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Review

Viewpoints on vessels and vanishing bones in Gorham–Stout disease

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ABSTRACT

Gorham–Stout disease (GSD) is a rare disorder characterized by the proliferation of endothelial-lined vessels in bone and the progressive destruction of bone. Although Jackson described the first case of GSD in 1838, the clinical and histological features of GSD were not defined until Gorham and Stout published their report on massive osteolysis in 1955. In the years since Gorham and Stout's groundbreaking publication, more than 300 cases of GSD have been described in the literature. These reports have revealed that the progressive resorption of bone in GSD causes severe physical deformities, disabilities, and life-threatening complications. Unfortunately, the underlying cause of GSD remains unknown and, as a result, the therapeutic options for individuals with GSD are limited. Here we review the latest advances in GSD research and present strategies to address basic and clinical research questions related to GSD.

Contents

Introduction

Gorham–Stout disease (GSD, also known as massive osteolysis, vanishing bone disease, phantom bone disease, Gorham's disease and Gorham–Stout syndrome) is a rare disease of unknown etiology characterized histologically by the proliferation of endothelial-lined vessels in bone and by the replacement of bone with fibrous tissue [1]. In 1838, J.B.S. Jackson published the first case of GSD [2]. In his paper titled "A

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Boneless Arm", Jackson describes Mr. Brown, a patient whose entire humerus gradually disappeared over a period of several years [2]. Over 100 years would pass before another substantial report on massive osteolysis would be published [3]. In 1954, Gorham and colleagues published a report on the histological changes they observed in a patient with massive osteolysis [3]. They found that several of the affected bones from their patient displayed a dramatic increase in vascularity [3]. This crucial finding, as well as previous reports describing vascular changes accompanying massive osteolysis [4–8], prompted Gorham and Stout to further define the histological and clinical features of massive osteolysis. By evaluating histological samples from 8 previously studied cases, Gorham and Stout were able to firmly establish that massive osteolysis is accompanied by the extensive proliferation of endothelial-lined channels in bone [1]. Furthermore, by reviewing an additional 16 cases from the literature, they were able to provide the first detailed report on the clinical features of this rare disease [1]. Despite advances in clinical and basic science research since Gorham and Stout's publication in 1955, much still remains unknown about the pathology of GSD. This lack of knowledge has hindered the identification of effective therapies for treating this devastating disease. To address this need, the Lymphatic Malformation Institute (LMI) and Lymphangiomatosis & Gorham's Disease Alliance (LGDA) recently sponsored an international scientific conference focused on developing strategies to address many of the basic and clinical research questions related to GSD. In this review we summarize clinical information for 185 previously published cases of GSD, highlight the latest advances in GSD research and address unanswered questions related to GSD.

Clinical features of GSD

GSD can present at any age (age range is from 7 months to 83 years), but is most commonly diagnosed in children and young adults (average age of diagnosis is 25 years; Supplemental Table 1). The disease does not display a clear sex predilection (1.6:1 male-to-female ratio; Supplemental Table 1) or inheritance pattern [9]. Although GSD can affect any bone in the body, it frequently affects the maxilla, mandible, clavicle, ribs, cervical vertebrae, pelvis and femur (Supplemental Table 1). Areas of bone resorption can arise in a single bone or in multiple contiguous bones (Supplemental Table 1). Osteolytic lesions in patients with GSD initially appear as small radiolucent foci in radiographic images [10]. These foci enlarge and coalesce as the disease progresses [10]. Additionally, tubular bones undergo concentric shrinkage causing them to have a "sucked candy" appearance. In severe cases, this process continues until the entire bone is resorbed and replaced by fibrous tissue. Eventually, for reasons that are not entirely clear, the disease can spontaneously arrest and stabilize. Importantly, new bone does not form to a notable extent after the disease has stabilized [1].

The symptoms of GSD vary and depend on which sites in the body are affected. The most common symptom is localized pain (Supplemental Table 1). Other symptoms include swelling, weakness and functional impairment of affected limbs. GSD patients may be asymptomatic until they suffer a bone fracture either spontaneously or following minor trauma. Patients with thoracic involvement may seek medical attention because they have difficulty breathing. This is typically caused by chylothorax, an accumulation of chyle (lymph rich in fat) in the pleural cavity [11]. Approximately 25% of GSD patients develop chylothorax, which can result in respiratory distress and failure (Supplemental Table 1). Additionally, involvement of the vertebrae can cause severe neurological defects, deformity, paralysis, and death.

Histological features of GSD

Gorham and Stout evaluated biopsy specimens from 8 previously reported cases of massive osteolysis to determine whether these patients displayed similar histopathological alterations in their affected tissues. They observed that the affected bone, and the fibrous tissue that had replaced bone, contained numerous dilated endothelial-lined vessels [1]. Numerous other investigators have observed the same changes in sections of affected bones stained with hematoxylin and eosin. However, the identity of the deranged vessels differs from case to case. In some cases, the abnormal channels are reported to be blood vessels [1,3,12–14] whereas in other cases they are reported to be lymphatic vessels [4,15–17]. The emergence of immunohistochemical markers of lymphatic endothelial cells has greatly facilitated the characterization of the abnormal vessels in GSD. Two commonly used molecular markers of lymphatic endothelial cells are LYVE-1, a receptor for the glycosaminoglycan hyaluronan, and podoplanin, a transmembrane glycoprotein recognized by the antibody D2-40 [18,19]. These markers have revealed that lymphatic vessels are not present in normal bones [20], but are present in medullary and cortical regions of bones in patients with GSD [20–25]. Affected soft tissues in GSD patients also display abnormal lymphatic vessels [26,27]. Although numerous lymphatic vessels are present in affected tissues in GSD, they are not widely labeled by MIB-1, a monoclonal antibody against the proliferation marker Ki-67 [21,28]. Therefore, according to the International Society for the Study of Vascular Anomalies (ISSVA) classification system, the lymphatic anomaly in GSD is a malformation rather than a tumor [21]. Together, these observations suggest that lymphatic vessels rather than blood vessels are primarily affected in GSD.

Etiology of GSD

The cause of excessive bone resorption in GSD is unclear. In the following sections we discuss the potential role of endothelial cells, osteoclasts and osteoblasts in the pathogenesis of GSD (Fig. 1).

Endothelial cells

Several investigators have proposed that the abnormal endothelial-lined channels in osteolytic zones promote bone resorption. Gorham and Stout believed that the local proliferation of endothelial-lined vessels could promote bone loss by increasing blood flow, changing local pH, or by exerting mechanical force [1]. Heyden et al. proposed that sluggish blood flow in osteolytic areas might cause local hypoxia, which could lower tissue pH and favor the activity of hydrolytic enzymes [29]. Importantly, these ideas attempt to explain how blood vessels could promote bone loss in GSD. However, there is mounting evidence that lymphatic vessels are primarily affected in GSD. The uncontrolled growth of fluid-filled lymphatic vessels could cause osteolysis by compressing bone. Alternatively, lymphatic endothelial cells may secrete factors that influence the activity of osteoclasts and/or osteoblasts.

Lymphangiogenesis, which is the sprouting of new lymphatic vessels from pre-existing vessels, occurs in an uncontrolled fashion in GSD. This process is driven, in part, by growth factors in the microenvironment that activate receptors on the surface of lymphatic endothelial cells. Members of the vascular endothelial growth factor (VEGF) family are thought to be the most important factors that drive lymphangiogenesis [30–32]. One prominent lymphangiogenic member of this family is VEGF-C, a ligand of the receptor tyrosine kinases VEGFR2 and VEGFR3 [33,34]. Although the signaling pathways stimulating lymphangiogenesis in many pathological settings have been characterized, the pathways driving lymphangiogenesis in GSD have not been defined. It is possible that a local increase in the level of VEGF-C or of another pro-lymphangiogenic factor (VEGF-A, -D, Ang-1, -2, etc.) could stimulate lymphangiogenesis in GSD [35–38]. Indeed, VEGF-C has been found to be elevated in the serum of one GSD patient [27] and VEGF-A has been found to be elevated in the serum of three GSD patients [27,39] and in the plasma of another patient [40] (Table 1). Alternatively, a decrease in the level of an anti-lymphangiogenic factor (sVEGFR2 [41], TGF-β [42], IFN-γ [43], etc.) could promote the uncontrolled growth of lymphatic vessels in the bones of patients with GSD.

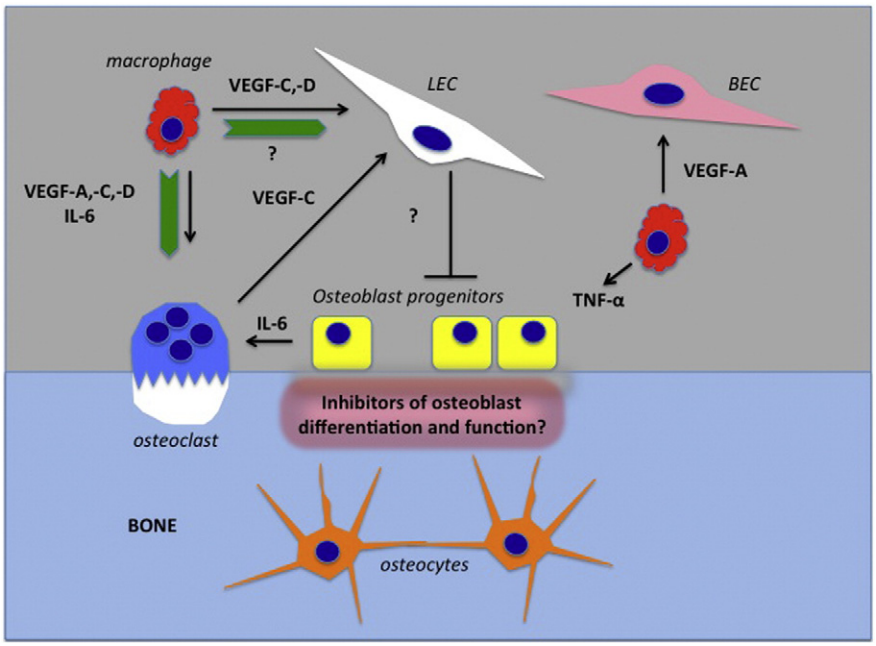

Fig. 1. Diagram illustrating cells and interactions that likely contribute to the disease mechanism in GSD. The proliferation of lymphatic endothelial cells (LECs) and blood endothelial cells (BECs) could be stimulated by increased levels of VEGF-C, and -D and macrophage-derived VEGF-A. Macrophages may also contribute to the formation of LECs and are the progenitors of osteoclasts (block arrows). In addition, they produce VEGF-A, -C, and -D and interleukin 6 (IL-6); all stimulate osteoclast differentiation. Osteoblast progenitor cells may be inhibited in their differentiation and function by factors secreted by LECs and by factors produced by osteocytes, including sclerostin, and Dickkopf- and soluble frizzled-related proteins. Although low levels of TNF-α can stimulate stromal cell recruitment and osteogenic differentiation [91], high levels of TNF-α produced by macrophages inhibit osteoblast differentiation and enhance osteoclastogenesis by stimulating RANKL production by stromal cells.

