European Review for Medical and Pharmacological Sciences 2016; 20: 426-432

Novel approach of treating Gorham-Stout disease in the humerus – Case report and review of literature

R. ELLATI[1], A. ATTILI[1], H. HADDAD[2], M. AL-HUSSAINI[2], A. SHEHADEH[3]

[1]Department of Surgery, King Hussein Cancer Center, Amman, Jordan
[2]Department of Pathology and Laboratory Medicine, King Hussein Cancer Center, Amman, Jordan
[3]Orthopedic Oncology Unit, Department of Surgery, King Hussein Cancer Center, Amman, Jordan

Abstract. – Gorham-Stout disease or the so-called vanishing bone syndrome is a rare disorder characterized by intra-osseous proliferation of vascular channels resulting in destruction and resorption of the osseous matrix. The exact pathology of this disease showed no evidence of malignant, neuropathic, or infectious components involved in the causation of this disorder except for the culprit of lympho-vascular malformations in the bone. The mechanism of bone resorption is yet to be clarified. The clinical presentation of Gorham's disease varies according to the organ of involvement. Patients diagnosed with Gorham's disease in the bone may initially present with insidious onset of dull aching pain, progressive weakness, or pathologic fractures as the initial presentation. Gorham's disease is progressive in most patients; yet it can be self-limiting in a few reported cases. The axes of treating this disease as reported in the literature include the use of medical treatment, surgical intervention, radiotherapy and/or the combination of any them. However, there is no consensus about the most effective approach for treating this rare disease. The challenge in this disease lies in both: how to diagnose and how to treat. Our novel approach combined surgical intervention, medication and radiotherapy as a treatment of Graham-Stout disease in the humerus, and showed no progression of the disease our case.

Key words:
Gorham-Stout disease, Bone resorption, Progressive weakness, Pathologic fractures

Case Report

An 18 year old gentleman was referred to our quaternary cancer center from private practice, for a non-healing mid-shaft humeral fracture after a sequence of conservative and operative management. The patient presented with a left arm pain after falling down. The physical exam then, showed swelling, bruises, deformity, tenderness and a decrease in the range of movement of the affected arm. Antero-posterior and lateral left humerus X-rays showed a mid shaft transverse non-displaced left humeral fracture (Figure 1-A). Initially, the patient was treated conservatively using a back- slab and arm sling. Six weeks later, the X-ray of his left arm showed persistence of the fracture (Figure 1-B), besides a noticeable bone resorption at the fracture site, and tapering of the bone ends. Twelve weeks after treatment a new x-ray was obtained and showed more resorption of bone and very clear tapering bone ends (Figure 1-C). Consecutively, the patient underwent an open-reduction, and a rush nail-fixation with iliac-bone grafting outside our facility. Eight weeks after surgery, X-ray showed surprisingly even more resorption at the fracture site and tapering of the bone edges (Figure1-D, E). Accordingly, the patient was referred to the Orthopedic Oncology Unit at King Hussein Cancer Center (KHCC).

Detailed evaluation at our institution included a new X-ray which showed further bone loss at mid humerus, tapering ends, yet no periosteal reaction or matrix formation were noted (Figure 1-F). Moreover, extensive blood work-up excluded secondary causes of bone resorption (secondary hyperparathyroidism, renal osteodystrophy, etc.). The next step was to obtain an open biopsy for histopathology, which later showed fibrous tissue, inflammatory cells but no malignant cells, further immune-staining with D2-40 (ABCAM®, Cambridge, UK) showed the presence of lymphatic vessels in the bone (Figure 2- A,B and C).

Eventually, the diagnosis of Gorham's disease was reached. The basis for the diagnosis was the non-healing nature of the fracture despite an adequate fixation, the classical radiological appearance of Gorham's disease (tapering bone ends or mouse

