

ORTHOPAEDICA BELGICA 2019
Oostende, 25-26 april

Gorham-Stout Disease

A CASE REPORT
♂, 03/02/1998.

M. BELLEMANS, J. LAMOUREUX

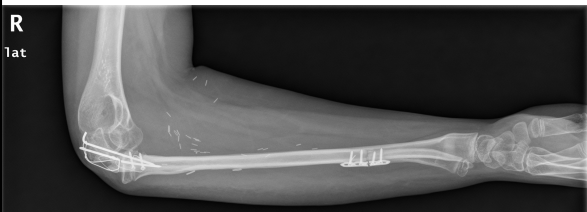


Prelude: treatment in Spain

- ▶ Diagnosis in 2006
- ▶ Treatment with interferon and biphosphonates
- ▶ Pediculated transfer of the fibula in 2009



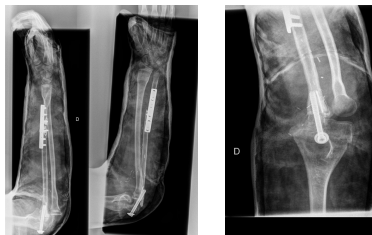
30/01/2010, first contact



Treatment: curettage of pseudarthrosis and osteosynthesis (22/02/2010)



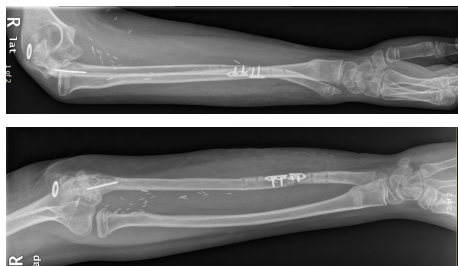
24/02/2010



Treatment: removal of material (04/11/2010)



05/11/2010



20/09/2011



Proximal fracture:
treatment by immobilisation



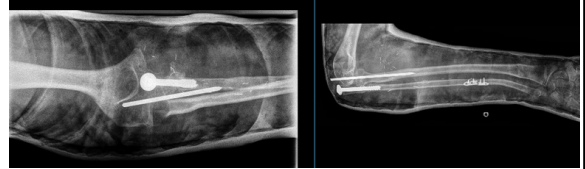
10/12/2011



Proximal fracture:
Failure of treatment by immobilisation
Solution:
Reduction of radial head and compression
screw. (21/12/2011)



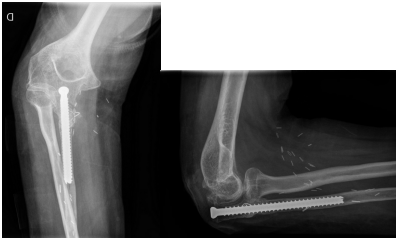
23/12/2011



After compression screw
Next step: take out pin and put a longer screw
because of osteolysis (17/02/2012)

17/02/2012

After pin removal and insertion of a longer screw



03/04/2012



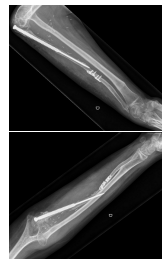
Fracture at the distal end of the screw: treatment by « guide wire » (03/04/2012)

04/04/2012



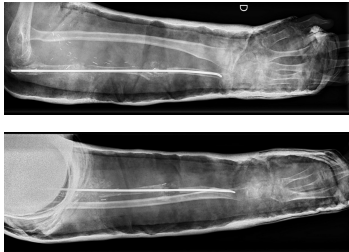
Result of treatment by « guide wire »

24/09/2012



Cutting out of guide wire:
Removal of material and
ECMES with bone grafting
(21/11/2012)

30/11/2012



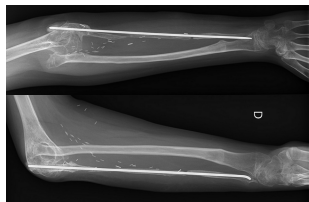
28/06/2013



Massive osteolysis



27/01/2014



Decision: removal of hardware
Reversed elbow prosthesis and creation of one-bone forearm (Prof O. Barbier, UCL)



The Classic

Jackson JS. A boneless arm. *Boston Med Surg J* 1898; 18:368-9.



