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REVIEW ARTICLE

Massive osteolysis (Gorham's disease) affecting the femur

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Gorham's massive osteolysis is one of the five classical types of idiopathic osteolysis. The femoral localisation is rare. The diagnosis is based on anamnestic data (non-hereditary), on biochemical data (absence of nephropathy), on radiographical data (progressive monocentric osteolysis without periosteal reaction), and on histological data (intraosseous angiomatosis with either capillaries or lymph vessels, or both ; eventually fibrosis). Nowadays, treatment mostly consists of amputation or arthroplasty, combined with radiotherapy. Spontaneous arrest of the disease occasionally occurs, but this is unpredictable. The possible role of gene-therapy in the regulation of osteoclastic activity has to be determined in the future. Review of the literature produced 22 cases of Gorham's massive osteolysis with a localisation at the femur massive osteolysis, including one personal case.

Keywords : Gorham's massive osteolysis ; idiopathic osteolysis ; femur.

INTRODUCTION

Gorham's massive osteolysis is one of the five types of idiopathic osteolysis described by Hardegger *et al* (*11*) : 1. hereditary multicentric osteolysis with dominant transmission ; 2. hereditary multicentric osteolysis with recessive transmission ; 3. non-hereditary multicentric osteolysis with nephropathy ; 4. Gorham's massive osteolysis ; 5. Winchester syndrome. Gorham's massive osteolysis is monocentric, but may affect contiguous bones, it occurs in any part of the skeleton, and may start at any age (one month to 77 years) (*20*) ; capillaries or lymph vessels or both are found in the osteolytic region. There is neither a hereditary pattern nor an associated nephropathy.

Idiopathic osteolysis as a whole was first described in 1838 by Jackson. Hardegger *et al* (*11*) reported 62 cases in 1985. "Gorham's massive osteolysis" was first individualised by Gorham *et al* (*7*) in 1955 ; they listed 24 cases.

Histologically the bone is at first replaced by numerous capillary-and/or lymphatic-like vessels, and afterwards by vascular fibrous tissue (*13, 15, 17, 18*).

Spontaneous fractures are common at presentation, and are problematic : nonunion is a known problem (*2, 4*). The osteolysis can stop spontaneously. There is no consensus about the most efficacious treatment, because of the small number of cases,

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the difficult diagnosis, and the tendency to combine various treatment options.

Exclusive involvement of the femur, first described in 1937 by Richard (*22*), is uncommon (*18*). A review of 52 cases by Bullough (*1*) showed only four cases with isolated femoral involvement. Localisation in long bones, especially in the femur, may cause severe invalidity in the occurrence of a pathological fracture and problematic fracture healing. Reviewing the literature we recorded twenty-one cases in which the femur was primary involved. We add and describe one personal case of femoral osteolysis with a follow-up of 27 years, which will be described as an illustrative case.

ILLUSTRATIVE CASE

A 14-year-old boy presented in 1976 with pain in his right knee. There was no swelling and no limitation in the range of motion. Laboratory data were within normal limits. Roentgenographic examination showed osteolysis of the right femoral diaphysis and an irregular cortical lesion. A bone scan showed a slightly increased uptake in the right femur.

Malignancy could not be excluded, and after irradiation an open biopsy was performed. Microscopic examination showed intraosseous growth of lymph vessels (fig 1a) and active osteolysis (fig 1b). The diagnosis of Gorham's disease was then made, also based on the radiological findings. Cultures were sterile.

Three months after onset, a spontaneous fracture occurred at the level of the biopsy (fig 2a) ; a plaster cast was applied. Radiation therapy (low fractioned, 25 to 33 Gy) was continued, but the osteolysis was progressive (fig 2b). A second course was then started (high fractioned, total 45 Gy). The fracture did not heal, in spite of the plaster cast immobilisation. Large autologous cortical tibial grafts and iliac bone chips were applied. The grafts incorporated, but fractured after three months. A condylar plate was then inserted (fig 2c). The fracture healed after two months, but with 10 cm shortening.

Fortunately, there was no further progression and the femur remodelled. At the last follow-up, in January 2004, 27 years later, there was some medial osteoarthritis of the knee. The range of motion was fully restored, and the patient led an active life (fig 2d, 2e).