Corresponding Author: Ahmed Shehadeh, MD, FRCS; e-mail: ashehadeh@khcc.jo

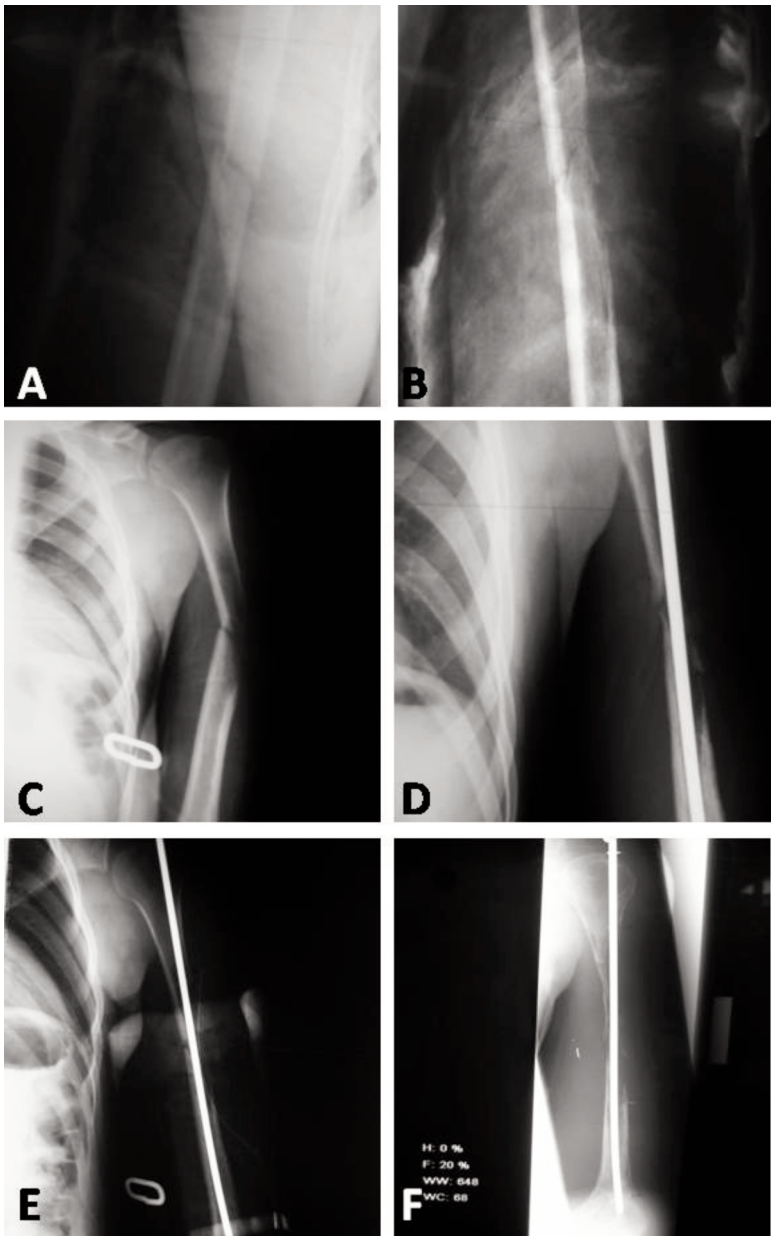

Figure 1. An antero-posterior X-ray of the left humerus over the course of treatment. ***A***, At time of first presentation at an outside facility. A transverse fracture at the mid-shaft humerus, post conservative management with U-slab immobilization. **B**, Six weeks after fracture, no signs of healing, increased bone resorption and tapering of the bone ends. **C**, 12 weeks after conservative treatment. **D**, Four weeks post-operative nailing done by other facility. **E**, Eight weeks after nailing, more bone loss, and more tapering ends of the fracture. **F**, At time of presentation to our facility.

tail appearance), exclusion of secondary causes of bone resorption, and the pathological findings of lymph-vascular tissue in the bone as seen in biopsy with positive D2-40 immunostain for lymph vessels sensitivity is 92.6% and specificity is 98.8%[1].

The treatment plan was discussed and confirmed in the meeting of the multidisciplinary clinic (doctors of different specialties: orthopedic oncology, pathology, medical oncology, radiation oncology and radiology). Since the patient is left-handed, and the limb was already immobilized for more than 5 months; therefore, there was a clear need for intervention which will allow early resumption of his left upper limb movement. Hence, the plan of treatment was to proceed with a reconstructive surgery and to withhold the treatment with bisphosphonates and radio therapy.

Surgical procedure

- Under general anesthesia, endotracheal intubation, supine position, painting, toweling and draping.
- Anterolateral approach to the mid humerus with ellipse skin incision around the old surgical scar.

