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ORIGINAL STUDY

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Gorham Stout disease: 3 additional cases with 2 very rare polyostotic diseases

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Gorham Stout disease is a very rare monostotic or polyostotic osteolysis and physiopathology of the osteolysis is not yet fully understood. Three new cases are reported with their evolution and treatment. Among these 3 cases, two are very rare cases of polyostotic involvement. One patient finally deceased from respiratory complications despite limb amputation. The two others are alive. Both needed final reconstruction with massive bone allograft for one and with a prosthesis for the other.

Monostotic osteolysis is the most frequent presentation of Gorham Stout disease and extensive polyostotic osteolysis is very rare. Treatment methods vary from one clinic to another, from drug treatment to surgical treatment with or without radiotherapy. Sometimes, as a last solution, an amputation of the affected limb is performed. The prognosis depends on the affected region and the reponse to various treatments. Chylothorax seems to be a factor of poor prognosis.

Keywords : Gorham Stout disease, osteolysis, massive allograft reconstruction, prosthesis reconstruction.

INTRODUCTION

Gorham Stout disease (GSD) is a rare bone disorder characterized by abnormal proliferation of thin-walled endothelial-lined channels of vascular and lymphatic origin and the presence of a large number of osteoclasts *(1)*, which leads to osteolysis of a bone or several adjacent bones. Jackson reported the first case in 1872, describing a complete disappearance of the humerus of an 18-year old boy *(2,3)*. Gorham et al. described the disease in 1954 *(4)*. In 1955 Gorham and Stout defined a specific disease entity and reviewed 24 cases from the literature *(1)*. Although more than 60 years have passed since the initial description, the etiology and pathogenesis of this disease still remain unknown. The diagnosis is made by exclusion. Initially, the most frequent symptom is pain in the affected bone, with or without fracture *(5-7)*. The osteolysis can last for years and progress to bone resorption. The bone resorption may stop spontaneously with

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a severe deformity and a functional disability *(1)* or lead to very important defect in the bone *(7-9)*. The definitive treatment for GSD still remains an enigma. Some patients respond to drug therapy *(5,6,9-12)* or radiation therapy *(13)*. However, there are also patients with severe bone defect who need reconstruction with allograft and prosthesis *(7,14)*. The prognosis depends on the response to treatment. In some cases, the resorption stops, while in others cases, it progresses to the allograft leading finally to amputation. The prognosis can also be very poor especially in patient with chylothorax or neurological defect *(5,14)*.

This report presents 3 additional cases of GSD, two of which are very rare polyostotic cases, with various clinical presentation and different prognosis.

PATIENTS DESCRIPTION (Table I)

Case 1: Female patient – humerus, radius, femur, ribs, scapula, thoracic vertebrae

At the age of 6 years, the patient presented a pathological fracture of the right humerus. As a lytic bone lesion was present, a misdiagnosis of unicameral bone cyst was given. Clinical exam revealed the existence of café au lait spots in right dorsal area, in the arm and right forearm and also a small colored stain on her right pupil. A misdiagnosis of phakomatosis was given. A radiograph of the right forearm showed also the presence of a lytic cyst of distal radius (Fig.1A). Infiltration of the cyst with Depo-Medrol and immobilization in a cast were performed. Three months later, the cyst seemed to be healed and filled. At the age of 7 years, a lytic cystic lesion was also discovered in the right distal femur. At the age of 8 years, the patient presented a refracture of the right humerus, treated through immobilization and Depo-Medrol injection. At the age of 16 years, renal sonography revealed cystic abnormalities in the renal parenchyma without renal polykystosis.

At the age of 33 years, the diagnosis of GSD was given associated with bowel lymphangiectasia responsible for exsudative enteropathy. A radiological assessment revealed a thickening of the 4th and 5th ribs in the right hemithorax and of the 10th rib in the left hemithorax. Bone rarefaction was present in the right humerus and right scapula, as well in the 9th and in the 10th thoracic vertebrae (Fig.1B). Presence of tubular structures in certain regions constituted an argument in favor of lymphangiomatosis. She was treated with interferon alpha-2 (IFNα2), replaced by Thalidomide followed by Sunitinib.

At the age of 37 years, the patient arrived at the hospital with a severe necrosis of her right hand and forearm and a deterioration of her general health. A right transhumeral amputation was performed (Fig.1C). The general condition improved. An immunosuppressive treatment with Sirolimus was started.