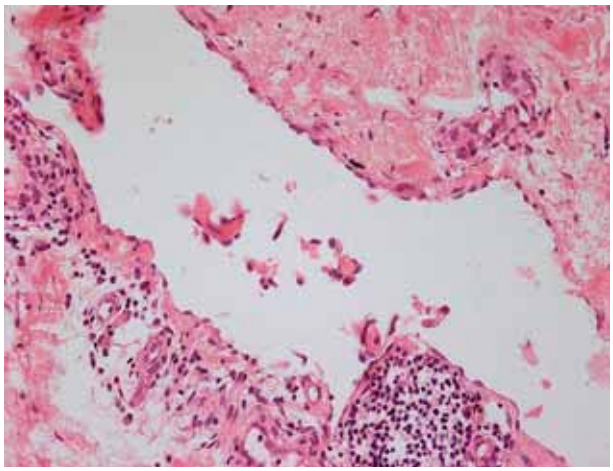


Fig. 1a. — The biopsy specimen shows lymphatic proliferation.

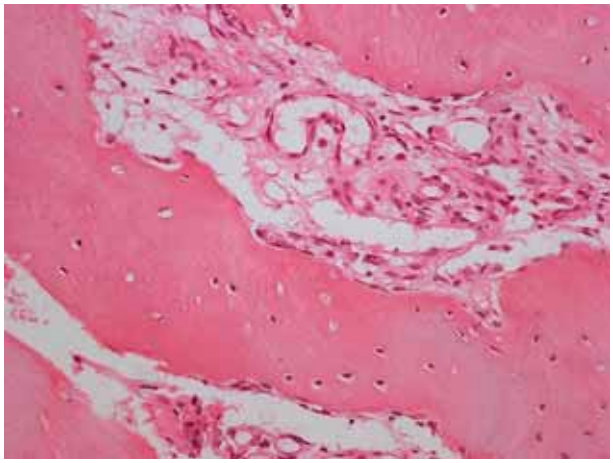
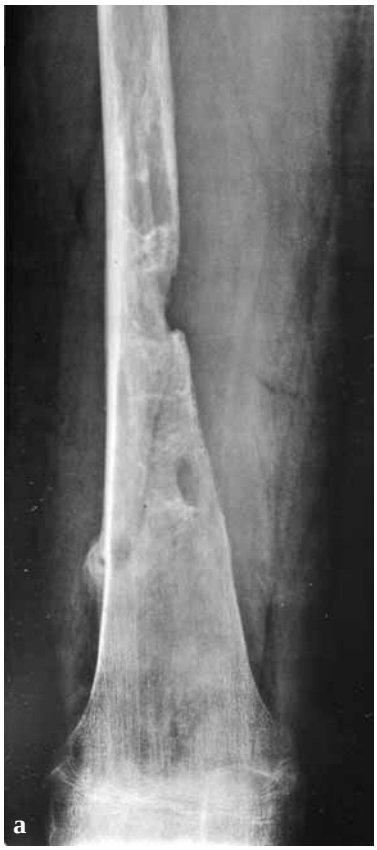
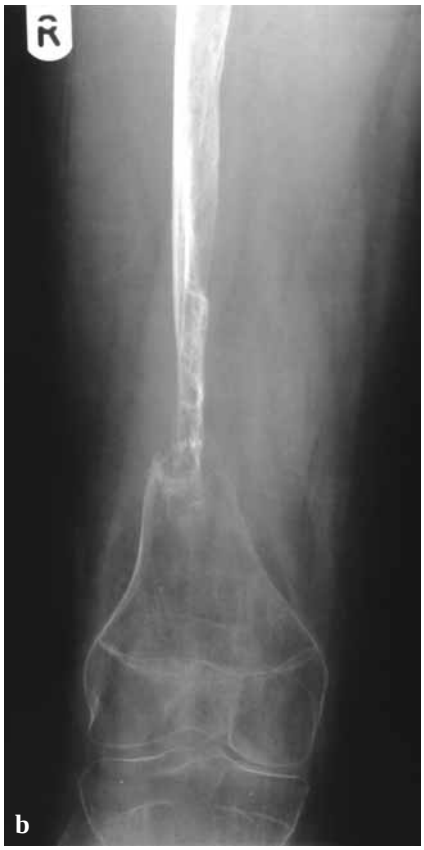


Fig. 1b. — Active osteolysis : bone resorption by osteoclasts ; the number of osteoclasts is not abnormally high. Proliferating vascular tissue invades the bone.