Osteoclasts

Osteoclasts are multi-nucleated cells, differentiated from myeloid progenitors, that resorb bone by locally secreting proteolytic enzymes and hydrogen ions [44]. Several growth factors and cytokines regulate their differentiation and activity, including the stimulatory factors CSF-1 (M-CSF), RANKL, IL-6, TNF-α, VEGF-A and VEGF-C and the inhibitory factor osteoprotegerin (OPG). Hyperactive osteoclasts participate in the pathogenesis of several human skeletal disorders in which bone is lost, including cherubism [45], familial expansile osteolysis [46], and juvenile Paget disease (also known as familial hyperphosphatasia) [47]. However, there are conflicting reports on whether osteoclasts are present in osteolytic zones in GSD. In fact, while some investigators have observed osteoclasts in osteolytic zones [12,13,21,48–56], Gorham and Stout, as well as other investigators, have reported that osteoclasts are not present in areas of bone resorption [1,15,29,57,58]. The reason for this discrepancy is unclear, but it has been proposed that it may be due to evaluations being conducted at different phases (active versus stable) of the disease [59].

Whether this explanation is correct is not clear, but studies of some cases of GSD suggest that patient osteoclast progenitor cells may be more sensitive to the osteoclast-inducing factors CSF-1 and RANKL than control cells [51] and that patient serum can induce osteoclast formation in an IL-6-dependent manner [60]. In addition, histochemistry and electron microscopy of tissue isolated from GSD bone lesions indicate the presence of an increased number of pericyte/macrophage-like mononuclear cells with abundant acid phosphatase positive lysosomal bodies [29,61]. These macrophage-like cells may serve as progenitors of osteoclasts in GSD lesions. In addition, macrophages are known to produce VEGF-A, VEGF-C and VEGF-D [62] and all three factors are able to stimulate osteoclast differentiation and lymphangiogenesis [63–65]. Finally, in an inflammatory environment macrophages may even directly contribute to lymphangiogenesis by expressing markers of lymphatic endothelium and forming tube-like structures [66,67].

Table 1
Circulating levels of biomarkers in patients with Gorham–Stout disease.

Protein	Level during active phase of disease	Level during inactive phase of disease	Reported normal value(s)	Reference
VEGF-A	163 pg/ml (Plasma)	25 pg/ml (Plasma)	1–63 pg/ml (Plasma)	Dupond et al. [40]
VEGF-A	277 pg/ml (Serum)	161 pg/ml (Serum)	50 pg/ml (Serum)	Morimoto et al. [39]
VEGF-A	730 pg/ml (Serum)	570 pg/ml (Serum)	62–707 pg/ml (Serum)	Brodszki et al. [27]
VEGF-A	1200 pg/ml (Serum)	370 pg/ml (Serum)	62–707 pg/ml (Serum)	Brodszki et al. [27]
VEGF-A	100 pg/ml (Serum)	N/A	N/A	Hagendoorn et al. [26]
VEGF-C	4050 pg/ml (Serum)	3910 pg/ml (Serum)	2459–6651 pg/ml (Serum)	Brodszki et al. [27]
VEGF-C	6930 pg/ml (Serum)	2260 pg/ml (Serum)	2459–6651 pg/ml (Serum)	Brodszki et al. [27]
PDGF-BB	108 pg/ml (Serum)	N/A	15 pg/ml (Serum)	Hagendoorn et al. [26]
IL-6	7 pg/ml (Serum)	15 pg/ml (Serum)	<8 pg/ml (Serum)	Brodszki et al. [27]
IL-6	6.7 times higher than the upper limit of the normal range	1.9 times higher than the upper limit of the normal range	N/A	Plasswilm et al. [76]
IL-6	8.4 pg/ml (Serum)	<5.4 pg/ml (Serum)	<5.0 pg/ml (Serum)	Hammer et al. [50]
IL-6	7 times higher than the upper limit of the normal range	1.75 times higher than the upper limit of the normal range	N/A	Devlin et al. [60]
IL-6	71.1 pg/ml (Serum)	N/A	<4.0 pg/ml (Serum)	Fujiu et al. [15]

Osteoblasts

A remarkable aspect of the osteolytic process in GSD is the absence of evidence for increased osteoblast activity along surfaces of remaining bone fragments in sections of affected tissues [61]. This is quite different from other skeletal disorders with bone loss due to increased differentiation and activity of osteoclasts. For example, the massive loss of maxillary and mandibular bones in cherubism, caused by mutations that result in increased sensitivity of myeloid cells to macrophage- and osteoclast-inducing signals [45], is associated with a robust increase in osteoblast activity. In active GSD lesions the disappearing bone is replaced by fibrovascular tissue rather than newly formed woven repair bone. Particularly striking are observations that osteoblastic cells within active lesions exhibit ultrastructural features suggesting that they have either decreased synthetic activity or are degenerating [61]. Finally, osteocytes within bone tissue close to the lesions have been reported to having pyknotic nuclei and occupying enlarged lacunae [29,61].

This lack of an osteoblastic repair response in GSD lesions is particularly puzzling in view of the high circulating levels of VEGF-A reported for many GSD patients [27,40,68] and the strong evidence that VEGF-A stimulates bone repair by promoting angiogenesis and bone turnover [69]. Also puzzling is that this loss of an osteoblastic response is restricted to the vanishing bone(s), while bone homeostasis appears to be relatively unaffected in other parts of the skeleton. This suggests that the pathophysiological events causing osteolysis in GSD are localized and that factors produced in the process might stimulate mesenchymal progenitors to differentiate along the fibroblastic, rather than osteoblastic lineage. The role of osteocytes in regulating osteoblast differentiation and activity may be important in this context. Osteocytes release factors that stimulate osteoblast differentiation [70,71] and recruitment of mesenchymal stem cells to bone fracture sites [72] and they inhibit osteoblast differentiation by producing Wnt signaling inhibitors such as sclerostin, Dickkopf-related proteins and soluble frizzled-related proteins [73]. Thus, it is possible that changes in such osteocyte-produced factors may contribute to the lack of osteoblastic repair responses in GSD.

Genetics and GSD

GSD is a sporadic disease potentially caused by specific genetic risk factors or by mosaicism for a somatic mutation. Approaches that have been used to identify the genetic basis of other sporadic diseases could be used to search for mutations that may be contributing to GSD. For example, Proteus and CLOVES are two sporadic overgrowth syndromes caused by somatic activating mutations in *AKT1* and *PIK3CA*, respectively [74,75]. These mutations were found by sequencing DNA purified from affected tissues. Importantly, the disease causing mutations were not present in DNA isolated from the blood or saliva of patients. Therefore, it has been suggested that DNA purified from affected tissues, rather than blood or saliva, be analyzed to search for the potential genetic underpinnings of GSD. Unfortunately, affected bones from GSD patients are frequently fixed, decalcified with acid, and embedded in paraffin, which makes exome sequencing technically challenging. To overcome this obstacle, it has been recommended that DNA from fresh tissues or from cell lines derived from affected tissues be used in exome sequencing experiments. Identification of mutations associated with GSD would help direct the development of animal models and the search for therapeutic strategies.

Biomarkers for monitoring the activity of GSD

The clinical course of GSD is unpredictable. In some patients the disease progresses slowly whereas in others it progresses rapidly and causes severe disability. A current challenge in the clinic is identifying which patients fall into the latter category and require close monitoring and aggressive treatment. To address this problem, several studies have examined whether lymphangiogenic and osteoclastogenic factors could serve as biomarkers of disease activity in GSD. Most of these reports have centered on the growth factor VEGF-A [27,39,40] and the cytokine IL-6 [15,50,60,76]. These studies have shown that VEGF-A and IL-6 can be elevated in the circulation of patients with GSD and that the level of these factors can decrease following treatment with various therapies (Table 1). However, VEGF-A [26] and IL-6 [27] are not elevated in all GSD patients. Therefore, additional factors are being analyzed with the hope of finding additional biomarkers. Other factors evaluated in the circulation of GSD patients include VEGF-C [27], PDGF-BB [26], sRANKL [50], and osteoprotegerin [50] (Table 1). While the clinical diversity of GSD makes it unlikely that a single biomarker for all GSD patients can be found, a universal set of biomarkers to monitor disease activity could provide diagnostic, prognostic or predictive information.

Therapies for treating GSD

Depending on the severity of the disease, the extent of organ-involvement and other signs, different strategies are used to treat GSD. These strategies include surgery, radiotherapy and pharmaceuticals (Supplemental Table 1). Surgery for GSD mainly consists of interventions to reduce or halt fluid build-up in the pleural cavity and these interventions include pleurectomy, pleurodesis, thoracentesis, and thoracic duct embolization or ligation [9]. Surgery is also performed to stabilize affected regions of the skeleton once the disease appears to have stabilized [77]. Radiotherapy has been used in cases where surgery is not possible or in combination with surgery [78–80]. Several case reports have described the successful use of radiotherapy, with an overall success rate in the case of local lesions being about 75% [78]. A total of 36–45 Gy, given in 2 Gy portions, appears to provide the most therapeutic benefit [78,79,81,82]. Several pharmaceuticals have also been used to treat patients with GSD [9]. However, since pharmaceuticals are most often used in combination with other therapeutic approaches, it is difficult to assess the benefit of the administered pharmaceutical(s). Moreover, a consensus regarding the effectiveness of specific pharmaceuticals cannot be derived from a review of the available literature. The most commonly prescribed pharmaceuticals to treat GSD are bisphosphonates and interferon alpha 2b [23,26,48,50,83–86]. These have been used as single agents or in combination with one another. Other pharmaceuticals that have been used to treat GSD include the anti-VEGF-A antibody, Bevacizumab [87], propranolol [88], low molecular weight heparin [27], steroids, vitamin D, and calcitonin [9].