Table I. – Clinical charateristics of patients

N°	Sex	Type	Bones involving	Others clinical features	Médical treatment	Surgical reatment	Outcome
1	female	polyostotic	Humerus, femur, ribs, wrist, scapula, T9, T10	Chylothorax, Agenesy of distal cava vena, ascite, encephalopathy	IFNα2 Thalidomide Sunitinib Sirolimus	Amputation	Dead at 37 years
2	male	polyostotic	ulna, radius humerus	Swelling of forearm	Sirolimus	Massive bone allograft of ulna Osteosynthesis of radius	Good
3	male	monostic	ulna	/	/	Total elbow artroplasty	Good

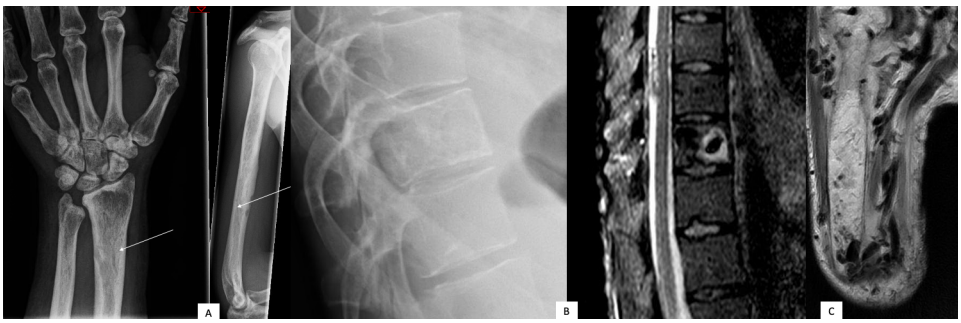

Fig. 1. – A) radiographs of the wrist and humerus showing endosteal thickening and sinusoid vascular structures inside the bone; B) vascular abnormality in the 10th vertebral body C) MRI of the amputated humeral limb showing numerous vascular structures.

At the age of 38 years, the general condition was good without signs of infection or necrosis. But the patient was complaining of dorsal spine pain. MRI displayed a heterogeneous aspect, with the replacement of trabecular bone with venous lakes of the vertebral body of the 10th thoracic vertebra (Fig.1B). A distal inferior vena cava agenesy was discovered under the 10th thoracic vertebra. This venous malformation induces a broadening of epidural plexus behind the 8th and 9th thoracic vertebrae. This malformation was extending over the entire retroperitoneal region. Important ascites and a left sided pleural effusion were also noted.

A few months later, she was admitted in the intensive care unit for encephalopathy, arterial hypotension and respiratory distress. She had important ascites. Assistive ventilation was performed. She developed respiratory acidosis, renal failure and multiple organe failure. She deceased.

Case 2: Male patient – humerus, radius, ulna

At the age of 10 years, the patient presented a right mid-shaft ulnar fracture (Fig.2A), treated conservatively with a cast. Despite fracture healing, a swelling was persisting in the forearm and the hand. At the age of 12 years, he presented refracture of the right mid-shaft ulna, treated by cast immobilisation. Because of persisting lymphedema, an isotopic lymphography with Tc99 was performed which revealed a lymphatic stasis due to an obstacle located in the right elbow. At the age of 13 years, the patient presented with a recurrence of the right mid-shaft ulnar fracture with signs of bone resorption in the ulnar shaft. Osteosynthesis of the ulna with elastic stable intramedullary nailing and an iliac graft were performed (Fig.2B). The peroperative biopsy revealed bone replacement by dilated vessels lined with flattened endothelium without cellular atypia. In the fibrous-inflammatory tissue the presence of vascular structures with stellar aspect and lined with smooth and flat endothelium, without signs of malignancy was identified. Six months postoperatively, the ulnar osteolysis was widened. At the age of 15 years, because of a bowing of both bones of forearm, an intramedullary nailing of the radius and plate osteosynthesis of the ulna were performed (Fig.2C). Progressive nonunion occurred with osteolysis around the screws. At the age of 16 years, a new osteosynthesis of the ulna was performed with a larger plate (Fig.2D). Evolution to complete osteolysis of the ulna was observed. At the age of 17 years, the patient was diagnosed with Gorham-Stout disease. Sirolimus treatment was initiated. At the age of 18 years, the patient showed a nonunion of the radius with a fracture of the nail and a quasi-complete osteolysis of the ulna. An allograft reconstructon of the ulna was performed with an osteosynthesis of the radius (Fig.2E). At the age of 19 years, following a new traumatism of the forearm, he sustained new fracture of both radius and ulna needing replacement of ulnar allograft and osteosynthesis of both ulna and radius (Fig.2F). At the age of 23 years, he presented with a pseudarthrosis of the distal radius, a cortical allograft was performed, the radius was stabilized by a longer palmar plate, reinforced by an additional plate on the radial styloid (Fig.2G). An immobilization with a splint was performed for 2 months, with a good