Lemuel Whittington Gorham



Arthur Purdy Stout

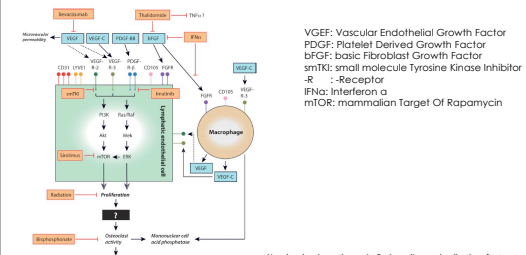
Graham LW, Stout AP. Massive osteolysis (acute spontaneous absorption of bone, phantom bone, disappearing bone): its relation to hemangiomatosis. *J Bone Joint Surg [Am]* 1955;37-A:985-1004.

Definition

- ▶ GSD is a **very rare** skeletal condition of **unknown cause**, characterized by the uncontrolled proliferation of distended, thin-walled vascular or lymphatic channels within bone, which leads to resorption and replacement of bone with angiomatous and/or fibrosis.
- ▶ **Key point:** cortical thinning and disappearance
- ▶ Osteolysis
 - ▶ By vascular proliferation
 - ▶ Osteoclast mediated?
- ▶ Soft tissue involvement
 - ▶ Chylothorax
- ▶ Single or multiple bone involvement
- ▶ Not described as isolated in the ulna



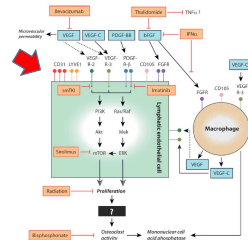
Actual knowledge:



Novel molecular pathways in Gorham disease: implications for treatment. Hagedoorn JJ, Teck TJ, Borel Rinkes HW, Padera TP, Ebb DH. *Pediatr Blood Cancer*. 2014 Mar;51(3):401-6.



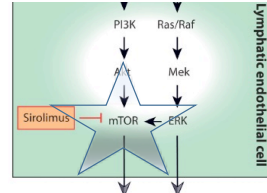
Actual knowledge:



VEGF: Vascular Endothelial Growth Factor
 PDGF: Platelet Derived Growth Factor
 bFGF: basic Fibroblast Growth Factor
 sMTK: small molecule Tyrosine Kinase Inhibitor
 -R : -Receptor
 IFN α : Interferon α
 mTOR: mammalian Target Of Rapamycin
CD31: panendothelial marker
LYVE1: Lymphatic Vessel endothelial Hyaluronan receptor

Novel molecular pathways in Gorham disease: implications for treatment.
 Hagendoorn J1, Yock TI, Borel Rinkes IH, Padera TP, Ebb DH.
 Pediatr Blood Cancer. 2014 Mar;51(3):401-6.

Actual knowledge:



mTOR:

« Central switch »

Novel molecular pathways in Gorham disease: implications for treatment.
 Hagendoorn J1, Yock TI, Borel Rinkes IH, Padera TP, Ebb DH.
 Pediatr Blood Cancer. 2014 Mar;51(3):401-6.

Actual knowledge:

- ▶ VEGF Bevacizumab
- ▶ bFGF Thalidomide/IFN α -2b
- ▶ VEGF-R2 smTKI
- ▶ PDGF-R β Imatinib
- ▶ mTOR **Sirolimus (rapamycin)**
- ▶ Proliferation Radiotherapy
- ▶ Osteoclast **Biphosphonates**

Pediatr Blood Cancer. 2014 Mar;51(3):401-6. Novel molecular pathways in Gorham disease: implications for treatment.
 Hagendoorn J1, Yock TI, Borel Rinkes IH, Padera TP, Ebb DH.