Clinical trials are needed to test the efficacy of existing and emerging therapies against GSD. An ongoing clinical trial is testing the efficacy of the mTOR inhibitor rapamycin (Sirolimus) in children and young adults with several different vascular anomalies involving bone, including GSD (www.clinicaltrials.gov; NCT00975819) [89,90]. Preliminary, but promising, findings from this trial were presented at the 1st International Conference on Generalized Lymphatic Anomaly and Gorham–Stout Syndrome held in Bethesda, MD in June 2013 and the final results from the study are expected in mid-2014. In the future, the recently launched Lymphangiomatosis & Gorham's Disease Alliance global patient registry (www.LGDARegistry.org) and Boston Children's Hospital lymphatic anomalies registry (contact the Vascular Anomalies Center at BCH for more information) could help gather patients for new trials.

GSD and generalized lymphatic anomaly

Generalized lymphatic anomaly (GLA, also known as lymphangiomatosis) is a rare disease highly related to GSD. GLA is characterized by the extensive proliferation of lymphatic vessels and frequently affects bone. A retrospective review of 32 GLA and 19 GSD patients in the Vascular Anomalies Center database at Boston Children's Hospital revealed that GLA and GSD patients display differences in bone disease [25]. GLA patients display lytic areas confined to the medullary cavity whereas GSD patients display progressive osteolysis resulting in the loss of cortical bone [25]. GLA patients typically have more bones

involved than GSD patients and the appendicular skeleton is more frequently involved in GLA than GSD patients [25]. Macrocystic lymphatic malformations are also more frequently observed in GLA than GSD patients [25]. Affected bones from GLA and GSD patients display abnormal lymphatic channels and appear similar to one another histologically [25]. Continued study of GLA and GSD will help delineate the clinical, histological, and genetic similarities and differences between these two rare diseases.

Concluding remarks

Our understanding of the features of GSD has increased dramatically since Gorham and Stout's publication in 1955. Case reports and case series have shed light on the disease process, identified potential biomarkers for monitoring disease activity, and pointed towards specific therapies for treating GSD. Despite these advances, much still remains unknown about GSD. The molecular mechanisms driving osteolysis and lymphangiogenesis in GSD remain unclear, a genetic basis of GSD has not been defined, and there are no FDA approved therapies for treating GSD. Importantly, numerous research projects are currently underway to address these and other basic science and clinical research questions. Together, these efforts will lead to a deeper understanding of the etiology of GSD and help identify therapies to treat patients suffering from this insidious disease.

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Conflict of interest

The authors declare no conflict of interest.

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References

[1] Gorham LW, Stout AP. Massive osteolysis (acute spontaneous absorption of bone, phantom bone, disappearing bone); its relation to hemangiomatosis. J Bone Joint Surg Am 1955;37-A:985–1004.
[2] Jackson JBS. A boneless arm. Boston Med Surg J 1838;18:368–9.
[3] Gorham LW, Wright AW, Shultz HH, Maxon Jr FC. Disappearing bones: a rare form of massive osteolysis; report of two cases, one with autopsy findings. Am J Med 1954;17:674–82.
[4] Bickel WH, Brodere AC. Primary lymphangioma of the ilium; report of a case. J Bone Joint Surg Am 1947;29:517–22.
[5] Branch HE. Acute spontaneous absorption of bone — report of a case involving a clavicle and a scapula. J Bone Joint Surg 1945;27:706–10.
[6] King DJ. A case resembling hemangiomatosis of the lower extremity. J Bone Joint Surg Am 1946;28:623–8.
[7] Simpson BS. An unusual case of post-traumatic decalcification of the bones of the foot. J Bone Joint Surg 1937;19:223–7.
[8] Thoma KH. A case of progressive atrophy of the facial bones with complete atrophy of the mandible. J Bone Joint Surg 1933;15:494–501.
[9] Patel DV. Gorham's disease or massive osteolysis. Clin Med Res 2005;3:65–74.
[10] Johnson PM, Mc CJ. Observations on massive osteolysis; a review of the literature and report of a case. Radiology 1958;71:28–42.
[11] Tie ML, Poland GA, Rosenow III EC. Chylothorax in Gorham's syndrome. A common complication of a rare disease. Chest 1994;105:208–13.
[12] Jones GB, Midgley RL, Smith GS. Massive osteolysis: disappearing bones. J Bone Joint Surg Br 1958;40-B:494–501.
[13] Pazzaglia UE, Andrini L, Bonato M, Leutner M. Pathology of disappearing bone disease: a case report with immunohistochemical study. Int Orthop 1997;21:303–7.
[14] Yoo SY, Hong SH, Chung HW, Choi JA, Kim CJ, et al. MRI of Gorham's disease: findings in two cases. Skeletal Radiol 2002;31:301–6.
[15] Fujiu K, Kanno R, Suzuki H, Nakamura N, Gotoh M. Chylothorax associated with massive osteolysis (Gorham's syndrome). Ann Thorac Surg 2002;73:1956–7.
[16] Riantawan P, Tansupasawasdikul S, Subhannachart P. Bilateral chylothorax complicating massive osteolysis (Gorham's syndrome). Thorax 1996;51:1277–8.
[17] Lee S, Finn L, Sze RW, Perkins JA, Sie KC. Gorham Stout syndrome (disappearing bone disease): two additional case reports and a review of the literature. Arch Otolaryngol Head Neck Surg 2003;129:1340–3.
[18] Banerji S, Ni J, Wang SX, Clasper S, Su J, et al. LYVE-1, a new homologue of the CD44 glycoprotein, is a lymph-specific receptor for hyaluronan. J Cell Biol 1999;144:789–801.
[19] Kahn HJ, Bailey D, Marks A. Monoclonal antibody D2-40, a new marker of lymphatic endothelium, reacts with Kaposi's sarcoma and a subset of angiosarcomas. Mod Pathol 2002;15:434–40.
[20] Edwards JR, Williams K, Kindblom LG, Meis-Kindblom JM, Hogendoorn PC, et al. Lymphatics and bone. Hum Pathol 2008;39:49–55.
[21] Bruder E, Perez-Atayde AR, Jundt G, Alomari AI, Rischewski J, et al. Vascular lesions of bone in children, adolescents, and young adults. A clinicopathologic reappraisal and application of the ISSVA classification. Virchows Arch 2009;454:161–79.
[22] Atalabi OM, Fishman SJ, Kozakewich HP, Alsamarah AY, Alomari AI. A lethal form of Gorham disease associated with extensive musculoskeletal pneumatosis: case report and review of the literature. Skeletal Radiol 2008;37:1041–6.
[23] Leite I, Hernandez-Martin A, Colmenero I, Lopez-Gutierrez JC, Torrelo A. Invasive lymphatic malformation (gorham–stout) of the pelvis with prominent skin involvement. Pediatr Dermatol 2013;30:374–8.
[24] Situma M, Alexander A, Weiselthaler N, Millar A. An aggressive lymphatic malformation (Gorham's disease) leading to death of a child. J Pediatr Surg 2013;48:239–42.
[25] Lala S, Mulliken JB, Alomari AI, Fishman SJ, Kozakewich HP, et al. Gorham–Stout disease and generalized lymphatic anomaly — clinical, radiologic, and histologic differentiation. Skeletal Radiol 2013;42:917–24.
[26] Hagendoorn J, Padera TP, Yock TI, Nielsen GP, di Tomaso E, et al. Platelet-derived growth factor receptor-beta in Gorham's disease. Nat Clin Pract Oncol 2006;3:693–7.
[27] Brodszki N, Lansberg JK, Dictor M, Gyllstedt E, Ewers SB, et al. A novel treatment approach for paediatric Gorham–Stout syndrome with chylothorax. Acta Paediatr 2011;100:1448–53.
[28] Franchi A, Bertoni F, Bacchini P, Mourmouras V, Miracco C. CD105/endoglin expression in Gorham disease of bone. J Clin Pathol 2009;62:163–7.
[29] Heyden G, Kindblom LG, Nielsen JM. Disappearing bone disease. A clinical and histological study. J Bone Joint Surg Am 1977;59:57–61.
[30] Karkkainen MJ, Haiko P, Sainio K, Partanen J, Taipale J, et al. Vascular endothelial growth factor C is required for sprouting of the first lymphatic vessels from embryonic veins. Nat Immunol 2004;5:74–80.
[31] Karkkainen MJ, Saaristo A, Jussila L, Karila KA, Lawrence EC, et al. A model for gene therapy of human hereditary lymphedema. Proc Natl Acad Sci U S A 2001;98:12677–82.
[32] Lohela M, Bry M, Tammela T, Alitalo K. VEGFs and receptors involved in angiogenesis versus lymphangiogenesis. Curr Opin Cell Biol 2009;21:154–65.
[33] Tammela T, Alitalo K. Lymphangiogenesis: molecular mechanisms and future promise. Cell 2010;140:460–76.
[34] Joukov V, Pajusola K, Kaipainen A, Chilov D, Lahtinen I, et al. A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases. EMBO J 1996;15:1751.
[35] Nagy JA, Vasile E, Feng D, Sundberg C, Brown LF, et al. Vascular permeability factor/vascular endothelial growth factor induces lymphangiogenesis as well as angiogenesis. J Exp Med 2002;196:1497–506.
[36] Dellinger M, Hunter R, Bernas M, Gale N, Yancopoulos G, et al. Defective remodeling and maturation of the lymphatic vasculature in Angiopoietin-2 deficient mice. Dev Biol 2008;319:309–20.
[37] Morisada T, Oike Y, Yamada Y, Urano T, Akao M, et al. Angiopoietin-1 promotes LYVE-1-positive lymphatic vessel formation. Blood 2005;105:4649–56.
[38] Tammela T, Saaristo A, Lohela M, Morisada T, Tornberg J, et al. Angiopoietin-1 promotes lymphatic sprouting and hyperplasia. Blood 2005;105:4642–8.
[39] Morimoto N, Ogiwara H, Miyazaki O, Kitamuara M, Nishina S, et al. Gorham–Stout syndrome affecting the temporal bone with cerebrospinal fluid leakage. Int J Pediatr Otorhinolaryngol 2013;77:1596–600.
[40] Dupond JL, Bermont L, Runge M, de Billy M. Plasma VEGF determination in disseminated lymphangiomatosis–Gorham–Stout syndrome: a marker of activity? A case report with a 5-year follow-up. Bone 2010;46:873–6.
[41] Albuquerque RJ, Hayashi T, Cho WG, Kleinman ME, Dridi S, et al. Alternatively spliced vascular endothelial growth factor receptor-2 is an essential endogenous inhibitor of lymphatic vessel growth. Nat Med 2009;15:1023–30.
[42] Oka M, Iwata C, Suzuki HI, Kiyono K, Morishita Y, et al. Inhibition of endogenous TGF-beta signaling enhances lymphangiogenesis. Blood 2008;111:4571–9.
[43] Shao X, Liu C. Influence of IFN-alpha and IFN-gamma on lymphangiogenesis. J Interferon Cytokine Res 2006;26:568–74.
[44] Edwards JR, Mundy GR. Advances in osteoclast biology: old findings and new insights from mouse models. Nat Rev Rheumatol 2011;7:235–43.
[45] Ueki Y, Lin CY, Senoo M, Ebihara T, Agata N, et al. Increased myeloid cell responses to M-CSF and RANKL cause bone loss and inflammation in SH3BP2 “cherubism” mice. Cell 2007;128:71–83.
[46] Hughes AE, Ralston SH, Marken J, Bell C, MacPherson H, et al. Mutations in TNFRSF11A, affecting the signal peptide of RANK, cause familial expansile osteolysis. Nat Genet 2000;24:45–8.