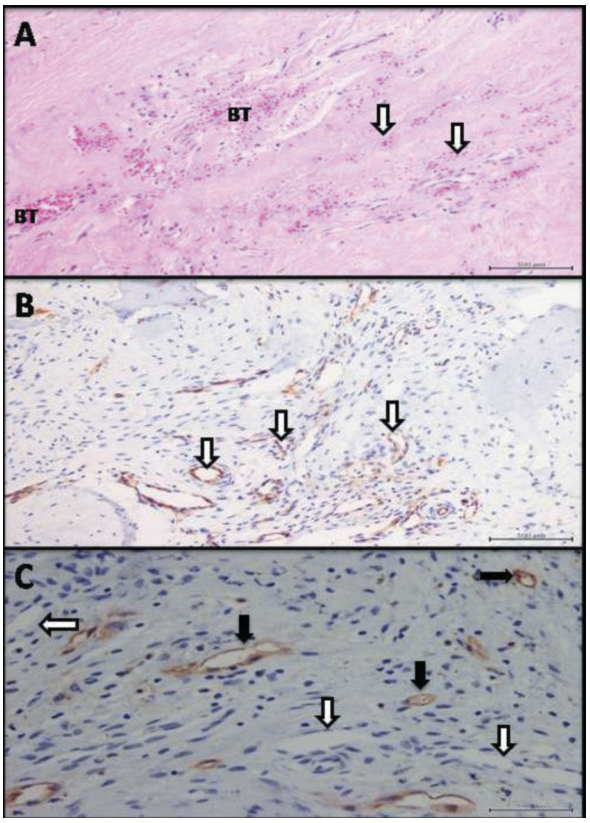

Figure 2. Histopathology of left mid-shaft humerus biopsy; showing lymphatic vessels in the bone. **A**, Bone trabeculae (BT) separated by vascular spaces (white arrow) stained by Hematoxylin and Eosin, magnified 20 times (X20). **B**, CD31 immunostain further highlighted the vascular spaces separating the bone trabeculae (X20). **C**, D2-40 immunostain labeled some of the vascular spaces confirming the lymphatic nature of some of the vessels (Solid black arrow), and unlabelled blood vessels (white arrow) (X40).

- Almost 15 cm of the mid-shaft humeral bone was replaced by highly vascular fibrous tissue. Identification, isolation and protection of the radial nerve.
- Resection of the middle 18 cm of the humerus and removal of the old rush nail.

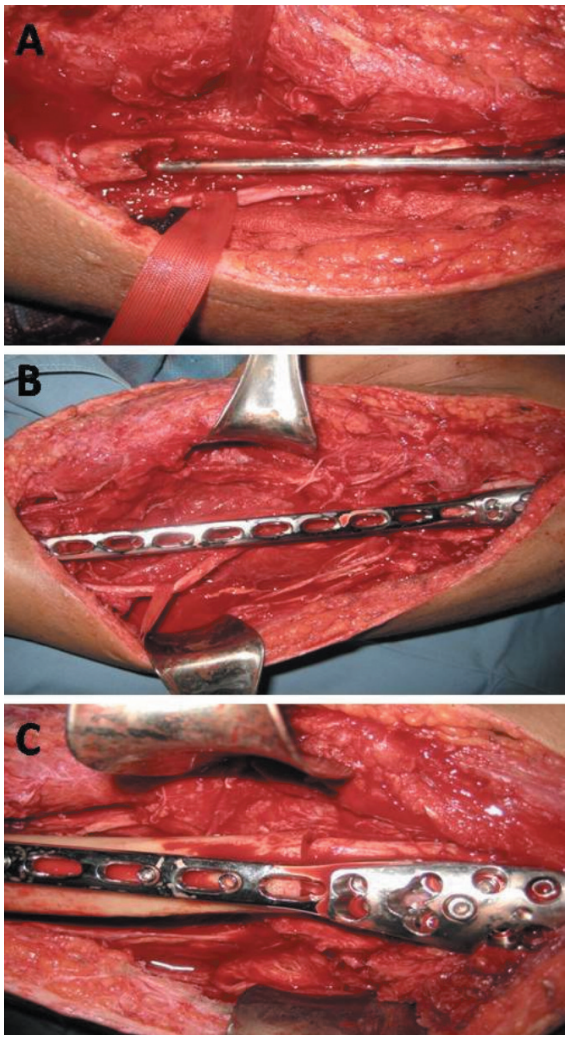

Figure 4. A, Intra operative photo showing the bone is destructed, and the fixation device (rush nail) is exposed with almost complete bone resorption from all directions and replaced by fibrous tissue. The radial nerve is identified and pulled by umbilical tape. **B**, The proximal humerus LCP plate is fixed to the host bone first. C. Introduction of the bone allograft at the gap, and fixing it to the proximal humerus LCP plate.