Actual knowledge: Rapamycin



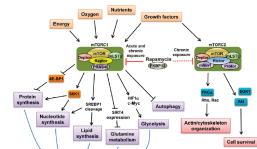
1964, Rapa Nui
Streptomyces hygroscopicus
 Antifungal metabolite with
 immunosuppressive and
 antiproliferative properties in
 mammalian cells.

1991 (m)TOR



Rapamycin: one drug, many effects.
 Li J, Kim SG, Blenis J.
 Cell Metab. 2014 Mar 4;19(3):373-9.

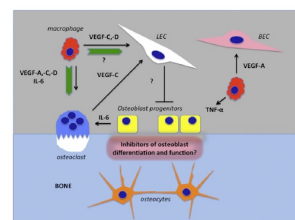
Mode of Action: mTOR pathway



Anabolic cell growth and proliferation
 Figure 1. The mTOR complex and the regulation of key cellular processes. mTOR exists as two heterodimeric kinase complexes: mTORC1 and mTORC2. mTORC1 is composed of mTOR, Raptor, and Protor1/2. mTORC2 is composed of mTOR, Rictor, and Sin1. mTORC1 is activated by growth factors, hypoxia, and amino acids. mTORC2 is activated by growth factors and phosphatidylinositol (3-OH) kinase (PI3K). mTORC1 and mTORC2 regulate cell growth and proliferation through various signaling molecules.

Rapamycin: one drug, many effects.
 Li J, Kim SG, Blenis J.
 Cell Metab. 2014 Mar 4;19(3):373-9.

Actual knowledge: osteogenesis ?



Viewpoints on vessels and vanishing bones in Gorham-Stout disease.
 Dellinger MT, Garg N, Olsen BK.
 Bone. 2014 Jun;63:47-52

Actual knowledge: applications

Sirolimus Therapy as Perioperative Treatment of Gorham-Stout Disease in the Thoracic Spine: A Case Report.
Mo AZ, Tenor CC 3rd, Hedequist DJ.
JBJS Case Connect. 2018 Jul-Sep;8(3):e70

24 month follow-up sirolimus and biphosphonates post op: return to normal activities

Efficacy of systemic sirolimus in the treatment of generalized lymphatic anomaly and Gorham-Stout disease.
Bical KW, Hammill AM, Moberley-Schuman P, Nelson SC, Blatt J, Bender JLG, McCuaig CC, Synakiewicz A, Frieden IJ, Adams DM.
Pediatr Blood Cancer. 2019 May;66(5):e27614.

5 GSD: 60% better; no progression of bone disease during treatment (12 months)
3/15 patients : temporarily stop because of side effects
Overall: 3/5 patients with no response



Actual knowledge: applications

Common and potentially severe side effects of Sirolimus

Peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, creatinine increased, constipation, abdominal pain, diarrhea, headache, fever, stomatitis, urinary tract infection, anemia, nausea, arthralgia, pain, and thrombocytopenia.



Remaining questions

- ▶ Candidate gene for GSD ?
- ▶ Absence of osteoblast recruitment
- ▶ Optimal dosage and duration of treatment
- ▶ Biologic markers of disease activity (IL-6 ?)
- ▶ Combination therapy
- ▶ Surgery: what, when, role of BMP *in loco*



The future



The future

Efficacy and safety of sirolimus treatment for intractable lymphatic anomalies: A study protocol for an open-label, single-arm, multicenter, prospective study (SILA).

Ozeki M, Asada R, Saito AM, Hashimoto H, Fujimura T, Kuroda T, Ueno S, Watanabe S, Nosaka S, Miyasaka M, Umezawa A, Matsuoka K, Maekawa T, Yamada Y, Fujino A, Hirakawa S, Furukawa T, Tajiri T, Kinoshita Y, Souzaki R, Fukao T.

Regen Ther. 2019 Jan 14;10:84-91.



Thank you for your attention