[47] Whyte MP, Obrecht SE, Finnegan PM, Jones JL, Podgornik MN, et al. Osteoprotegerin deficiency and juvenile Paget's disease. N Engl J Med 2002;347:175–84.
[48] Avelar RL, Martins VB, Antunes AA, de Oliveira Neto PJ, Andrade ES. Use of zoledronic acid in the treatment of Gorham's disease. Int J Pediatr Otorhinolaryngol 2010;74:319–22.
[49] Choma ND, Biscotti CV, Bauer TW, Mehta AC, Licata AA. Gorham's syndrome: a case report and review of the literature. Am J Med 1987;83:1151–6.
[50] Hammer F, Kenn W, Wesselmann U, Hofbauer LC, Delling G, et al. Gorham–Stout disease — stabilization during bisphosphonate treatment. J Bone Miner Res 2005;20:350–3.
[51] Hirayama T, Sabokbar A, Itonaga I, Watt-Smith S, Athanasou NA. Cellular and humoral mechanisms of osteoclast formation and bone resorption in Gorham–Stout disease. J Pathol 2001;195:624–30.
[52] Lehmann G, Pfeil A, Bottcher J, Kaiser WA, Fuller J, et al. Benefit of a 17-year long-term bisphosphonate therapy in a patient with Gorham–Stout syndrome. Arch Orthop Trauma Surg 2009;129:967–72.
[53] Moller G, Priemel M, Amling M, Werner M, Kuhlmey AS, et al. The Gorham–Stout syndrome (Gorham's massive osteolysis). A report of six cases with histopathological findings. J Bone Joint Surg Br 1999;81:501–6.
[54] Silva S. Gorham–Stout disease affecting both hands: stabilisation during biphosphonate treatment. Hand (N Y) 2011;6:85–9.
[55] Spieth ME, Greenspan A, Forrester DM, Ansari AN, Kimura RL, et al. Gorham's disease of the radius: radiographic, scintigraphic, and MRI findings with pathologic correlation. A case report and review of the literature. Skeletal Radiol 1997;26:659–63.
[56] Poirier H. Massive osteolysis of the humerus treated by resection and prosthetic replacement. J Bone Joint Surg Br 1968;50:158–60.
[57] Ross JL, Schinella R, Shenkman L. Massive osteolysis. An unusual cause of bone destruction. Am J Med 1978;65:367–72.
[58] Tauro B. Multicentric Gorham's disease. J Bone Joint Surg Br 1992;74:928–9.
[59] Heffez L, Doku HC, Carter BL, Feeney JE. Perspectives on massive osteolysis. Report of a case and review of the literature. Oral Surg Oral Med Oral Pathol 1983;55:331–43.
[60] Devlin RD, Bone III HG, Roodman GD. Interleukin-6: a potential mediator of the massive osteolysis in patients with Gorham–Stout disease. J Clin Endocrinol Metab 1996;81:1893–7.
[61] Dickson GR, Hamilton A, Hayes D, Carr KE, Davis R, et al. An investigation of vanishing bone disease. Bone 1990;11:205–10.
[62] Granata F, Frattini A, Loffredo S, Staiano RI, Petraroli A, et al. Production of vascular endothelial growth factors from human lung macrophages induced by group IIA and group X secreted phospholipases A2. J Immunol 2010;184:5232–41.
[63] Motokawa M, Tsuka N, Kaku M, Kawata T, Fujita T, et al. Effects of vascular endothelial growth factor-C and -D on osteoclast differentiation and function in human peripheral blood mononuclear cells. Arch Oral Biol 2013;58:35–41.
[64] Niida S, Kaku M, Amano H, Yoshida H, Kataoka H, et al. Vascular endothelial growth factor can substitute for macrophage colony-stimulating factor in the support of osteoclastic bone resorption. J Exp Med 1999;190:293–8.
[65] Zhang Q, Guo R, Lu Y, Zhao L, Zhou Q, et al. VEGF-C, a lymphatic growth factor, is a RANKL target gene in osteoclasts that enhances osteoclastic bone resorption through an autocrine mechanism. J Biol Chem 2008;283:13491–9.
[66] Maruyama K, Ii M, Cursiefen C, Jackson DG, Keino H, et al. Inflammation-induced lymphangiogenesis in the cornea arises from CD11b-positive macrophages. J Clin Invest 2005;115:2363–72.
[67] Harvey NL, Gordon EJ. Deciphering the roles of macrophages in developmental and inflammation stimulated lymphangiogenesis. Vasc Cell 2012;4:15.
[68] Colucci S, Taraboletti G, Primo L, Viale A, Roca C, et al. Gorham–Stout syndrome: a monocyte-mediated cytokine propelled disease. J Bone Miner Res 2006;21:207–18.
[69] Street J, Bao M, deGuzman L, Bunting S, Peale Jr FV, et al. Vascular endothelial growth factor stimulates bone repair by promoting angiogenesis and bone turnover. Proc Natl Acad Sci U S A 2002;99:9656–61.
[70] Heino TJ, Hentunen TA, Vaananen HK. Osteocytes inhibit osteoclastic bone resorption through transforming growth factor-beta: enhancement by estrogen. J Cell Biochem 2002;85:185–97.
[71] Vezeridis PS, Semeins CM, Chen Q, Klein-Nulend J. Osteocytes subjected to pulsating fluid flow regulate osteoblast proliferation and differentiation. Biochem Biophys Res Commun 2006;348:1082–8.
[72] Raheja LF, Genetos DC, Yellowley CE. Hypoxic osteocytes recruit human MSCs through an OPN/CD44-mediated pathway. Biochem Biophys Res Commun 2008;366:1061–6.
[73] Bonewald LF, Johnson ML. Osteocytes, mechanosensing and Wnt signaling. Bone 2008;42:606–15.
[74] Kurek KC, Luks VL, Ayturk UM, Alomari AI, Fishman SJ, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. Am J Hum Genet 2012;90:1108–15.
[75] Lindhurst MJ, Sapp JC, Teer JK, Johnston JJ, Finn EM, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. N Engl J Med 2011;365:611–9.
[76] Plasswilm L, Hennig I, Spoendlin M, Wegmann W. The phantom. Respiration 1998;65:417–20.
[77] Ruggieri P, Montalti M, Angelini A, Alberghini M, Mercuri M. Gorham–Stout disease: the experience of the Rizzoli Institute and review of the literature. Skeletal Radiol 2011;40:1391–7.
[78] Heyd R, Micke O, Surholt C, Berger B, Martini C, et al. Radiation therapy for Gorham–Stout syndrome: results of a national patterns-of-care study and literature review. Int J Radiat Oncol Biol Phys 2011;81:e179–85.
[79] Dunbar SF, Rosenberg A, Mankin H, Rosenthal D, Suit HD. Gorham's massive osteolysis: the role of radiation therapy and a review of the literature. Int J Radiat Oncol Biol Phys 1993;26:491–7.
[80] Duffy BM, Manon R, Patel RR, Welsh JS. A case of Gorham's disease with chylothorax treated curatively with radiation therapy. Clin Med Res 2005;3:83–6.
[81] Fontanesi J. Radiation therapy in the treatment of Gorham disease. J Pediatr Hematol Oncol 2003;25:816–7.
[82] McNeil KD, Fong KM, Walker QJ, Jessup P, Zimmerman PV. Gorham's syndrome: a usually fatal cause of pleural effusion treated successfully with radiotherapy. Thorax 1996;51:1275–6.
[83] Kuriyama DK, McElligott SC, Glaser DW, Thompson KS. Treatment of Gorham–Stout disease with zoledronic acid and interferon-alpha: a case report and literature review. J Pediatr Hematol Oncol 2010;32:579–84.
[84] Venkatramani R, Ma NS, Pitukcheewanont P, Malogolowkin MH, Mascarenhas L. Gorham's disease and diffuse lymphangiomatosis in children and adolescents. Pediatr Blood Cancer 2011;56:667–70.
[85] Hagberg H, Lamberg K, Astrom G. Alpha-2b interferon and oral clodronate for Gorham's disease. Lancet 1997;350:1822–3.
[86] Pedroletti F, Rangarajan S, McCain JP, Velez I. Conservative treatment of a pathologic fracture in a patient with Gorham–Stout disease. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:e49–52.
[87] Grunewald TG, Damke L, Maschan M, Petrova U, Surianinova O, et al. First report of effective and feasible treatment of multifocal lymphangiomatosis (Gorham–Stout) with bevacizumab in a child. Ann Oncol 2010;21:1733–4.
[88] Nir V, Guralnik L, Livnat G, Bar-Yoseph R, Hakim F, et al. Propranolol as a treatment option in Gorham–Stout syndrome: a case report. Pediatr Pulmonol 2013, http://dx.doi.org/10.1002/ppul.22869 (Electronic publication ahead of print).
[89] Hammill AM, Wentzel M, Gupta A, Nelson S, Lucky A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. Pediatr Blood Cancer 2011;57:1018–24.
[90] Trenor III CC. Sirolimus for refractory vascular anomalies. Pediatr Blood Cancer 2011;57:904–5.
[91] Glass GE, Chan JK, Freidin A, Feldmann M, Horwood NJ, et al. TNF-alpha promotes fracture repair by augmenting the recruitment and differentiation of muscle-derived stromal cells. Proc Natl Acad Sci U S A 2011;108:1585–90.

