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Gorham-Stout syndrome in mainland China: a case series of 67 patients and review of the literature[#]

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Abstract: Objective: Gorham-Stout syndrome (GSS) is a rare disorder of uncertain etiology and unpredictable prognosis. This study aims to present a comprehensive understanding of this rare entity. Methods: A literature search in PubMed and three Chinese databases was performed to screen histologically proven GSS cases among Chinese residents in the mainland. We analyzed the patients' clinical characteristics, the value of different treatment modalities and their influence on the clinical outcome. Results: Sixty-seven cases were finally enrolled. There were 43 men (64.2%) and 24 women (35.8%). The mean age at diagnosis was 28 years (1.5–71 years). The most common clinical symptoms included pain (*n*=40, 59.7%), functional impairment (*n*=13, 19.4%), and swelling (*n*=12, 17.9%). The radiographic presentation of 37 cases (55.2%) was disappearance of a portion of the bone. The others presented as radiolucent foci in the intramedullary or subcortical regions. A total of 42 cases provided data on therapy, these included surgery (*n*=27, 40.3%), radiation therapy (*n*=6, 9.0%), surgery combined with radiation therapy (*n*=2, 3.0%), and medicine therapy (*n*=7, 10.4%). For 30 of these 42 cases, follow-up data were available: 21 cases had the disorder locally controlled and 9 had a symptom progression. Fortunately, the disease is not fatal in the majority of cases. Conclusions: GSS has no specific symptoms and it should be taken into consideration when an unclear massive osteolysis occurs. The efficacies of different treatment modalities are still unpredictable and further research is required to assess the values of different treatments.

Key words: Gorham-Stout syndrome (GSS), Massive osteolysis, Chinese
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1 Introduction

Gorham-Stout syndrome (GSS) is a very rare disorder characterized by recurrent spontaneous resorption of bones in different regions. This rare entity was initially reported by Jackson (1838) in a 12-year-old boy. Gorham and Stout (1955) originally described the disease as a distinct entity. It may affect any part of the skeleton. Involvement of the scapula, ribs, or thoracic vertebra can result in pleural effusions or chylothorax (Tie *et al.*, 1994). The diagnosis is established via the combination of clinical, radiologic, and histologic features after excluding neoplastic, endocrinologic, infectious, and inflammatory diseases. The treatment of GSS includes surgery, radiation therapy, and medicine therapy. Generally,

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the prognosis is considered to be good when only the limbs or the pelvic bones are involved (Kulenkampff *et al.*, 1990; Stove and Reichelt, 1995; Rauh and Gross, 1997; Boyer *et al.*, 2005). However, involvement of vital structures may be fatal (Hagberg *et al.*, 1997; Ng and Sell, 2003; Patel, 2005).

Since this disease has been first described in Jackson (1838), so far, no more than 200 cases have been documented in the English literature, and current knowledge of GSS is largely based on sporadic case reports. Herein, to present a comprehensive understanding of this entity, we screened and analyzed all the cases of histologically proven GSS among Chinese residents in the mainland.

2 Materials and methods

All cases of GSS were screened from a literature search in PubMed and three Chinese databases (Chinese Biomedicine Literature Database (CBM), VIP Database for Chinese Technical Periodicals, and Wanfang Database). Combinations of the keywords "China" and MeSH (Medical Subject Headings) words "Osteolysis, Essential" or text words like Gorham-Stout syndrome, Gorham syndrome, Gorham disease, Gorham's massive osteolysis, Morbus Gorham Stout disease, massive osteolysis, vanishing bone disease, disappearing bone disease, disappearing bone, or disappearing bone disease were used for the search. We manually examined references in selected articles and studies. We analyzed the patients' clinical characteristics, values of different treatment modalities and their influences on the clinical outcome. Inclusion criteria were as follows (Heffez *et al.*, 1983): (1) a positive biopsy; (2) the absence of cellular atypia; (3) minimal or no osteoblastic response and absence of dystrophic calcification; (4) evidence of local, progressive osseous resorption; (5) nonexpansile, nonulcerative lesion; (6) absence of visceral involvement; (7) osteolytic radiographic pattern; (8) no known hereditary, metabolic, immunological, or infectious cause; (9) Chinese residents in the mainland. Therapy response was defined as "Controlled" (the radiographic presentation of the affected bone had not changed, and no newly emerging bone destruction) or "Progression" (the progressive resorption of the affected bone and/or newly emerging bone destruction).