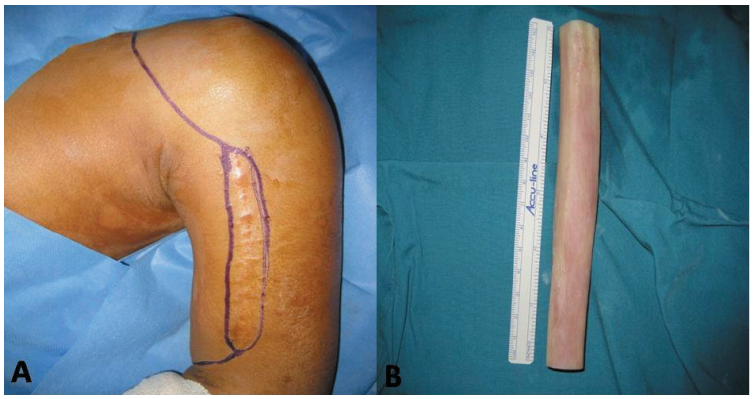

Figure 3. A, An intra-operative photo shows the left shoulder and proximal humerus. Marker shows the planned surgical approach with excision of the previous biopsy tract in the new incision. **B**, The frozen structural bone allograft that we used, after heating for 20 minutes in 40° C normal saline solution.

- Fixation of the host proximal humerus with 3.5 mm Titanium LCP proximal humerus plate (Synthes®, Warsaw, IN, USA) and fixation of the distal part with anatomical 3.5 mm Titanium LCP medial distal humerus plate (Synthes®, Warsaw, IN, USA).
- Introduction of structural bone allograft with matching size and laterality into the gap (18cm). The allograft was brought frozen and heated at 35°C in a sterile saline for 30 minutes. The graft was then fixed to the proximal and distal parts of the host bone using the proximal humerus plate to fix the graft to the proximal part of the humerus, and anatomical distal humerus plate to fix the graft to the distal part of the host humerus.
- Re-attachment of the deltoid muscle to the allograft using anchor suture techniques.
- Drain inserted and closure in layers.

The multidisciplinary clinic was held again in regards to this case and the decision was made to start radiotherapy as the next step followed by bisphosphonates (Fosamax 70 mg once weekly for 2 years). The patient received the following regimen of radiotherapy (Total number of fractions: 20. Regional dose cGY: 4000. Type of radiation: radical).

The patient felt progressive pain and a draining sinus was formed from the lateral aspect of the arm. Cultures were obtained and were positive for infection. He was diagnosed with chronic osteomyelitis, and received suppressive antibiotic treatment, with drainage of the local abscesses in 2 occasions in the six-year course post operatively. His infection was well controlled using the suppressive antibiotics and only minor drainage was needed. Despite the infection, our team decided to avoid the risk of plate removal, and the likelihood of no healing at the interface of the host allograft proximally and distally. Since stable infected non union is better than an unstable infected non union.

At the last follow-up seven years after surgery, the patient continued to have an active movement at the left elbow. No recurrence of the condition was found i.e. no resorption of the structural bone allograft. However, signs of non-union at the distal host-allograft junction were still evident. He nevertheless continues to follow the infectious disease clinic for chronic osteomyelitis and treatment with antibiotics.

Discussion

Gorham-Stout disease or the so-called vanishing bone syndrome is a rare disorder characterized by intra-osseous proliferation of vascular