Supplemental Table 1. Clinical Features of GSD. NR = Not Reported

Year Published	Reference	Bones Involved	Sex	Age Diagnosed	Chylothorax	Pericardial Effusion	Signs/Symptoms	Treatment - Radiation	Treatment - Bisphosponate	Treatment - Interferon	Treatment(s) - Other	Age when patient expired	Osteoclasts Present	Vessel Staining
1955	Gorham and Stout 1955. J Bone Joint Surg. 37;985-1004.	Cervical and Thoracic Vertebrae, Clavicle, Humerus, Ribs, Scapula	Male	16	Right-Sided	NR	NR	NO	NO	NO	NR	18	NO	NR
1955	Gorham and Stout 1955. J Bone Joint Surg. 37;985-1004.	Femur, Ilium, Ischium, Lumbar Vertebrae, Pubis, Sacrum	Female	5	NR	NR	NR	NO	NO	NO	NR	NR	NO	NR
1955	Gorham and Stout 1955. J Bone Joint Surg. 37;985-1004.	Femur	Male	11	NR	NR	NR	NO	NO	NO	Amputation	NR	NO	NR
1955	Gorham and Stout 1955. J Bone Joint Surg. 37;985-1004.	Clavicle	Male	44	NR	NR	NR	NO	NO	NO	NR	NR	NO	NR
1955	Gorham and Stout 1955. J Bone Joint Surg. 37;985-1004.	Clavicle, Humerus, Ribs, Scapula, Thoracic Vertebrae	Male	20	NR	NR	Pain	NO	NO	NO	NR	NR	NO	NR
1955	Gorham and Stout 1955. J Bone Joint Surg. 37;985-1004.	Ribs,Sternum	Male	21	NR	NR	Pain	NO	NO	NO	NR	NR	NO	NR
1955	Gorham and Stout 1955. J Bone Joint Surg. 37;985-1004.	Mandible, Maxilla	Female	36	NR	NR	Pain	NO	NO	NO	NR	NR	NO	NR
1955	Gorham and Stout 1955. J Bone Joint Surg. 37;985-1004.	Clavicle, Ribs, Scapula	Female	41	NR	NR	Pain	NO	NO	NO	NR	NR	NO	NR
1958	Aston 1958. J Bone Joint Surg. 40B;514-518.	Femur	Female	18	NR	NR	Pain	NO	NO	NO	Amputation	NR	NR	NR
1958	Branco and Horta 1958. J Bone Joint Surg. 40B;519-527.	Femur, Fibula, Ilium, Sacrum, Tibia	Male	13	NR	NR	NR	NO	NO	NO	Vitamin D, Calcium	NR	NO	NR
1958	Butler et al., 1958. J Bone Joint Surg. 40B;487-493.	Femur	Male	5	NR	NR	Weakness	NO	NO	NO	Vitamin D, Bone Graft	NR	NR	NR
1958	Johnson and McClure 1958. Radiology 71;28-41.	Ischium	Female	29	NR	NR	Pain	YES	NO	NO	NR	NR	NO	NR
1958	Jones et al., 1958. J Bone Joint Surg. 40B;494-501.	Clavicle, Ribs, Scapula	Male	23	Bilateral	NR	Weakness	NO	NO	NO	Thoracentesis	28	YES	NR
1958	Milner and Baker 1958. J Bone Joint Surg. 40B;502-513.	Humerus	Female	68	NR	NR	Pain	NO	NO	NO	No treatment	NR	YES	NR
1964	Castlman and McNeely 1964. NEJM 270;731-736.	Cervical Vertebrae	Male	24	NR	NR	Pain	NO	NO	NO	Surgery	NR	YES	NR
1964	Halliday et al., 1964. Radiology 82;637-644.	Ribs, Vertebrae	Male	27	Right-Sided (PE)	NR	Dyspnea	YES	NO	NO	NR	34	NR	NR
1964	Halliday et al., 1964. Radiology 82;637-644.	Femur	Male	18 months	NR	NR	Fracture	YES	NO	NO	Surgery	NR	NR	NR
1964	Halliday et al., 1964. Radiology 82;637-644.	Ilium	Male	23	NR	NR	Pain	NO	NO	NO	Surgery	NR	NR	NR
1964	Halliday et al., 1964. Radiology 82;637-644.	Ribs	Female	15	Right-Sided (PE)	NR	Trauma, Dyspnea	NO	NO	NO	Surgery	NR	NR	NR
1967	Kyllonen 1967. Ann Thorac Surg. 4;559-563.	Ribs	Male	16	Right-Sided	NR	Pain, Dyspnea	YES	NO	NO	NR	NR	NR	NR
1968	Poirier 1968. J Bone Joint Surg. 50B;158-160.	Humerus	Male	37	NR	NR	Pain	NO	NO	NO	Surgery, Prosthetic Replacement			
1970	Kery and Wouters 1970. J Bone Joint Surg. 52B;452-459.	Femur, Pelvis	Female	12	NR	NR	Fracture	NO	NO	NO	NR	14 - septic shock	NR	NR
1970	Kery and Wouters 1970. J Bone Joint Surg. 52B;452-459.	Fibula, Tibia	Male	10	NR	NR	Pain, Swelling	NO	NO	NO	Surgery	NR	NR	NR
1971	Ellis and Adams 1971. J Oral Surg. 29;659-663.	Cervical Vertebrae, Mandible, Maxilla	Female	55	Right-Sided	NR	NR	NO	NO	NO	No treatment	72	NR	NR
1972	Cherrick et al., 1972. J Oral Med. 27;67-74.	Mandible, Maxilla	Male	27	NR	NR	Food came out nose when ate	NO	NO	NO	Surgery	NR	NO	NR

Year Published	Reference	Bones Involved	Sex	Age Diagnosed	Chylothorax	Pericardial Effusion	Signs/Symptoms	Treatment - Radiation	Treatment - Bisphosponate	Treatment - Interferon	Treatment(s) - Other	Age when patient	Osteoclasts Present	Vessel Staining
1974	Booth and Burke 1974. J Oral Surg. 32;787-791.	Mandible	Male	29	NR	NR	Fracture	NO	NO	NO		NR	YES	NR
1974	Thompson and Schuman 1974. Clin. Orthop. 103;206-211.	Acetabulum, Ilium	Male	48	NR	NR	Pain	NO	NO	NO	NR	NR	NO	NR
1976	Patrick 1976. J Bone Joint Surg. 58B;347.	Clavicle, Ribs, Vertebrae	Male	28	Left-Sided	NR	Pain	NO	NO	NO	Pleurodesis	NR	NR	NR
1977	Heyden et al., 1977. J Bone Joint Surg 59;57-59.	Ilium	Male	3	NR	NR	Pain	YES	NO	NO	NR	NR	NO	Acid Phosphatase and Aminopeptidase
1977	Heyden et al., 1977. J Bone Joint Surg 59;57-59.	Vertebrae	Male	34	NR	NR	Pain	YES	NO	NO	NR	NR	NO	Acid Phosphatase and Aminopeptidase
1977	Heyden et al., 1977. J Bone Joint Surg 59;57-59.	Scapula	Male	15	NR	NR	Pain	YES	NO	NO	NR	NR	Few	Acid Phosphatase and Aminopeptidase
1978	Murphy et al., 1978. J Oral Surg. 36;318-322.	Mandible	Male	34	NR	NR	Pain	NO	NO	NO	Surgery	NR	NR	NR
1979	Heuck 1979. Skeletal Radiol. 3;241-243.	Mandible	Male	22	NR	NR	Pain, Swelling	YES	NO	NO	NR	NR	NR	NR
1980	Abrahams et al., 1980. AJR 135;1084-1086.	Ilium, Ischium, Pubis, Sacrum	Male	14 months	NR	NR	Swelling	NO	NO	NO	NR	NR	NR	NR
1981	Kurczynski and Horwitz 1981. Cancer 48;255-256.	Mandible, Skull	Female	14	NR	NR	Pain	YES	NO	NO	NR	NR	NR	NR
1983	Heffez et al., 1983. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 4;331-343.	Mandible, Maxilla, Clavicle, Cervical Vertebrae	Male	13	NR	NR	Loose Teeth	YES	NO	NO	NR	NR	NR	NR
1985	Hanly et al., 1985. J Rheumatology 2;580-582.	Carpals	Female	62	NR	NR	Pain, Swelling	YES	NO	NO	NR	NR	NR	Factor VIII
1987	Carneiro and Steglich 1987. J Hand Surg 12A;629-634.	Carpals	Female	13	NR	NR	Fracture	YES	NO	NO	NR	NR	NR	NR
1987	Choma et al., 1987. Am J Med 83;1151-1156.	Scapula, Clavicle, Humerus, Ribs	Male	16	Right-Sided	NR	Pain, Dyspnea	YES	NO	NO	TD Ligation	27	YES	NR
1989	Dunkelman et al., 1989. Arch. Dis Childhood 64;1058-1060.	Femur, Humerus, Ribs	Male	9 months	Left-Sided	NR		NO	NO	NO	TD Ligation, Pleurodesis	NR	NR	NR
1990	Dickson et al., 1990. Bone 11;205-210.	Carpals, Radius, Ulna	Female	44	NR	NR						NR	VERY FEW - DID ELECTRON MICROSCOPY - SAW DEGENERATING OSTEOBLASTS	NO
1992	Tauro et al., 1992. J Bone Joint Srug Br 74;9289-29.	Humerus, Scapula	Male	52	NR	NR	Deformity	NO	NO	NO	No treatment	NR	NO	NR
1993	Schiel and Prein 1993. Head & Neck 15;352-356.	Maxilla	Female	14	NR	NR	Pain	YES	NO	NO	NR	NR	NR	NR
1994	Tie et al., 1994. Chest 105;208-213.	Ribs	Male	26	Bilateral	Yes	Pain	YES	NO	NO	MCT Diet, Pleurodesis,	30	NR	NR
1994	Tie et al., 1994. Chest 105;208-213.	Scapula, Clavicle, Humerus, Ribs, Tibia, Femur	Male	18	Left-Sided	NR	Pain, Dyspnea	NO	NO	NO	TD Ligation	NR	NO	NR