REVIEW OF THE LITERATURE

Twenty-one cases of Gorham's disease affecting the femur were found in the literature (table I). The average follow-up was 5.6 years (range 6 months to 27 years). The mean age at diagnosis was 24 years.





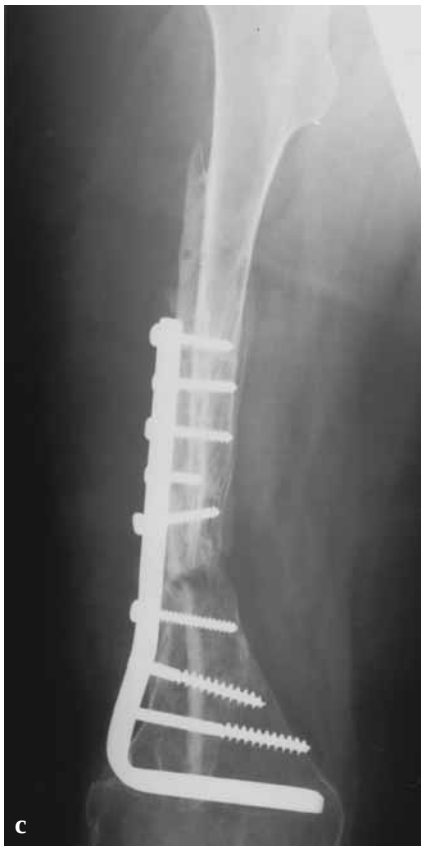


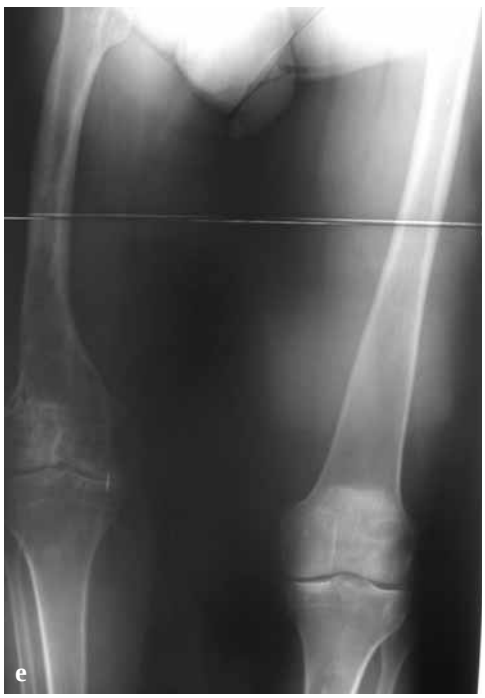
Fig. 2a. — A-P view of the right femur showing fracture of the shaft through the biopsy lesion. There are irregular osteolytic changes. Some callus formation is seen on the lateral side.

Fig. 2b. — Radiograph after one year, showing markedly increased osteolysis in spite of radiotherapy. There is a typical tapered 'sucked candy' deformation of the proximal femur, without any callus formation.

Fig. 2c. — An autogenous tibial graft, implanted because of an ununited fracture, has fractured, and internal fixation with a condylar plate has been necessary. The graft has not resorbed.

Fig. 2d. — At follow-up, 28 years later, the femur is shortened but remarkable remodeling is visible.

Fig. 2e. — Normal alignment of the right lower limb. Shoe adjustment on the affected site.