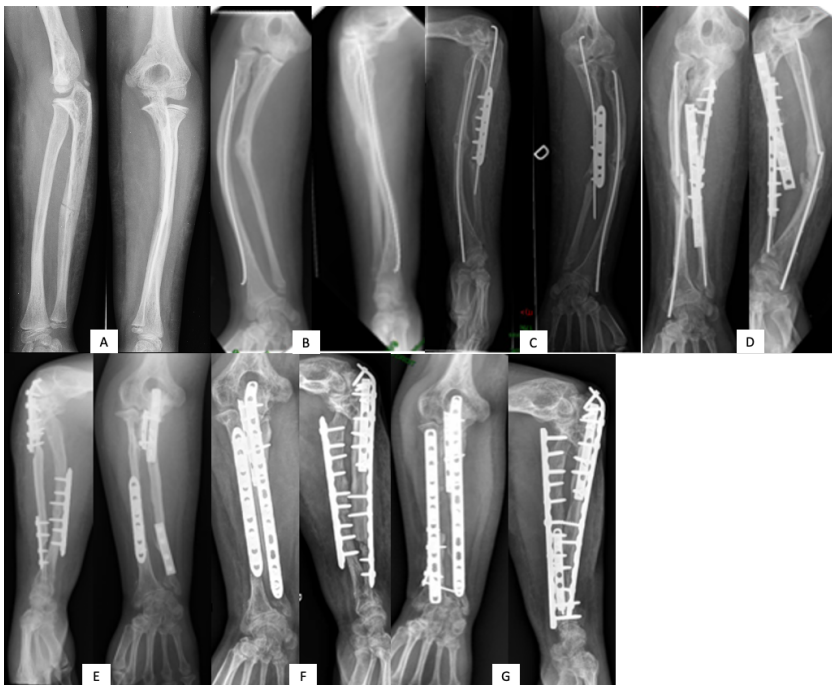

Fig. 2. – A) right mid-shaft ulnar fracture at the age of 10; B) Osteosynthesis of the ulna with intramedullary nailing and iliac graft at 13 years after refracture of ulna; C) Intramedullary nailing of the radius and plate osteosynthesis of the ulna at the age of 15; D) Nonunion of the radius with a fracture of the nail and a quasi-complete osteolysis of the ulna at the age of 17 years; E) Allograft reconstructon of the ulna and osteosynthesis of the radius; F) Replacement of ulnar allograft and osteosynthesis of both ulna and radius after a refrature. G) Cortical alograft of the radius, stabilized by a longer palmar plate and reinforced by additional plate on the radial styloid.

evolution. The Sirolimus treatment had a good effect with disappearance of the pain of the patient.

Case 3: Male patient - ulna

The patient presented to our institution at the age of 16 years with the diagnosis of Gorham-Stout disease affecting the right ulna. A significant limitation in the elbow mobility was present due to a radial head dislocation and a quasi-complete resorption of the ulna. A few years earlier, he underwent an ulnar reconstruction in an other hospital using a vascularized fibular autograft. In our institution, a total elbow arthroplasty with a brachial triceps transfer to the radius was performed. Because of the resorption of the ulna, the prosthesis was fixed in the humerus and in the diaphysis of the radius (Fig.3). Histopathological examination proved a rarefied bone structure associated with the presence of numerous vessels of varied caliber. Immunohistochemical examination revealed the presence of CD31 and D2-D40, markers for lymphatic vessels in the fibrous tissue.

DISCUSSION

Gorham Stout disease (GSD) is a rare disease characterized by uncontrollable channels proliferation of vascular and lymphatic origins in bones or adjacent tissues with resorption of the bone matrix. Natural evolution is unpredictable. The literature reports of spontaneous stop of bone resorption *(15,16)* but osteolysis can also progress until complete extinction of the bone *(1)* or quasi-complete as presented in the Case 2 and 3. Among the different presentations, pathological bone fracture may be the first reason for patients to come

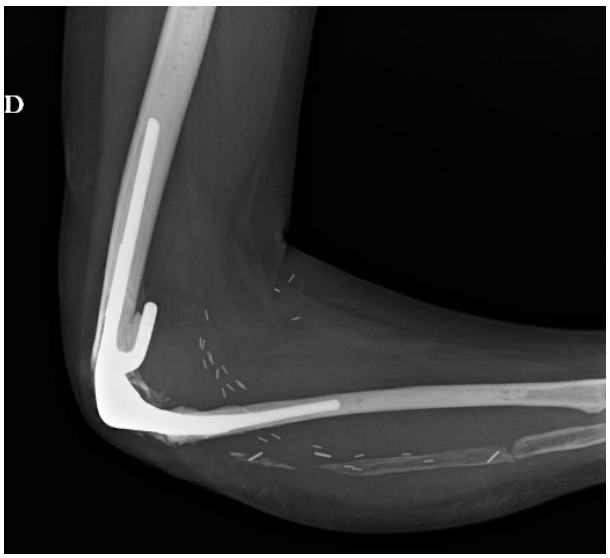

Fig. 3. – Total elbow arthroplaty perfomed in case 3 after vascularized fibula graft resorption. The prosthesis is fixed at the level of the humerus and in the diaphysis of the radius.