Year Published	Reference	Bones Involved	Sex	Age Diagnosed	Chylothorax	Pericardial Effusion	Signs/Symptoms	Treatment - Radiation	Treatment - Bisphosponate	Treatment - Interferon	Treatment(s) - Other	Age when patient expired	Osteoclasts Present	Vessel Staining
1994	Prabhu et al., 1994. Indian Pediatr 31;1542-1544.	Clavicle, Ribs	Male	10	Right-Sided (PE)	NR	Pain	NO	NO	NO	NR	NR	NR	NR
1995	Stove and Reichelt 1995. Arch Ortop Trauma Surg 114;207-210.	Acetabulum, Femur, Ilium, Pubis, Sacrum	Female	49	NR	NR	Pain	YES	NO	NO	NR	NR	NR	NR
1996	Devlin et al., 1996. J Clin Endocrinol Metab 81;1893-1897.	Mandible, Skull	Male	9	NR	NR	NR	NO	Bisphosphonate (Pamidronate)	NO	NR	NR	NR	NR
1996	Livesley et al., 1996. Skeletal Radiol 25;403-405.	Vertebrae	Male	5	NR	NR	Pain	NO	Bisphosphonate (Pamidronate)	NO	Surgery	NR	NR	NR
1996	McNeil et al., 1996. Thorax 51;1275-1276.	Ribs, Vertebrae	Male	21	Right-Sided	NR	Pain, Dyspnea	YES	NO	NO	NR	NR	NR	NR
1996	Nemec et al., 1996. J Bone Joint Surg Br 78;666-667.	Ilium, Ischium, Pubis	Male	25	NR	NR	Pain	NO	NO	NO	Surgery	NR	NR	NR
1996	Riantawan et al., 1996. Thorax 51;1277-1278.	Clavicle, Ribs, Scapula, Vertebrae	Male	27	Bilateral	NR	Dyspnea	NO	NO	NO	NR	27	NR	NR
1997	Chung et al., 1997. Skeletal Radiol 26;55-59.	Ribs, Cervical and Thoracic Vertebrae	Female	48	NR	NR	Pain	YES	NO	NO	NR	NR	NR	NR
1997	Frankel et al., 1997. Pediatr Radiol 27;265-267.	Femur, Ilium, Skull	Female	14	NR	NR	Hearlng Loss	YES	NO	Interferon Alpha	Steroids,	NR	NR	NR
1997	Hagberg et al., 1997. Lancet 350;1822-1823.	Clavicle, Ribs, Vertebrae	Male	19	Left-Sided	NR	Pain	YES	Bisphosphonate (Clodronate)	Interferon Alpha 2b	Radiation, Bisphosphonate (Clodronate), Interferon Alpha 2b	NR	NR	NR
1997	Khosrovi et al., 1997. J Neurosurg 87;773-780.	Cervical Vertebrae, Occipital	Male	62	NR	NR	NR	YES	NO	NO	NR	NR	NR	NR
1997	Mawk et al., 1997. Childs Nerv Syst 13;622-625.	Clavicle, Cervicle Vertebrae, Skull	Male	6	YES	YES	NR	YES	NO	NO	TD Ligation, Pleurodesis	NR	NR	Factor VIII
1997	Pazzaglia et al., 1997. Int Orthop 21;303-307.	Femur	Male	55	NR	NR	Pain	NO	NO	NO	Surgery	NR	YES - KP1 positive	CD31, Factor VIII
1997	Sato et al., 1997. Arch Orthop Trauma Surg 116;510-513.	Humerus	Male	15	NR	NR	Fracture	NO	NO	NO	Surgery	NR	YES	NR
1997	Speith et al., 1997. Skeletal Radiol 26;659-663.	Radius	Female	46	NR	NR	Pain	NO	NO	NO	Surgery	NR	YES	NR
1998	Manisali and Ozaksoy 1998. Eur Radiol 8;1647-1650.	Humerus	Male	60	NR	NR	Pain	NO	NO	NO	NR	NR	YES	NR
1998	Plasswilm et al., 1998. Respiration 65;417-420.	Ribs	Male	19	Right-Sided	NR	Pain, Dyspnea	YES	Bisphosphonate	NO	NR	NR	YES - only a few observed	NR
1999	Hofbauer et al., 1999. Rheumatology 38;904-905.	R-Scapula, R-Clavicle	Male	8	NR	NR	Weakness	NO	NO	NO	NR	NR	NR	NR
1999	Moller et al., 1999. J Bone Joint Surg Br. 81;501-506.	R-Humerus	Female	56	NR	NR	NR	NO	NO	NO	Surgery	NR	YES	NR
1999	Moller et al., 1999. J Bone Joint Surg Br. 81;501-506.	R-Humerus	Female	83	NR	NR	NR	NO	NO	NO	NR	NR	YES	NR
1999	Moller et al., 1999. J Bone Joint Surg Br. 81;501-506.	R-Ribs	Female	19	NR	NR	Pain	NO	NO	NO	Resection	NR	YES	NR
1999	Moller et al., 1999. J Bone Joint Surg Br. 81;501-506.	R-Femur	Female	70	NR	NR	Pain	NO	NO	NO	NR	NR	YES	NR
1999	Moller et al., 1999. J Bone Joint Surg Br. 81;501-506.	R-Femur	Female	77	NR	NR	Pain	NO	NO	NO	Surgery, Hip Replacement	NR	YES	NR
1999	Moller et al., 1999. J Bone Joint Surg Br. 81;501-506.	R-Pubis, R-Ischium	Female	78	NR	NR	Pain	NO	NO	NO	Surgery	NR	YES	NR
2000	Szabo and Habre 2000. Anaesthesia 55;157-159.	Clavicle, Ribs	Male	8	NR	NR	Pain, Dyspnea	NO	NO	NO	NR	NR	NR	NR
2001	Hirayama et al., 2001. J Pathol 195;624-630.	Mandible	Female	7	NR	NR	Loose Teeth	NO	NO	NO	Surgery	NR	YES - Increased number	NR

Year Published	Reference	Bones Involved	Sex	Age Diagnosed	Chylothorax	Pericardial Effusion	Signs/Symptoms	Treatment - Radiation	Treatment - Bisphosponate	Treatment - Interferon	Treatment(s) - Other	Age when patient expired	Osteoclasts Present	Vessel Staining
2002	Bode-Lesniewska et al., 2002. Skeletal Radiol 31;724-729.	Humerus, Ribs, Scapula, Skull, Sternum, Vertebrae	Female	15	NR	NR	Pain	YES	NO	NO	NR	65	NR	CD31
2002	Fujiu et al., 2002. Ann Thorac Surg. 73;1956-1957.	Scapula, Clavicle, Humerus, Sternum, Ribs	Male	15	Bilateral	NR	Pleural Effusion	NO	NO	NO	TD Ligation	15	NO	NR
2002	Krohel et al., 2002. Am J Opthalmol 133;729-730.	Orbit	Female	43	NR	NR	Headache	NO	NO	NO	Surgery	NR	NR	NR
2002	Lee et al., 2002. J Korean Med Sci 17;826-829.	Ribs, Vertebrae	Female	25	Right-Sided	NR	Dyspnea	YES	NO	NO	Pleurodesis	NR	NR	NR
2002	Miller 2002. Can J Surg 45;381-382.	Vertebrae	Male	2	Right-Sided	NR	Dyspnea	NO	NO	NO	TD Ligation	4	NR	NR
2002	Yoo et al., 2002. Korean J Radiol 2002. 3;130-132.	Clavicle, Sternum	Male	38	Left-Sided	NR	Pain	YES	NO	NO	NR	NR	NR	NR
2002	Yoo et al., 2002. Skeletal Radiol 31;301-306.	Femur, Acetabulum, Pubis, Ischium, Tibia, Fibula	Female	20	NR	NR	Pain	NO	NO	NO	NR	NR	NR	NR
2002	Yoo et al., 2002. Skeletal Radiol 31;301-306.	Ribs, Thoracic and Lumbar Vertebrae	Female	25	Right-Sided	NR	Pain, Dyspnea	YES	NO	NO	NR	NR	NR	NR
2003	Bruch-Gerharz et al., 2003. JAMA 289;1479-1480.	Femur, Metatarsals	Male	21	NR	NR	Pain, Lymphatic Malformations	YES	NO	NO	NR	NR	NR	NR
2003	Chong et al., 2003. Spine 28;e355-358.	Vertebrae	Male	49	NR	NR	Pain, Fracture	NO	NO	NO	Stabilization	NR	NR	NR
2003	Fontanesi 2003. J Pediatr Hematol Oncol 25;816-817.	Humerus	Male	21	Right-Sided	NR	Fracture	YES	NO	NO	NR			
2003	Lee et al., 2003. Arch Otolaryngol Head Neck Surg 129;1340-1343.	Skull	Female	9	YES	NR	Lymphatic Malformation	YES	NO	NO	Chemotherapy	14	NR	NR
2003	Lee et al., 2003. Arch Otolaryngol Head Neck Surg 129;1340-1343.	Mandible, Skull	Female	7 months	Right-Sided	NR	Lymphatic Malformation					6	NR	NR
2003	Motamedi et al., 2003. J Oral Maxillofac Surg. 61;957-963.	Mandible	Male	19	NR	NR	Swelling					NR	NR	NR
2003	Ricalde et al., 2003. Int J Oral Maxillofac Surg 32;222-226.	Mandible	Male	5	NR	NR	Fracture	YES	NO	NO	NR	NR	NR	CD34, Factor VIII
2004	Brown et al., 2004. Clin Nucl Med 29;709-711.	Pelvis	Male	24	NR	NR	Pain	NO	NO	NO	NR	NR	NR	NR
2004	Lo et al., 2004. AJNR Am J Neuroradiol 25;415-418.	Skull	Male	23	NR	NR	Asymptomatic	NO	NO	NO	Surgery	NR	NR	NR
2004	Tsang et al., 2004. J Oal Maxillofac Surg 62;225-230.	Mandible	Female	9	NR	NR	Pain, Swelling	NO	Bisphosphonate	NO	Curettage	NR	NR	NR
2004	Tsang et al., 2004. J Oal Maxillofac Surg 62;225-230.	Mandible, Skull	Female	26	NR	NR	Swelling	NO	NO	NO	NR	NR	YES - osteoclast like aggregates	NR
2005	Aizawa et al. 2005. Tohoku J Exp Med 205;187-196.	Vertebrae	Male	10	NR	NR	Pain	NO	NO	NO	Stabilization	NR	YES - but not increased - TRAP staining	NR
2005	Boyer et al., 2005. Clin Rheumatol 24;551-555.	Acetabulum, Ischium, Pubis	Male	22	NR	NR	Pain	NO	NO	NO	No treatment/Long-term Follow-Up	NR	NR	NR
2005	Duffy et al., 2005. Clin Med Res 3;83-86.	R-Scapula, R-Ribs, Thoracic and Lumbar Vertebrae	Female	31	YES	YES	Dyspnea	YES	NO	NO	Pleurodesis	NR	NR	NR
2005	Hammer et al., 2005. J Bone Miner Res 20;350-353.	Ribs	Female	45	NR	NR	Pain	NO	Bisphosphonate (Pamidronate)	NO	NR	NR	YES	NR
2005	Mignogna et al., 2005. Oral Oncol. 41;747-750.	Mandible	Female	23	NR	NR	Bone Loss	NO	Bisphosphonate (Zoledronic Acid)	NO	NR	NR	NR	NR