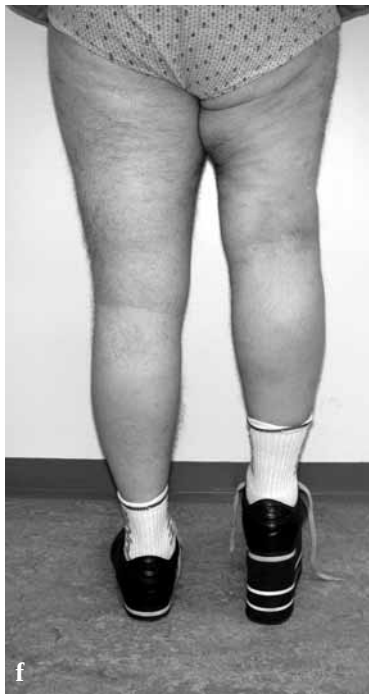


Table I. — Reported cases of Gorham's massive osteolysis of the femur

Number	*Patient + age*	*First Author*	*Localisation in the femur.*	*Fracture*	*Treatment*	*Follow-up*
1	M 21	Richard '37	Proximal	Yes	salicylate ?	3 yr
2	M 11	King '46	Middle	Unknown	Mid-thigh amputation	3 yr
3	F 18	Aston '58	Middle	Yes	Autogenous tibial graft, above-knee amputation	6 yr
4	M 13	Branco '58	Proximal	Yes	Radiation therapy, transfusion, hormonal therapy (testosterone), amputation	12 yr
5	F 12	Kery '58	Proximal	Yes	Splint	2 yr
6	M 5	Butler '58	Middle	Yes	Traction, vitamin D, splint, autogenous bone grafts	10 yr
7	M 59	Fornasier '70	Middle	Yes	Intramedullary nailing, above-knee amputation because of haemorrhage	6 yr
8	F 19	Cannon '86	Distal	Yes	Bone graft, total knee arthroplasty	11 yr
9	F 12	Mendez '89	Proximal	Yes	ORIF (compression plate), chemotherapy (cis-platinum, actinomycin D), hip disarticulation	2 yr
10	F 20	Friedman '91	Distal	Yes	ORIF (angled plate), distal femur resection, total knee arthroplasty	2 yr
11	M 14	Shives '93	Proximal	Yes	ORIF, bone graft, electrical stimulation, radiation therapy (20 Gy), hip disarticulation	≥ 3 yr
12	F 27	Shives '93	Proximal	Yes	Nail, autogenous bone graft, radiation therapy (30 Gy), rush pin, total hip arthroplasty	≥ 3 yr
13	F 7	Shives '93	Proximal	Yes	Curettage, autogenous bone graft,internal fixation, total hip arthroplasty	≥ 3 yr
14	F 12	Kareem '94	Proximal	Yes	Calcitonin nasal spray	4 yr
15	M 11	Dominguez '94	Proximal	Yes	None, surgery and chemotherapy refused	8 yr
16	M 31	Giraudet '95	Proximal	Yes	Total hip arthroplasty with allograft, radiation therapy (45 Gy)	6 m
17	M 55	Pazzaglia '97	Proximal	Yes	Dynamic hip screw plate, curettage, cement, total hip arthroplasty	4 yr
18	F 77	Möller '99	Proximal	No	Local resection, total hip arthroplasty	6 m
19	F 70	Möller '99	Proximal	No	Total hip arthroplasty	3 yr
20	F 20	Yoo '02	Proximal	Yes	Further treatment unknown	10 yr
21	F 5	Somoza '03	Middle	Yes	Biphosphonates	2 yr
22	M 14	van der Linden '05	Middle	Yes	Autogenous tibial bone graft, ORIF (angled plate), radiation therapy (30 + 45 Gy)	27 yr

Two patients died : one because of infection with *Staphylococci* (case 5), and one following extension into the pelvis (case 14). This also occurred in case 4, but without a lethal issue.

Aetiology and pathogenesis

The aetiology and pathogenesis of Gorham's disease remain unknown. It often takes a long time before the diagnosis is made. It has histologically benign features but may extend rapidly and aggressively, thereby leading to serious complications and even death.

Exclusive involvement of the femur is uncommon.

Diagnosis

Localised pain is the usual presenting symptom. Sometimes a minor trauma is mentioned, possibly triggering the disease (*8*). Occasionally there is some soft tissue swelling (*11, 26*). Biochemical and haematological tests including serum calcium and alkaline phosphatase are usually normal despite extensive bone resorption.

The diagnosis is based on anamnestic data (no heredity), biochemical data (no nephropathy), radiographic data (osteolysis), and histological data (intraosseous growth of vessels, either capillaries or lymphatics, or both, leading to osteolysis ; progressive fibrosis). The differential diagnosis includes skeletal angioma, skeletal sarcoma, endothelioma, osteomyelitis, metastasis and other forms of osteolysis (*3, 20*).

