiratory failure, obstruction of the airway or compression of the spinal cord.3,7,16

Spontaneous arrest of osteolysis after years of bone destruction is common. The end result is severe deformity and functional disability. If the process is progressive or the
osteolysis extensive, treatment by local resection, with or without replacement by a prosthesis, radiotherapy or even amputation has been tried. Curettage with incomplete resection rarely cures the disease. Bone grafts will be resorbed. Radiotherapy using total doses from 30 Gy up to 45 Gy has been reported to arrest the osteolysis, but not all cases respond. Immobilisation of the affected bone does not influence the prognosis. Improvement did not occur after the administration of oestrogen, androgen, magnesium, calcium fluoride, adrenal extracts, vitamin D, aluminium acetate solution, ultraviolet radiation, ionised calcium, somatotrophin, placental extracts, vitamin B12, amino acids, or transfusions of placental blood or blood from growing young children.

Because of the rarity of the condition, we report six cases of the Gorham-Stout syndrome from the Bone Tumour Registry of the Hamburg University School of Medicine.

Case Reports

Case 1. In 1997, a 77-year-old woman was admitted with increasing pain, a slightly reduced range of movement in the right hip and a radiolucent lesion in the head of the femur. After a fall the right femoral head resorbed within ten weeks (Fig. 1a). Clinical examination showed that her right leg was 5 cm shorter than the left. Laboratory investigations were normal apart from a slight elevation of the alkaline phosphatase (189 U/l), lactate dehydrogenase (26-28)
U/l), hydroxybutyrate dehydrogenase (149 U/l), and cholesterol (289 mg/dl) and a slight decrease in iron (10.9 µmol/l). An open biopsy was taken and followed, two weeks later, by a local resection with a total prosthetic hip replacement. All microbiological tests proved negative. Histological examination of both the biopsy and resected specimen revealed granulation tissue with distinct vascularisation and a reactive fibrosing synovitis. There was also a marked stimulation of and an increased number of osteoclasts in both the trabecular and, especially, the cortical bone (Fig. 2). The patient made an uneventful recovery. Six months after surgery, there was no evidence of recurrent osteolysis.  

Case 2. In 1972, a 70-year-old woman with slowly progressive pain in the right hip, showed radiological destruction of the proximal right femur over a period of less than six months. The affected part was resected and replaced by a hip prosthesis. Histological examination of the specimen showed vigorous osteoclastic resorption which was still clearly active at the margins, and a stroma rich in fibres with numerous blood vessels. During the following three years there was no sign of recurrent disease. 

Case 3. In February 1984, a 19-year-old girl with no definite history of injury, complained of pain in the sternum and the right side of her chest. Radiographs showed a pathological fracture of the tenth rib with partial osteolysis of the tenth, eleventh and twelfth ribs on the right. Biopsy of the tenth rib revealed fibrous tissue with dilated blood vessels as well as evidence of very active osteoclastic resorption. The patient was treated by local resection of all three affected ribs. She was seen one month after surgery at which stage she had made a good recovery. 

Case 4. In January 1987, a 78-year-old woman presented with gradual spontaneous disappearance of her right pubis and ischium two weeks after an operation to replace her left hip because of arthritis. Biopsy of the ischium showed markedly vascularised fibrous tissue and osteoclastic resorption (Fig. 3a). Inside the vascular fibrous tissue were found small isolated fragments of bone surrounded by osteoclasts (Fig. 3b). The patient was treated conservatively by physiotherapy and discharged seven weeks after the initial arthroplasty of the left hip, with no sign of further progressive osteolysis. She was reviewed 11 months later with no clinical or radiological signs of progression or recurrence of the disease. 

Case 5. An 83-year-old woman presented in 1991 with a massive osteolysis of the right proximal humerus (Fig. 1b). There was no history of trauma or other relevant events. Histological examination of an open biopsy specimen showed bone fragments resorbed by osteoclasts and vascular fibrous tissue. The subsequent course is unknown. 

Case 6. A 56-year-old woman was admitted to hospital in August 1991 with increasing pain in her right shoulder of eight weeks’ duration. Radiographs showed destruction of the head of the right humerus (Fig. 1c). Open biopsy of the head was carried out, followed ten days later by a shoulder arthroplasty. The excised specimen showed much vascular fibrous tissue with destruction of the spongiosa, fragments of which were surrounded by active osteoclasts (Fig. 4). The patient made an uneventful recovery. She was seen two months after surgery with no evidence of recurrent disease. 

Discussion 

Based on the radiological, morphological and clinical findings in previous reports, we diagnosed these cases as idiopathic osteolysis, distinguishable from the many local and systemic conditions which are associated with bone resorption (secondary osteolysis). These include disseuse atrophy, acute inflammatory atrophy associated with trauma (Sudeck’s atrophy or algodystrophy), primary and metastatic tumours, hyperparathyroidism, gout, congenital pseudarthrosis, granulomatous diseases, rheumatoid arthritis, diabetes mellitus,
psoriatic arthritis, osteomyelitis, systemic mastocytosis, aseptic necrosis, neurogenic arthropathy, prolonged steroid therapy, bony aneurysm, and cystic angiomatosis of bone.