2005	Okafuji et al., 2005. J Thorac Imaging 20;284-287.	Ribs	Male	29	Left-Sided	NR	Dyspnea	NO	NO	NO	Draining	NR	NR	NR
Year Published	**Reference**	**Bones Involved**	**Sex**	**Age Diagnosed**	**Chylothorax**	**Pericardial Effusion**	**Signs/Symptoms**	**Treatment - Radiation**	**Treatment - Bisphosponate**	**Treatment - Interferon**	**Treatment(s) - Other**	**Age when patient expired**	**Osteoclasts Present**	**Vessel Staining**
2005	Paley et al., 2005. Br J Oral Maxillofac Surg 43;166-168.	Mandible	Female	55	NR	NR	Pain	NO	NO	NO	Surgery	NR	NR	NR
2005	Takahashi et al., 2005. 40;e47-50.	Femur, Ribs, Vertebrae	Female	2	Left-Sided	YES	NR	NO	NO	Interferon Alpha	OK 432	NR	NR	NR
2006	Agrawal et al., 2006. J Thorac Cardiovasc Surg 131;1205-1206.	Ribs, Vertebrae	Female	25	Left-Sided (PE)	NR	Fatigue	NO	NO	NO	NR	NR	NR	NR
2006	Colucci et al., 2006. J Bone Miner Res 21;207-218.	Ribs, Clavicle, Vertebrae, Scapula, Humerus	Female	40	YES	NR	NR	NO	NO	NO	NR	NR	CD68	CD34
2006	Girn et al., 2006. Acta Neurochir 148;909-913.	Skull, Spine, Ribs, Pelvis, Femur	Female	2	Bilateral	NR		YES	Bisphosphonate	NO	NR	10?	YES	NR
2006	Hagerndoorn et al., 2006. Nat Clin Pract Oncol 3;693-697.	Ribs, Vertebrae	Male	17	Right-Sided	NR	Pain, Dyspnea	NO	Bisphosphonate (Zoledronic Acid)	Interferon Alpha 2b	Spine stabilization, thalidomide, celecoxib, pamidronate, thoracotomy, pleurectomy, talc pleurodesis, and imatinib mesylate	23	NR	CD31, LYVE-1, VEGFR3, PDGFRB - note-VEGF-A and PDGF-B ELISA
2006	Kai et al., 2006. Clinical Radiology 61;1058-1064.	Radius, Ulna, Carpus	Male	49	NR	NR	Pain	YES	NO	NO	NR	NR	NR	NR
2006	Kai et al., 2006. Clinical Radiology 61;1058-1064.	Radius, Ulna	Male	5	NR	NR	Pain, Swelling	NO	NO	NO	Bone Grafting, Curetted	NR	NR	NR
2006	Kai et al., 2006. Clinical Radiology 61;1058-1064.	Cervical Vertebrae	Female	35	NR	NR	Pain, Weakness	NO	NO	NO	Vertebrectomy, Bone Grafting	NR	NR	NR
2006	Pfleger et al., 2006. J Pediatr Hematol Oncol 28;231-233.	Vertebrae, Ribs, Scapula Humerus, Pelvis Femur	Male	18	Left-Sided	NR	Dyspnea	YES	NO	Interferon Alpha 2b	TD Ligation			
2007	Bruch-Gerharz et al., 2007. J Am Acad Dermatol. 56;S21-25.	Femur	Male	21	NR	NR	Pain	YES	NO	NO	NR	NR	NR	NR
2008	Atalabi et al., 2008. Skeletal Radiol 2008. 37;1041-10146.	Vertebrae, Ribs, Pelvis, Femur	Female	4	Bilateral	NR	Fracture					18	YES - In figure but don't comment on #	D2-40
2008	Boyle et al., 2008. Heart Lung Circ 17;64-66.	Sternum, Clavicle, Rib	Male	17	Bilateral	NR		YES	NO	NO	TD Ligation	17		
2008	Newland et al., 2008. Pathology 40;420-423.	Mandible, Skull	Male	27	NR	NR	Nasal Discharge	NO	NO	NO	Surgery	NR	NR	NR
2008	Yalniz et al., 2008. J BR-BTR 91;14-17.	Humerus	Male	14	NR	NR	Pain	NO	NO	NO	No treatment	NR	NR	NR
2009	Bruder et al., 2009. Virchows Arch 454;161-179.	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	YES	D2-40, Low MIB1
2009	Franchi et al., 2009. J Clin Pathol 62;163-167.	Ilium	Male	13	NR	NR	NR	NO	NO	NO	Curettage	NR	NR	Endoglin and MIB-1
2009	Franchi et al., 2009. J Clin Pathol 62;163-167.	Femur	Male	13	NR	NR	NR	NO	NO	NO	Curettage	NR	NR	Endoglin and MIB-1
2009	Franchi et al., 2009. J Clin Pathol 62;163-167.	Femur, Pelvis	Male	23	NR	NR	NR	NO	NO	NO	Curettage	NR	NR	Endoglin and MIB-1
2009	Franchi et al., 2009. J Clin Pathol 62;163-167.	Pelvis	Female	58	NR	NR	NR	NO	NO	NO	Curettage	NR	NR	Endoglin and MIB-1

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2010	Gondivkar et al., 2010. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 109;e41-e48.	Mandible	Male	58	NR	NR	Bone Loss	NO	NO	NO	Mandibulectomy	NR	NR	NR
2009	Kose et al., 2009. Pediatr Pulmonol 44;613-615.	L-Clavicle, Thoracic and Lumbar Vertebrae, Sternum, Sacrum, Ribs	Female	9	Right-Sided	NR	Pain, Dyspnea	YES	NO	Interferon Alpha 2b	TD Ligation	NR	NR	NR
2009	Lehmann et al., 2009. Arch Ortop Trauma Surg 129;967-972.	Pelvis, Femur	Female	61	NR	NR	NR	YES	Bisphosphonate	NO	NR	NR	YES	NR
2009	Xin et al., 2009. Cases 2;7499.	L-Ulna, L-Radius, L-Carpal	Female	45	NR	NR	Pain, Swelling	YES	NO	NO	Resection	NR	NR	NR
2009	Yildiz et al., 2009. Paediat Anaesth 19;190-191.	Ribs	Male	6	Bilateral	NR	Dyspnea	NO	NO	NO	TD Ligation	NR	NR	NR
2009	Zacharia et al., 2009. J Foot Ankle Surg 48;347-352.	Fibula	Male	13	NR	NR	Pain	NO	NO	NO	No treatment	NR	NR	NR
2010	Avelar et al., 2010. Int J Pediatr Otorhinolaryngol 74;319-322.	Mandible	Male	9	NR	NR	Pain, Swelling	NO	Bisphosphonate (Zoledronic Acid)	NO	NR	NR	YES	NR
2010	Chiang et al., 2010. Neurology 75;e65.	Calvarium	Male	46	NR	NR	NR	NO	NO	NO	NR	NR	NO	NR
2010	Cushing et al., 2010. Otol Neurotol 31;789-792.	Skull	Male	12	NR	NR	Headache	NO	NO	NO	Surgery	NR	NR	NR
2010	De Smet et al., 2010. Emerg Radiol 17;503-505.	Ribs, Clavicle	Male	8	Bilateral	NR	Dyspnea	NO	Bisphosphonate	Interferon Alpha 2b	NR	NR	NR	NR
2010	Dupond et al., 2010. Bone 46;873-876.	Femur, Humerus, Skull, Ilium, Ribs	Female	16	No	NR	NR	NO	NO	Interferon Alpha 2b	NR	NR	NR	NR
2010	Grunewald et al., 2010. Ann Oncol 21;1733-1734.	Sternum, L-Clavicle, L-Ribs	Male	2.5	YES	NR	Fracture	NO	Bisphosphonate	Interferon Alpha 2b	Imatinib, Avastin	NR	NR	NR
2010	Kuriyama et al., 2010. J Pediatr Hematol Oncol 32;579-584.	Ribs	Female	16	Left-Sided	NR	Pain, Dyspnea	NO	Bisphosphonate (Zoledronic Acid)	NO	NR	NR	NR	NR
2010	Migliorati, 2010. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 109;242-243.	Mandible	Male	58	NR	NR	NR	NO	NO	NO	Hemimandibulectomy	NR	NR	NR
2010	Mowry et al., 2010. Laryngoscope 120;598-600.	Skull, Spine	Female	9	NR	NR	NR	NO	NO	NO	NR	NR	NR	NR
2010	Perschbacher et al., 2010. Dentomaxillofac Radiol 39;119-123.	Maxilla	Male	56	NR	NR	Loose Teeth	YES	NO	NO	NR	NR	YES - not prominent	NR
2010	Seok et al., 2010. Thorac Cardiovasc Surg 58;492-493.	R-Ribs, Thoracic Vertebra	Male	14	Right-Sided	NR	Dyspnea	YES	NO	NO	TD Ligation	NR	NR	NR
2010	Tong et al., 2010. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 109;238-241.	Mandible	Female	9	NR	NR	NR	NO	Bisphosphonate	NO	NR	NR	NR	NR
2010	Zhang et al., 2010. Neurol India 58;144-145	Calvarium	Male	40	NR	NR	NR	NO	NO	NO	NR	NR	NR	NR
2011	Brodszki et al., 2011. Acta Paediatr 100;1448-1453.	Vertebrae, Pelvis, R-Clavicle	Male	2	Right-Sided	NR	NR	YES	NO	Interferon Alpha 2b	LMW Heparin, Surgery	NR	NR	LYVE-1 Pluera
2011	Brodszki et al., 2011. Acta Paediatr 100;1448-1453.	Vertebrae, Humerus, Femur, Pelvis, Sacrum	Female	4	Bilateral	NR	NR	YES	NO	Pegylated Interferon Alpha 2b	Octreotide, LMW Heparin	NR	NR	LYVE-1 Staining of Bone
2011	Deng et al., 2011. J Craniofac Surg 22;2386-2388.	Mandible	Male	46	NR	NR	Pain	NO	NO	NO	Surgery	NR	NR	NR
2011	Deveci et al., 2011. Indian J Pediatr 78;737-739.	Ribs, Cranium, Vertebrae, Humerus, Femur	Male	6	Bilateral	NR	Dyspnea	NO	Bisphosponate (Clodronate)	Interferon Alpha 2b	Interferon Alpha 2b, Bisphosponate (Clodronate)	6	NR	NR
2011	Heyd et al., 2011. Int J Radiat Oncol Phys 81;e179-85.	Pelvis, Hip, Femur	Male	22	NR	NR	NR	YES	NO	NO	NR	NR	NR	NR