Histology

The main structural feature is the replacement of bone by an aggressively expanding angiomatous or lymphatic tissue, sometimes both (*3*). Criteria formulated by Heffez (*12*) to distinguish Gorham's disease from other bone destructive conditions are : positive biopsy for angiomatous or lymphatic tissue without cellular atypia, minimal or absent osteoblastic response, no dystrophic calcification, progressive bone resorption, no visceral involvement, no hereditary background, absence of metabolic, neoplastic, immunologic or infectious aetiology. According to Johnson and McClure (*14*) there are two stages : the first with vascular proliferation, followed by a second stage in which residual fibrous tissue replaces resorbed bone. The pathologic findings in our case presented above were consistent with the literature and revealed more lymphatic than vascular invasion of the bone (fig 1a, 1b) (*10, 18, 22*).

Role of osteoclasts

The normal serum level of calcium and alkaline phosphatase suggests a lack of osteoclastic activity in the underlying process. In the literature there is controversy regarding the presence or absence of osteoclasts (*7*). However, recent studies showed that osteoclasts do play an important if partial role (*2, 25*). Möller *et al* (*20*) stated that the resorption is due to an increased number of (hyperactive) osteoclasts. Perivascularly arranged cells with strong acid phosphatase and leucine aminopeptidase activities might also play a role (*13*). In our patient there was no increase in the number of osteoclasts at the site of resorption (fig 2b).

Imaging

In an early stage, *plain radiographs* demonstrate progressive bone destruction without any periosteal reaction. It starts with intramedullary and subcortical foci resembling "patchy osteoporosis". Subsequently these foci enlarge and coalesce. The extraosseous stage begins with the onset of cortical erosion and adjacent soft tissue involvement. In later stages, gradual tapering and progressive resorption of cortical bone is one of the most characteristic features, giving the appearance of "sucked candy" (fig 1b), possibly due to resorption resulting from pressure by the extra-osseous soft tissue component (*9, 14*). The bone is now replaced with fibrous tissue. Absence of new bone formation, even under the stimulus of a pathological fracture, is typical. Gorham's massive osteolysis is radiologically distinguishable from a skeletal haemangioma by its more extensive destruction.

There are very few reports about *scintigraphic* findings in Gorham's disease (*6, 25, 26*) ; most often there is no or slightly increased uptake (*2*). *Arteriography, venography, and/or lymphography* show no or only indirect evidence of a tumour. In our case an arteriogram showed no abnormal vessels, unlike the findings in angiomatous malformations. The use of *CT and/or MRI* was described in more recent articles (*6, 17, 25, 29, 30*). There is usually a low-signal intensity on T1-weighted images, a high-signal intensity on T2-weighted images, and contrast-enhancement. The variability of signal intensity on T1- and T2-weighted images is likely to be caused by the variable degree of neovascular progression and fibrosis, or by the proportion of vascular and / or lymphatic tissue (*28*).

Treatment and prognosis

Treatment aims at arresting the growth of angiomatous tissue, and thus the progression of bone resorption. Moreover, treatment focuses on the prevention of complications. Often different treatment methods have been used at the same time ; this and the variable localisation and course of the disease make evaluation of their efficacy difficult. Sixteen different treatment methods were used in the 22 listed cases of femoral osteolysis. The prognosis *quo ad vitam* depends on the extent of involvement and presence or absence of complications, such as pathological fractures. The overall mortality rate is 13%, increasing to 33% when the spine is involved and even to 52% when the thorax is involved (*5*).

Radiotherapy

The radiosensitivity of the endothelial cells of proliferating capillary-like or lymphatic-like vessels is thought to be essential because of the intended involution of the angiomatous tissue after radiotherapy. The possible positive effect of radiation (30 up to 45 Gy) was first published in 1958 and was confirmed later on (*5, 13, 14*). Even after unsuccessful operative treatment, complete arrest with radiation therapy has been described. Sometimes (partial) recalcification or regrowth of the destroyed bone is seen (*13*). However, other studies showed only temporary response or even no response at all to 40 Gy radiation, with or without previous surgery (*2, 4, 10, 26*). A moderate dose of 30 to 45 Gy in 2 Gy fractions is advised and is generally used. In recent years, radiation therapy has been used, either immediately at the time of diagnosis, to prevent extension of the process, or later on for the treatment of complications. In our case, after initial radiotherapy (25 Gy femur, 33 Gy at fracture site), the therapy was prolonged with a further dose of 45 Gy, because of progressing osteolysis. Eventually, 5 months after the last radiation course the osteolysis stopped. There was even recalcification and remodelling. Among the other 21 cases, four patients (number 4, 11, 12, and 16) had one or more courses of radiation therapy with 20 to 45 Gy or less, which stopped the progression in cases 12 and 16. The long-term effectiveness or even risks of radiation therapy in Gorham's disease are not known. But the dose used is the same as in hamartoma and juvenile angiofibroma. The risk of radiation-induced cancer following treatment of these diseases is low.