Idiopathic osteolysis comprises a heterogeneous group of rare diseases, characterised by the spontaneous onset of mostly peripheral osteolysis, without obvious reason. It has to be differentiated from familial and sporadic cases and from multicentric and unicentric osteolysis. Hardegger, Simpson and Segmüller proposed a classification with five types of idiopathic osteolysis, based on the reports of Torg et al and Macpherson, Walker and Kowall (Table I). Multicentric osteolysis can be divided into a hereditary form with either dominant or recessive transmission and a non-hereditary variety with nephropathy. It usually presents in childhood or adolescence. The Gorham-Stout syndrome and the Winchestter syndrome belong to the monocentric types of osteolysis.

There have been a number of publications and case reports which do not readily fit into this classification. White reported four patients with multifocal osteolysis in association with severe skin lesions. Beals and Bird observed one case of carpotarsal osteolysis without associated nephropathy and a hereditary pattern. Tookman, Paice and White described a woman with osteolytic lesions of the metacarpal and metatarsal bones and terminal phalanges without a family history or renal involvement; Burkhard et al and Tauro noted cases of ‘multicentric Gorham-Stout syndrome’ and Downing, Garnavos and Lunn published one case of multicentric osteolysis in both hand and feet, especially of the phalanges, associated with normal renal function and with no genetic basis.

The patients whom we present had monocentric osteolytic changes as adults; there was no family history of bone disease or of renal involvement. According to the classification proposed by Hardegger et al they belong to the group defined as the Gorham-Stout syndrome.

**Hypotheses.** The exact pathogenetic mechanism of Gorham-Stout syndrome is still unknown. There is controversy even over the presence or absence of osteoclasts in the condition. Several authors believe that angiomatosis is responsible.

In 1955, Gorham and Stout reported eight patients from whom biopsy material was available. Histological examination revealed a progressive osteolysis always associated with an angiomatosis of blood vessels and sometimes of lymphatics, which seemingly were responsible for the destruction. Neither they nor other authors found osteoclasts in areas of bone resorption and there was no evidence of reparative osteogenesis.

A variety of pathogenetic explanations for Gorham-Stout syndrome has been offered. Knoch suggested that a previous silent hamartoma becomes active after a minor trauma and leads to resorption of bone. Neurovascular changes, like those seen in Sudeck’s atrophy, have been described. Thompson and Schurman suggested that the disease is a primary aberration of vascular tissue in bone, related to

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**Table I.** Classification of idiopathic osteolysis according to Hardegger et al

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<th>Type</th>
<th>Description</th>
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<tr>
<td>1. Hereditary multicentric osteolysis with dominant transmission</td>
<td>Between the age of two and seven years, spontaneous pain and swelling begin in the hands and feet. Carpotarsal osteolysis occurs over the period of a few years. Progression ceases normally in adolescence.</td>
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<tr>
<td>2. Hereditary multicentric osteolysis with recessive transmission</td>
<td>Similar to type 1, but may be associated with severe generalised osteoporosis.</td>
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<tr>
<td>3. Non-hereditary multicentric osteolysis with nephropathy</td>
<td>Appears in childhood. There is a gradual disappearance of the carpus with the tarsal bones involved, but to a less degree, and an association with proteinuria. Death occurs usually due to renal failure and malignant hypertension.</td>
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<td>4. Gorham’s massive osteolysis (Gorham-Stout syndrome)</td>
<td>Monocentric occurrence in any part of the skeleton may start at any age. Normally ‘haemangiomatous tissue’ is found in the osteolytic region. It has neither a hereditary pattern nor an associated nephropathy. The disease is benign and the osteolysis usually stops after a few years.</td>
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<tr>
<td>5. Winchester syndrome</td>
<td>Autosomal recessive transmission. Rare childhood carpotarsal osteolysis in association with contractures, shortness of stature, skin lesions, corneal clouding and osteoporosis without nephropathy.</td>
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hyperaemic granulation tissue. Young et al. believed that osteolysis is attributable to a basic underlying endothelial dysplasia of lymphatics, blood vessels or both. Heyden et al. suggested that angiomiomatous disease might induce local hypoxia and acidosis and that this might favour the activity of local hydrolytic enzymes.

By contrast, osteoclasts have been found by other authors. In the cases which we have reported and in previous publications by our own group, and by Spieth et al., there was clear evidence that bone resorption was osteoclast-specific. In all six of our patients a very large number of multinucleated osteoclasts were seen with hyperreactive resorptive function.

The role of the osteoclast. Since the osteoclast is the only cell capable of resorbing bone, it is assumed that the Gorham-Stout syndrome may represent a pathological derangement of osteoclastic activity. Any defect of the osteoclasts could lead to idiopathic osteolysis.

The important role of proto-oncogenes in the autocrine regulation of the differentiation of osteoclasts and their function has become more clear, as well as the paracrine osteoclastic regulation mechanisms. These phenomena are relevant in the pathogenesis of the Gorham-Stout syndrome.

Essential genes for the differentiation (colony stimulating factor-1 and c-fos) and the function (c-src, cbl, c-myc) of osteoclasts were proved by elimination or overexpression of single genes in vivo and in vitro. Hormones and cytokines stimulate osteoclastic differentiation and function by paracrine stimulation. Stimulating effects on osteoclastic activity have been observed in the presence of parathyroid hormone, @, and prostaglandins (for example, PGE2).

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