3 Results

A total of 67 cases (64 in Chinese and 3 in English) of GSS in 54 papers were enrolled for analysis (Table S1), of whom 43 patients were male (64.2%), and 24 cases were female (35.8%). The mean age at diagnosis was 28 years (1.5–71 years). No family history of GSS was found in any of the patients. A history of preceding trauma was present in 4 cases (6.0%). Of the 67 cases, the femur (n=18, 26.9%) was the most common site of involvement. Involvement of more than three sites in the skeletal system occurred in 17 patients (25.4%). Pleural effusion was found in 10 cases, of which 8 had an accompanying chylothorax (11.9%). Only 5 patients had involvement of the bony structures of joints (7.5%). The most common manifestations included pain (n=40, 59.7%), functional impairment (n=13, 19.4%), and swelling (n=12, 17.9%). Eighteen patients (26.9%) were diagnosed after a pathological fracture. Three patients (4.5%) were found with massive osteolysis by coincidence, and 4 patients (6.0%) presented with tooth loss. One case was reported where both the affected bone and the adjacent soft tissue were involved with dilated lymphatic channels. On radiographic evaluations, the disappearance of a portion of the bone was described in 37 cases (55.2%), and the others presented as radiolucent foci in the intramedullary or subcortical regions. In the long bones, the tapering of the residual bone may show "licked candy stick" deformity (n=14, 20.9%). The most common pathological findings were the presence of numerous thin-walled blood vessels, lymphatic vessels, or fibrous tissue (n=67, 100%). The osteoclast in areas of bone resorption was found in 5 cases (7.5%), and chronic inflammatory cells in the affected areas were found in 12 cases (17.9%). Results of laboratory analysis were normal, except an elevated erythrocyte sedimentation rate in 2 cases (3.0%) and an increased alkaline phosphatase in 1 case (1.5%).

A total of 42 cases had complete data for therapy protocol (Table 1). For 30 of these 42 cases, follow-up data were available. The mean follow-up time was 20.7 months (2–72 months). Twenty-seven cases underwent surgery (Table 2), of which 11 cases had the diseases locally controlled (the mean follow-up time was 16.4 months), 5 had a symptom progression

(the mean follow-up time was 12.0 months), 1 patient died (the follow-up time was 18.0 months), and the remaining 10 cases were lost to follow up. Six cases underwent radiation therapy, of which 4 cases had the diseases locally controlled (the mean follow-up time was 14.0 months, 1 case at a total dose 50 Gy, and 3 cases lack of details on radiotherapy), and 2 cases had a symptom progression (the mean follow-up time was 66.0 months, 1 case at a total dose 57 Gy, and 1 case lack of details on radiotherapy). Two patients who underwent a combination of surgery and radiation therapy had the disorder locally controlled (the mean follow-up time was 14.0 months, one case at a total dose 30.6 Gy, one case lack of details on radiotherapy). Seven patients only underwent medicine therapies (Table 3), of which 4 cases had the diseases locally controlled (the mean follow-up time was 22.5 months), 1 had a symptom progression (the follow-up time was 22.0 months), and the remaining 2 cases were lost to follow up. Among the 27 cases who underwent surgery, 13 cases underwent resection of the lesion (3 cases had the diseases locally controlled, 2 had a symptom progression and the remaining 8 cases were lost to follow up), 8 cases underwent reconstruction using prostheses (6 cases had the diseases locally controlled and 2 cases were lost to follow up), 3 cases underwent reconstruction using bone grafts (2 cases had a symptom progression, 1 case died), 1 case underwent thoracic duct ligation combined with chest drainage (the disease was locally controlled), 1 case underwent thoracic duct ligation combined with pleurodesis (the disease was locally controlled), and 1 case underwent pleurodesis combined with chest drainage (had a symptom progression).

Table 1 Outcome of different treatment modalities

Treatment modality	*n*	Controlled	Progression	Died	Lost to follow up
Surgery	27	11	5	1	10
Radiation	6	4	2	0	0
Medicine therapy	7	4	1	0	2
Surgery+radiation	2	2	0	0	0

Controlled: the radiographic presentation of the affected bone had not changed, and no newly emerging bone destruction; Progression: progressive resorption of the affected bone and/or newly emerging bone destruction

Table 2 Outcome of different surgeries

Surgery	*n*	Controlled	Progression	Died	Lost to follow up
Resection of the lesion	13	3	2	0	8
Reconstruction using prostheses	8	6	0	0	2
Reconstruction using bone grafts	3	0	2	1	0
Thoracic duct ligation+chest drainage*	1	1	0	0	0
Thoracic duct ligation+pleurodesis*	1	1	0	0	0
Pleurodesis+chest drainage*	1	0	1	0	0