Anti-osteoclastic/-neovascularisation medication

Biphosphonates are considered as a useful conservative treatment method because of their anti-osteoclastic action (*24*), but they are not always successful. Their success can only be expected when osteoclasts are a major factor in the disease.

Also the use of Interferon-alpha has been reported recently, given its inhibiting effect on haemangiomata. Whether gene-therapy can be used in Gorham's disease is still unknown. In recent times, more became known about the genes involved in the differentiation and function of osteoclasts and their role in bone resorption (*27*). Inhibition of osteoclast function by an adenovirus expressing antisense protein-tyrosine kinase 2 or adenovirus vector induced csk gene has already been studied (*16*). Another possible 'genetic'-target is the neo-vascularisation : Vikkula *et al* in 2001 (*28*) have identified mutated genes in vascular malformations, directly giving proof of their important role

in the regulation of angiogenesis. Enhancing the anti-tumour efficacy of radiation therapy might also be possible using recombinant viral-mediated gene transfer. Last but not least, even the possibility of new bone formation / osteo-induction by gene-therapy has recently been described in animals.

Treatment of pathological fractures

Fractures must be frequent, given the tendency of the osteolysis to extension (*2*). In many cases the disease is not recognised until a fracture occurs. A fracture was reported in 19 of the 22 cases of primary femoral osteolysis which we listed. Four patients (number 5, 7, 9, 20) had a fracture at the time of presentation ; in two patients the fracture occurred subsequently through the site of the open biopsy. There was callus formation in 3 (number 4, 7 and 22) of the 19 fracture cases, but later on it was reabsorbed. In general, although a tendency towards fracture healing is seen, the fractures fail to unite. Maybe the fracture itself acts as a further trigger to the disease.

As the bone is replaced by vascular or lymphatic tissue, fracture healing is delayed or hampered and the osteolytic process can continue through the fragments (*9, 12*). Re-osteolysis of the callus is also possible : we saw this in a single patient. There is no consensus about the most efficacious treatment of pathologic fractures in Gorham's disease. In earlier series surgical treatment has consisted of autogenous bone grafting with or without internal fixation, amputation, or local resection, with and without replacement arthroplasty.

Bone grafting

Attempts at bone grafting have met with variable success, sometimes because of involvement of the graft in the osteolytic process (*10*). Complete reabsorption of the graft (allogeneic corticocancellous chips or even a rigid cortical strut) similar to that of the original bone has been noted (*2, 4, 5, 13, 18*). On the other hand, an autologous bone graft has led to a definitive cure in a few cases (*2*).

Amputation or arthroplasty

In 6 of the 22 patients we collected, an above-knee amputation or hip disarticulation was performed, after failure of other treatment modalities. Massive osteolysis treated by local resection and prosthetic replacement was first described by Poirier (*22*) in 1968. There were no recurrences afterwards. Nowadays even larger resections are possible, since special prostheses have become available. The current series includes two patients with osteolysis of the distal femur, successfully treated with total knee arthroplasty (number 8 and 10), and five patients with osteolysis of the proximal femur, treated with total hip arthroplasty. One (number 13) needed a revision because of a stem fracture. Radiation therapy was used in only two of them.

Spontaneous arrest

Spontaneous arrest of the process is possible after a variable number of years (*7, 11, 15*). This means that it is difficult to assess the results of radiotherapy and other conservative treatment modalities.

CONCLUSION

Gorham's massive osteolysis in general but especially when primarily involving the femur is a rare entity, which explains why the diagnosis is often missed initially**.** It almost always leads to a pathological fracture in the proximal femur. The current treatment trend is towards arthroplasty or in some cases amputation, combined with radiation therapy.

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