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2011	Heyd et al., 2011. Int J Radiat Oncol Phys 81;e179-85.	Pelvis	Female	23	NR	NR	NR	YES	NO	NO	NR	NR	NR	NR
2011	Heyd et al., 2011. Int J Radiat Oncol Phys 81;e179-85.	Skull, Cervical Vertebrae	Female	24	NR	NR	NR	YES	NO	NO	Surgery	NR	NR	NR
2011	Heyd et al., 2011. Int J Radiat Oncol Phys 81;e179-85.	Pelvis, Lumbar Vertebrae	Male	30	NR	NR	NR	YES	NO	NO	Surgery	NR	NR	NR
2011	Heyd et al., 2011. Int J Radiat Oncol Phys 81;e179-85.	Mandible	Female	34	NR	NR	NR	YES	NO	NO	NR	NR	NR	NR
2011	Heyd et al., 2011. Int J Radiat Oncol Phys 81;e179-85.	Skull, Cervical Vertebrae	Male	38	NR	NR	NR	YES	NO	NO	Surgery	NR	NR	NR
2011	Heyd et al., 2011. Int J Radiat Oncol Phys 81;e179-85.	Skull base, Cervical Vertebrae	Male	44	NR	NR	NR	YES	NO	NO	NR	NR	NR	NR
2011	Heyd et al., 2011. Int J Radiat Oncol Phys 81;e179-85.	Lumbar Vertebrae, Skull, Ribs	Male	46	NR	NR	NR	YES	NO	NO	Surgery	NR	NR	NR
2011	Heyd et al., 2011. Int J Radiat Oncol Phys 81;e179-85.	Skull base	Female	55	NR	NR	NR	YES	NO	NO	NR	NR	NR	NR
2011	Heyd et al., 2011. Int J Radiat Oncol Phys 81;e179-85.	Pelvis, Femur, Lumbar Vertebrae	Female	61	NR	NR	NR	YES	NO	NO	NR	NR	NR	NR
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	R-Femur	Male	13	NR	NR	Fracture	NO	NO	NO	Bridge Plating	NR	NR	NR
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	L-Humerus	Female	68	NR	NR	Fracture	NO	NO	NO	Allograft	NR	NR	NR
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	L-Femur	Female	36	NR	NR	NR	NO	NO	NO	Cast	NR	NR	NR
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	Femur	Male	38	NR	NR	Pain	NO	Bisphosphonate	NO	Calcitonin	NR	NR	NR
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	Cervical Vertebrae	Male	4	NR	NR	Pain	NO	NO	NO	NR	NR	NR	NR
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	R-Calcaneus	Male	8	NR	NR	Pain	NO	NO	NO	Cast	NR	NR	NR
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	R-Ilium, R-Ischium	Male	17	NR	NR	Pain	NO	NO	NO	NR	NR	NR	NR
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	L-Femur	Male	31	NR	NR	Pain	NO	NO	NO	Calcitonin	NR	NR	NR
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	Femur, Tibia	Male	63	NR	NR	Pain	NO	NO	NO	Steroids	NR	NR	NR
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	R-Ischium	Female	58	NR	NR	Pain	NO	Bisphosphonate (Zoledronic Acid)	NO	Embolization	NR		
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	L-Femur	Male	31	NR	NR	Pain, Fracture	YES	NO	NO	Bone Graft	NR	NR	NR
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	R-Femur	Male	18	NR	NR	Pain, Fracture	NO	NO	NO	Intramedullary Nail	NR	NR	NR
2011	Ruggieri et al., 2011. Skeletal Radiol 40;1391-1397.	R-Femur, Ischium	Male	25	NR	NR	Pain, Swelling	NO	NO	NO	Intramedullary Nail, IFN gamma	NR	NR	NR
2011	Silva 2011. Hand 6;85-89.	L-Metacarpal, R-Metacarpal	Female	42	NR	NR	Pain	NO	Bisphosphonate (Alendronate)	NO	NR	NR	YES	NR
2011	Venkatramani et al., 2011. Pediatr Blood Cancer 56;667-670.	Skull, Mandible, L-Scapula, R-Scapula, Ribs, Clavicle, Tibia, Femur, Humerus, Ulna, Radius, Thoracic and Lumbar Vertebrae	Male	9	NR	NR	Fracture	NO	NO	NO	NR	NR	NR	NR
2011	Venkatramani et al., 2011. Pediatr Blood Cancer 56;667-670.	Skull, Pelvis, L-Humerus, R-Humerus, Ulna, Radius, Femur, Tibia, Fibula	Female	9	NR	NR	Incidental Finding	NO	NO	NO	NR	NR	NR	NR

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2011	Venkatramani et al., 2011. Pediatr Blood Cancer 56;667-670.	Pelvis, Lumbar and Thoracic Vertebrae, Ribs	Male	7	NR	NR	Mass Present	NO	NO	NO	NR	NR	NR	NR
2011	Venkatramani et al., 2011. Pediatr Blood Cancer 56;667-670.	R-Ilium	Female	11	NR	NR	Pain	NO	NO	NO	NR	NR	NR	NR
2011	Venkatramani et al., 2011. Pediatr Blood Cancer 56;667-670.	Pelvis, Vertebrae	Male	12	NR	NR	Pain	NO	NO	NO	NR	NR	NR	NR
2011	Venkatramani et al., 2011. Pediatr Blood Cancer 56;667-670.	L-Scapula, R-Scapula, R-Humerus, L-Femur, R-Femur, L-Tiba, R-Tibia, Thoracic Vertebrae	Female	13	Left-Sided	NR	Pain	NO	NO	NO	NR	NR	NR	NR
2011	Venkatramani et al., 2011. Pediatr Blood Cancer 56;667-670.	Cervical and Thoracic Vertebrae, Ribs	Male	12	Bilateral	NR	Weakness	YES	NO	NO	TD Ligation	17	NR	NR
2011	Venkatramani et al., 2011. Pediatr Blood Cancer 56;667-670.	Thoracic and Lumbar Vertebrae, Ribs	Male	14	Bilateral	NR	Weakness	NO	NO	NO	NR	NR	NR	NR
2012	He et al., 2012. J Craniofac Surg 23;e293-295.	Maxilla	Male	37	NR	NR	Loose Teeth	NO	NO	NO	NR	NR	NR	NR
2012	Huang et al., 2012. J Craniomaxillofac Surg 40;e174-177.	Mandible	Male	32	NR	NR	Pain					NR	NR	NR
2012	Kotecha et al., 2012. Clin Radiol 2012. 67;782-788.	Ribs, Scapula, Thoracic and Lumbar Vertebrae, Pelvis, Femur, Tibia Fibula, Radius, Ulna	Female	9	Right-Sided	NR	NR	NO	NO	NO	NR	NR	NR	NR
2012	Kotecha et al., 2012. Clin Radiol 2012. 67;782-788.	Ribs, Scapula, Clavicle, Lumbar and Thoracic Vertebrae, Pelvis	Male	7	No	NR	NR	NO	NO	NO	NR	NR	NR	NR
2012	Kotecha et al., 2012. Clin Radiol 2012. 67;782-788.	Ribs, Scapula, Cervical, Thoracic and Lumbar Vertebrae, Pelvis, Humerus, Radius, Ulna	Male	9	No	NR	NR	NO	NO	NO	NR	NR	NR	NR
2012	Kotecha et al., 2012. Clin Radiol 2012. 67;782-788.	Lumbar Vertebrae, Pelvis	Female	11	No	NR	NR	NO	NO	NO	NR	NR	NR	NR
2012	Kotecha et al., 2012. Clin Radiol 2012. 67;782-788.	Sacrum, Pubis, Pelvis	Male	12	No	NR	NR	NO	NO	NO	NR	NR	NR	NR
2012	Kotecha et al., 2012. Clin Radiol 2012. 67;782-788.	Ribs, Cervical and Thoracic Vertebrae, Fibula	Male	12	Bilateral	NR	NR	NO	NO	NO	NR	NR	NR	NR
2012	Kotecha et al., 2012. Clin Radiol 2012. 67;782-788.	Ribs, Scapula, Thoracic Vertebrae, Pelvis, Humerus, Tibia, Fibula, Tarsals	Female	13	Bilateral	NR	NR	NO	NO	NO	NR	NR	NR	NR
2012	Kotecha et al., 2012. Clin Radiol 2012. 67;782-788.	Ribs, Scapula, Clavicle, Thoracic Vertebrae	Male	14	Bilateral	NR	NR	NO	NO	NO	NR	NR	NR	NR
2012	Ray et al., 2012. Indian J Pathol Microbiol. 55;399-401.	L-Humerus, L-Radius	Male	20	NR	NR	Pain, Swelling	NO	Bisphosphonate	NO	NR	NR	NR	NR
2013	Leite et al., 2013. Pediatr Dermatol 30;374-378.	L-Acetabulum, L-Ilium, R-Acetabulum, R-Ilium, Pubis, Lumbar Vertebrae	Female	7	NR	NR	Skin Lesion	YES	Bisphosphonate (Zoledronic Acid)	Interferon Alpha 2b	NR	NR	NR	D2-40
2013	Scheller et al., 2013. Oral Maxillofac Surg Epub	Mandible	Male	76	NR	NR	NR	NO	NO	NO	Resection	NR	YES	D2-40
2013	Situma et al., 2013. J Pediatr Surg 2013. 48;239-242.	L-Femur, L-Ilium, Pubis	Male	10	Bilateral	NR	Lymphatic Malformation	NO	NO	NO	Doxycycline, Sirolimus, Pleurodesis, MCT Diet	12?	NR	D2-40