* In patients with chylothorax. Controlled: the radiographic presentation of the affected bone had not changed, and no newly emerging bone destruction; Progression: progressive resorption of the affected bone and/or newly emerging bone destruction

Table 3 Outcome of different medicine therapies

Therapy	*n*	Controlled	Progression	Lost to follow up
Interferon	2	1	0	1
Diphosphonate	1	1	0	0
Calcium salts+vitamin D	1	1	0	0
Cyclophosphamide+fluorouracil	2	0	1	1
Calcitonin salmon+alendronate sodium	1	1	0	0

Controlled: the radiographic presentation of the affected bone had not changed, and no newly emerging bone destruction; Progression: progressive resorption of the affected bone and/or newly emerging bone destruction

4 Discussion

GSS is a very rare disorder characterized by spontaneous resorption of bones with mono- or polyostotic lesions. In most cases, the disease occurs in children or young adults with no clear genetic cause. In the 67 cases, the mean age at diagnosis was 28 years and only 13 patients (19.4%) were older than 40 years. We found that there was a male preference (43 males vs. 24 females, the gender ratio was about 1.8). However, some authors believe that there is no gender preference (Patel, 2005; Collins, 2006; Tong *et al.*, 2010). The clinical complaint of GSS varies depending on the affected site, making the diagnosis of this uncommon entity difficult. The most common clinical symptoms of the 67 cases included pain (n=40, 59.7%), functional impairment (n=13, 19.4%), and swelling (n=12, 17.9%).

The pathogenesis of the disorder is poorly understood, and a large variety of possible causes have been reported in the literature. The osteoclast is the only cell capable of bone destruction. However, the role of the osteoclast in this disorder is in dispute. Gorham and Stout (1955) suggested that "osteoclastosis" was not necessary and Foult *et al.* (1995) found that osteolysis was secondary to angiomatosis. In contrast, Spieth *et al.* (1997) reported that there was a clear relationship between osteoclasts and this rare syndrome, and Möller *et al.* (1999) found a large number of multi-nucleated osteoclasts with hyperactive resorptive function in their patients. In our case series, the osteoclast in areas of bone resorption was found in only five cases (7.5%), which suggested "osteoclastosis" may be not necessary in this entity. Some authors described that interleukin-6 (IL-6) may cause bone resorption because it can stimulate osteoclast activity and increase sensitivity of osteoclast precursors to humoral factors (Möller *et al.*, 1999; Hirayama *et al.*, 2001; Hammer *et al.*, 2005). Devlin *et al.* (1996) demonstrated that the blood level of IL-6 was seven times the upper limit of the normal range, and fell to one quarter the pretreatment value after further treatment. In our case series, chronic inflammatory cells in the affected areas were found in 12 cases [IL-6/vascular endothelial growth factor (VEGF) levels are not known for the patients in our case series]. As we know, IL-6 level is closely related to chronic inflammatory cells, so we suggest that IL-6 may play an important role in this entity. Aviv *et al.* (2001) suggested that disseminated lymphangiomatosis and GSS might represent two varieties of a single rare disease. Radhakrishnan and Rockson (2008) suggested that GSS was a disease of disordered lymphangiogenesis. Dupond *et al.* (2010) reported that serum VEGF showed a marked elevation at diagnosis, which was normalized after 18 months of interferon treatment. VEGF recruits monocytes/macrophages (Barleon *et al.*, 1996) which are reported to secrete the lymphangiogenic growth factors VEGF-C (von Marschall *et al.*, 2003). The VEGF-C/VEGF receptor-3 signaling system is the most efficient pathway in regulating lymphangiogenesis (Li *et al.*, 2011). In the 67 cases, numerous thin-walled blood vessels, lymphatic vessels, or fibrous tissue are common pathologic findings, which indicated the important role of lymphangiogenesis. Obviously, further research on the relationship between lymphangiogenesis and GSS may help to understand the mechanism of this rare entity.