to the hospital *(17-19)*. All patients reported here had pathological fracture. Our first case presented with humerus fracture, the other two patients had fractures of ulna and/or radius. Neurogical manifestation as a severe motor deficit due to spine deformity can also be encountered *(5,14)*. Other symptoms include dyspnea particularly in patient with chylothorax *(6,14,20)*. The first patient reported here was admited with respiratory distress and pleural effusion corresponding probably to chylothorax. Sometime the fracture can be associate to swelling of the affected limb due to the lymphatic stasis, as demonstrated in Case 2 by a lymphography with Tc 99. The fracture can heal in time or not. Although Cases 1 and 2 evolved to nonunion, bone callus was however present on radiographs. The refractures may be caused by the progressive osteolytic changes *(21,22)*.

The diagnostic process of GSD is long, because it can be established only after ruling out all other possible diseases *(8)*,by multi-disciplinary teams. The final diagnosis is based on the eight criteria for GSD established by Heffez : (1) histopathological examination showing cells of vascular or lymphatic origins that invades the bone or the adjacent tissues; (2) absence of cellular atypia; (3) minimal or no osteoblastic response and absence of dystrophic calcifications; (4) evidence of progressive local bone resorption; (5) the lesion is not ulcerative and does not cause cortical expansion; (6) absence of visceral involvement; (7) osteolytic radio-graphic pattern; and (8) negative hereditary, metabolic, neoplastic, immunological, and infectious etiology *(6,23,24)*. In cases 2 and 3, the immuno-histopathological exam revealed cells of vascular and lymphatic origins lining the channels of bone structure.

The treatment can be medical, surgical or combinaition of both *(5,7,14,20)*. The medical treatment includes biphosphonates and interferon alpha-2 (IFNα2) witch are known to have good results in some studies *(5,20)*. Other medical traitement are calcium salts and D-vitamin; cyclophosphamide and fluorouracil; and calcitonin and sirolimus. Surgical treatment depends on the affected bone and the complications. It includes osteosynthesis, bone grafting, joint replacement *(5,7,14)* and sometime amputation. All the three cases we present here received surgical treatment, in case 1, we performed a transhumeral amputation because of severe necrosis of hand and forearm. Massive ulnar bone graft was performed in case 2 and a prosthetic elbow arthroplasty was performed in case 3. Only two of them received medical treatment with Sirolimus: IFNα2, Thalidomide, Sunitinib and Sirolimus in case 1, and only Sirolimus in case 2.

The natural evolution of this disease is very unpredictable, the bone resorption can stop after years 4 or the bone can completely disappear. In case 2, there was a quasi-complete resorption of the ulna. The resorption phenomenon of the autograft and allograft remains unexplained. If the scapula and the ribs are affected, then besides the osteolysis, a chylothorax may develop due to a lymphangiectatic invasion of the thoracic duct or mediastinal extension of the disease into the pleural cavity *(16)*.

It is well known that lysis progresses to bones and the surrounding soft tissues. The process of GSD is in most of the cases monostotic, but there are also cases of polyostotic osteolysis *(16)*. So far, one case affecting the forearm by osteolytic extension from the distal humerus was described in the literature *(25)*. In our case 1, the forearm osteolysis had a diffuse infiltration in both bones, and an extended

bone resorption was present in the humerus, scapula and in vertebral bodies of 9th and 10th thoracic vertebrae with concomitant pleural effusion and ascites. In case 2, although the affected bone was resected several times and a cancellous bone graft was used, the disease did not stop. The ulna was reconstructed with an allograft. In case 3, the patient presented to our clinic with a vascularized fibula graft resorption. Elbow prosthesis seemed to be the best solution to keep the forearm and to have a functional upper limb. In this cases, the disease was very aggressive.

The complications encountered in case 1 are very rare: the patient presented a extensive skin necrosis of the hand and forearm, requiring a life-saving amputation. Because this complication has not been described yet, we do not have a scientific explanation for this phenomenon.

Due to the rarity of the disease there is still no defined treatment. Sometimes patients present themselves to the hospital with an advanced stage of GSD where the only solution is to treat the complication.

CONCLUSION

Gorham Stout disease (GSD) is a rare disorder. Even though there are different theories, the etiology and pathogenesis of this disease is still unkown. Monostotic osteolysis is the most frequent presentation and extensive polyostotic osteolysis is very rare. Treatment methods vary from one clinic to another, from drug treatment to surgical treatment with or without radiation and as a last solution, an amputation of the affected limb is performed. The prognosis depends on the affected region and the reponse to various treatments. Chylothorax seems to be a factor of poor prognosis.

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