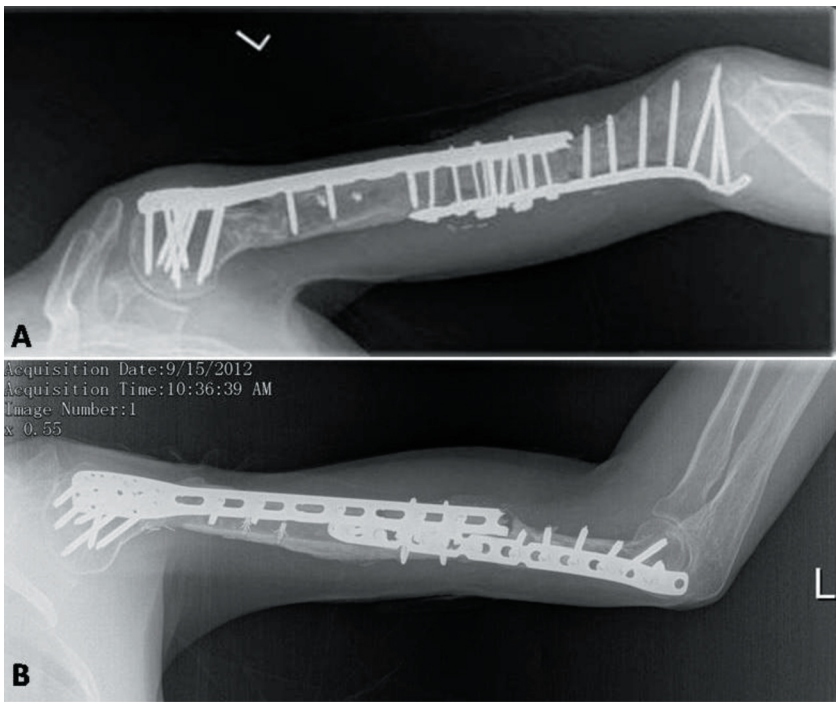

Figure 5. X-ray of the left humerus same day postoperatively showing effective sufficient fixation of the fracture **A**, Antero-posterior view. **B**, Lateral view.

Table I. Different Anatomical locations for multiple cases of Gorham's disease as prescribed in literatures.

Anatomical location	Number
Thorax	25
Femur	17
Mandible	4
Pelvis	4
Scapula	2
Humerus	2
Vertebra	2
Tibia	2
Clavicle	1
Joints	5
Total	**64**

channels resulting in destruction and resorption of the osseous matrix[2]. The exact pathology of this disease showed no evidence of malignant, neuropathic, or infectious components involved in the causation of his disorder except for the culprit of lympho-vascular malformations in the bone[3]. The mechanism of bone resorption is yet to be clarified. Gorham's disease is progressive in most patients; yet it can be self-limiting in a few reported cases[4]. The axes of treating this disease as reported in the literature include the use of medical treatment, surgical intervention, radiotherapy and/or the combination of any them[5]. However, there is no consensus about the most effective approach for treating this rare disease. The challenge in this disease lies in both; its diagnosis and treatment.

A thorough literature review revealed there are a total of 64 cases reported. Nineteen of them presented with involvement of multiple bones. Isolated bone disease was most commonly found in the rib cage followed by the femur (Table I). Treatment outcome in literature was divided into: controlled and not controlled disease. Controlled disease means the radiographic presentation of the affected bone did not change, and no emerging bone resorption is seen[6]. Not controlled disease means the disease is progressive and bone resorption is noted[6].

The different modalities of treatment used in the published cases can be summarized as surgical, medical and radiation intervention (Table II and Figure 6)[7-21]. Surgical treatment for Gorham's disease includes: resection alone, resection with endo-prosthetic reconstruction, and resection with biological reconstruction. Biological reconstruction can include either autogenous bone grafting or allogenous bone graft.

Table II. Different modalities used in litereture for the treatment of Gorham's disease.

Modality of treatment	Number of cases	Controlled	Not controlled	Lost follow up
Radiation alone	8	6	2	—
Surgery combined with radiation	2	2	0	—
Surgery alone	29	13	6	10
Medical treatment	25	19	4	2
Total	**64**	**40**	**12**	**12**