Because of the rarity of the disease, a standardized treatment strategy is not available. The treatment modalities include medicine therapy, radiation therapy, and surgery. Medicine treatments include calcium salts, vitamin D supplements, hormone (calcitonin), interferon, bisphosphonate. One patient in our case series who just underwent calcium salts and vitamin D supplements achieved partial recovery after a follow-up of 5.5 years. However, Vinée *et al.* (1994) reported that treatment with hormone combined with calcium salts and vitamins showed no efficacy. Interferon may be useful in disorders with vessel proliferation because of its antiangiogenic properties (Takahashi *et al.*, 2005). Interferon α-2b was successfully used to treat one patient at a dosage of (7.5–15) million IU three times a week for five years (Dupond *et al.*, 2010). Bisphosphonate is helpful because of its putative antiosteoclastic and anti-angiogenic activity. Lehmann *et al.* (2009) reported that a case of GSS was successfully treated with bisphosphonates for more than 17 years. Hammer *et al.* (2005) reported that mono-therapy with bisphosphonates (30 mg intravenous every three months) controlled the disorder during two years of follow-up. However, one patient who was treated with interferon α-2b and bisphosphonate died four months after the diagnosis of GSS (Deveci *et al.*, 2011).

GSS was treated effectively with radiation therapy in several reports (Bruch-Gerharz *et al.*, 2007; Johnstun *et al.*, 2010; Browne *et al.*, 2011; Heyd *et al.*, 2011b). Dunbar *et al.* (1993) reviewed the 22 published cases of GSS treated with radiation therapy and found that definitive radiation therapy in moderate doses (40–45 Gy at 1.8–2.0 Gy per fraction) was effective. Recently, the German Cooperative Group on Radiotherapy for Benign Diseases conducted a national patterns-of-care study to evaluate the value of radiation therapy in the treatment of GSS. They concluded that radiation therapy may prevent disease progression effectively in GSS in 77% to 80% of cases at a total dose ranging from 30 to 45 Gy (Heyd *et al.*, 2011a). However, for young adults and particularly in children, a very critical indication for radiation therapy is required, due to the increased risk of radiotherapy-induced neoplasms and severe late toxicity (McNeil *et al.*, 1996; Ricalde *et al.*, 2003).

Surgical therapy includes resection of the lesion, reconstruction using bone grafts and/or prostheses (Woodward *et al.*, 1981; Vinée *et al.*, 1994; Wang and Lin, 2004; Escande *et al.*, 2008), thoracic duct ligation, pleurodesis, and chest drainage. It has been reported that progression of bone graft has led to failure of reconstruction (Woodward *et al.*, 1981; Kulenkampff *et al.*, 1990; Paley *et al.*, 2005); however, reconstruction using prostheses seems to be more effective. In our case series, six patients who underwent reconstruction using prostheses had the disorder controlled and three patients who underwent reconstruction using bone grafts had a symptom progression. However, further clinical studies are needed to evaluate the efficacy of different surgeries. In patients with chylothorax, thoracic duct ligation, pleurodesis, and chest drainage were used. Tie *et al*. (1994) reviewed 146 cases of Gorham-Stout syndrome and found that 25 patients (17%) had chylothorax. They reported that some patients underwent successful thoracic duct ligation and survived. However, thoracic duct ligation does not always lead to a lasting resolution of chylothorax (Choma *et al.*, 1987; Fujiu *et al.*, 2002). In our case series, 2 of the patients who underwent thoracic duct ligation combined with chest drainage or thoracic duct ligation combined with pleurodesis had the disorder controlled, and the patient who underwent pleurodesis combined with chest drainage had a symptom progression. We advise that more research is required to further elucidate the pathogenesis of patients with chylothorax, and further studies are needed to seek effective therapies.

5 Conclusions

The characteristics of GSS reported in Mainland China are similar to those reported in Western studies. GSS has no specific symptoms, and it should be taken into consideration when an unclear massive osteolysis occurs in children or adolescents. Due to the rarity of the disorder, no standardized treatment regimen is available. Bone grafts appear to be ineffective and reconstruction using prostheses may be worth considering for cases of pathological fracture and/or massive bone resorption. Assessment of the efficiency of different therapeutic regimen was not allowed because of limited cases in our study, and further clinical studies are needed.

Compliance with ethics guidelines

Po HU, Xiang-gui YUAN, Xin-yang HU, Fa-rong SHEN, and Jian-an WANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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List of electronic supplementary materials

Table S1 Baseline characteristics of the 67 cases

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Mark	Rank	Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor® Metrics	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor® Score	Article Influence® Score
	1	J ZHEJIANG UNIV-SC B	1673-1581	1150	1.108	1.285	0.190	116	4.5	0.00331	0.292

For the last 3 years, *JZUS-B* has seen the following Impact Factor trend:

Year	Impact Factor	Citations
2012	1.108	1150
2011	1.099	946
2010	1.027	770