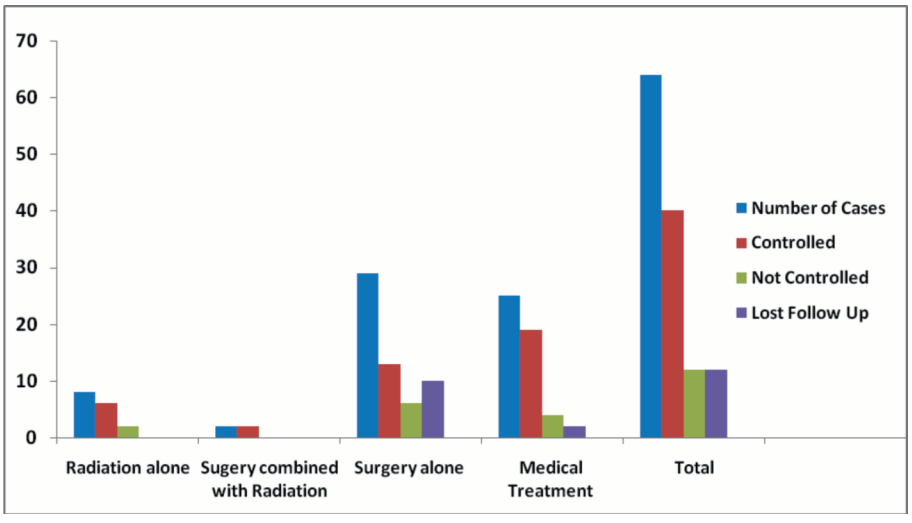

Figure 6. Different modalities used in litereture for the treatment of Gorham's Disease.

Table III. Different surgical modalities in treating patients with Gorham's disease.

Surgery	Number of treated cases	Controlled	Uncontrolled	Lost to follow up
Resection of the lesion	13	3	2	8
Reconstruction using prosthesis	10	8	0	2
Reconstruction with bone graft	3	0	3	0
Thoracic duct ligation with chest drainage	1	1	0	0
Thoracic duct ligation with pleurodesis	1	1	0	0
Pleurodesis with chest drainage	1	0	1	0
Total	**29**	**13**	**6**	**10**

Resection alone is more suitable for expendable bone like: fibula, iliac bone, pubic bone, and clavicle. While for weight bearing bones like femur, tibia in the lower limb, and long bones in the upper limbs, reconstruction is mandatory (Table III). None of the previously mentioned surgical techniques showed high success rate in controlling the progression of the disease in long bones.

The disease was controlled in only 13 cases out of 29 cases that received surgical treatment, six were progressive and not controlled and ten were lost from follow up. Regarding humerus bone, two cases were reported. In the first case: a segment of proximal 25 centimeters (9 inches) of the right humerus was resected by extra-periosteal dissection and replaced by a hollow Titanium 160 prosthesis that was sealed by welding and no recurrence for more than 3 years[15]. While in the second case the patient was an adolescent male of Noonan syndrome presented with a non-healing fracture of the proximal right humerus. He was treated with radiotherapy which showed recurrence after 7 years of follow up[10].

Medical treatment includes: Interferon, bisphophonates, calcium salts and vitamin D, and cyclophosphamides (Table IV). Bisphosphanates gained a high success rate, Zoledronic acid was effective in the treatment with no recurrence in a 9 year old boy[6] and a 24 year old lady with mandible affection[11].

Radiation therapy has been reported also in literature, definitive radiation therapy in moderate doses (40-45 Gcy in 2 Gcy fractions) appears to have a good outcome as three out of four survived with no recurrence except for few long-term complications[9]. Taking into consideration the above mentioned tables of treatment options to control this rare disease, we chose to combine surgical modalities with the other modalities.

In our case the intercalary segment was involved, we decided to keep both ends of the humerus, resect the diaphysis, and replace it with structural bone allograft matching laterality and size of the resected bone. Surgery was followed by radiotherapy based on its added benefit from the literature and the use of oral bisphosphantaes for two years. At seven-year follow up, the disease was controlled, and no father resorption of bone was noted.

Based on the outcomes of the different modalities of treatment and exemplified by our case, the combination of surgery, medication, and radiotherapy gave an added benefit to control this rare disease. This novel approach was adopted and gave results of well-controlling the disease and no progression.

Table IV. Different medical treatments used in treating patients with Gorham's disease.

Medical treatment	Number of Treated cases	Controlled	Uncontrolled	Lost to follow up
Interferon	11	8	2	1
Bisphosphonate	6	6	0	0
Interferon + Zolendronic acid	2	2	0	0
Bevacizumab	2	1	1	0
Calcium Salts + Vitamin D	1	1	0	0
Cyclophosphamide +Fluorouracil	2	0	1	1
Calcitonin Salmon + Alendronate Sodium	1	1	0	0
Total	**25**	**19**	**4**	**2**

Conclusions

This case is a successful story of multimodality treatment of Gorham's disease of the long bone. Surgical resection plus adjuvant radiotherapy followed by oral bisphosphonates for 2 years. This novel combination was not previously reported in literature for the treatment of Gorham's disease, and showed a success at seven-year follow up.

Acknowledgment

We extend our thanks to our beloved patient who chose to be anonymous.

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

1. Evangelou E, Kyzas PA, Trikalinos TA. Comparison of the diagnostic accuracy of lymphatic endothelium markers: Bayesian approach. Mod Pathol 2005; 18: 1490-1497.
2. Patel DV. Gorham's disease or massive osteolysis. Clin Med Res 2005; 3: 65-74.
3. Elluru RG, Balakrishnan K, Padua HM. Lymphatic malformations: diagnosis and management. Semin Pediatr Surg 2014; 23: 178-185.
4. Dellinger MT, Garg N, Olsen BR. Viewpoints on vessels and vanishing bones in Gorham-Stout disease. Bone 2014; 63: 47-52.
5. Liu Y, Zhong DR, Zhou PR, Lv F, Ma DD, Xia WB, Jiang Y, Wang O, Xing XP, Li M. Gorham-Stout disease: radiological, histological, and clinical features of 12 cases and review of literature. Clin Rheumatol 2014 Sep 18. [Epub ahead of print].
6. Hu P, Yuan XG, Hu XY, Shen FR, Wang JA. Gorham-Stout syndrome in mainland China: a case series of 67 patients and review of the literature. J Zhejiang Univ Sci B 2013; 14: 729-735.
7. 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: 319-322.
8. Grunewald TG, Damke L, Maschan M, Petrova U, Surianinova O, Esipenko A, Konovalov D, Behrends U, Schiessl J, Wörtler K, Burdach S, von Luettichau I. First report of effective and feasible treatment of multifocal lymphangiomatosis (Gorham-Stout) with bevacizumab in a child. Ann Oncol 2010; 21: 1733-1734.
9. 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: 491-497.
10. Fontanesi J. Radiation therapy in the treatment of Gorham disease. J Pediatr Hematol Oncol. 2003; 25: 816-817.
11. Mignogna MD, Fedele S, Lo Russo L, Ciccarelli R. Treatment of Gorham's disease with zoledronic acid. Oral Oncol 2005; 41: 747-750.
12. 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: 667-670.
13. Hammer F, Kenn W, Wesselmann U, Hofbauer LC, Delling G, Allolio B, Arlt W. Gorham-Stout disease--stabilization during bisphosphonate treatment. J Bone Miner Res 2005; 20: 350-353.
14. Zheng MW, Yang M, Qiu JX, Nan XP, Huang LY, Zhang WD, Gong L, Huang ZZ. Gorham-Stout syndrome presenting in a 5-year-old girl with a successful bisphosphonate therapeutic effect. Exp Ther Med 2012; 4: 449-451.
15. Poirier H. Massive osteolysis of the humerus treated by resection and prosthetic replacement. J Bone Joint Surg Br 1968; 50: 158-160.
16. Vitali M. The prosthetic management of a case of essential osteolysis. J Bone Joint Surg Br 1962; 44-B: 652-654.
17. Kakuta Y, Iizuka H, Kobayashi R, Iizuka Y, Takahashi T, Mohara J, Takagishi K. Gorham disease of the lumbar spine with an abdominal aortic aneurysm: a case report. Spine J 2014; 14: e5-9.
18. Heyd R, Rabeneck D, Dornenburg O, Tselis N, Zamboglou N. Gorham-Stout syndrome of the pelvic girdle treated by radiation therapy: a case report. Strahlenther Onkol 2011; 187: 140-143.
19. 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: 579-584.
20. Kose M, Pekcan S, Dogru D, Akyuz C, Ozcelik U, Ozsurekci Y, Gulhan B, Demircin M, Kiper N. Gorham-Stout Syndrome with chylothorax: successful remission by interferon alpha-2b. Pediatr Pulmonol 2009; 44: 613-615.
21. Takahashi A, Ogawa C, Kanazawa T, Watanabe H, Suzuki M, Suzuki N, Tsuchida Y, Morikawa A, Kuwano H. Remission induced by interferon alfa in a patient with massive osteolysis and extension of lymph-hemangiomatosis: a severe case of Gorham-Stout syndrome. J Pediatr Surg 2005; 40: E47-50.