An overview of the neurosurgical implications, pathophysiology, diagnosis and recent treatment strategies for Grade IV idiopathic osteolysis, also known as Gorham-Stout or phantom bone disease

Mario Ganau[1,2] **MD, PhD, FEBNS, FACS,**
Vishal Prasad[1] **MD,**
Gianfranco K.I. Ligarotti[2] **MD,**
Nikolaos Ch. Syrmos[3] **MD, MSc, PhD**
Habib Ellamushi[1] **MBBS, FRCS (SN)**

1. Department of Neurosurgery, The Royal London Hospital, London, UK
2. Department of Neurosurgery, Queen Elizabeth Hospital Birmingham, UK
3. School of Medicine, Aristotle University of Thessaloniki, Macedonia, Greece

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Corresponding author:
Mario Ganau MD, PhD, FEBNS, FACS
Department of Neurosurgery, The Royal London Hospital, Barts Health NHS Trust
Whitechapel Rd, Whitechapel, London E1 1BB, United Kingdom
Tel: 020 7377 7000
mario.ganau@alumni.harvard.edu

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Abstract

Objective: Gorham-Stout disease (GSD), commonly referred as vanishing bone or phantom bone disease, is a rare disorder characterized by spontaneous bone osteolysis due to proliferation of lymphangiomatous tissue. This disease can involve multiple bones and cause pathologic fractures. The exact cause of GSD is unknown and its severity is unpredictable: the disorder can potentially cause disfigurement or functional disability. According to CARE guidelines, we studied a 46 years old lady with a progressive defect of the skull. Differential diagnosis included: benign and malignant diploic lesions (eosinophylic granuloma of the skull, myeloma, lytic metastasis from unknown primary tumour, etc) and osteomyelitis. A suspicion of GSD was raised by coupling information from laboratory and nuclear medicine investigations, and eventually confirmed histologically. **Conclusion:** We included early in the investigation protocols a total body fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) scan that was extremely helpful to promptly rule out malignant or infective nature of osteolysis. An update on the diagnostic and management options available for GSD, with particular reference to the role of nuclear medicine and the latest clinical trials from international patients registries and classification of idiopathic osteolysis is provided

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Introduction

Gorham-Stout disease (GSD) or Grave IV idiopathic osteolysis or phantom bone diseae is a rare disorder (to date around 300 cases have been reported in the literature) originally described in 1955 and commonly referred as vanishing bone or phantom bone disease [1]. This condition is characterized by spontaneous bone osteolysis due to proliferation of lymphangiomatous tissue [2]. The latter creates overlapping with other pathological conditions (i.e. Cowden Syndrome, Proteus Syndrome, Generalized Lymphatic Anomaly, Kaposiform Hemangioendothelioma, etc) given the common involvement of the mTOR, the PTEN, as well as other pathways, like the RANKL/RANK/OPG, in the altered angiogenic signalling and osteoclasts activation [2, 3].

Gorham-Stout disease can involve multiple bones including pelvis, clavicles and ribs, facial bones and spine leading to diffuse osteopenia and pathologic fractures. Individuals experience flairs of subjective or mechanical pain localized in the affected region, at times associated with swelling of the surrounding tissues. The exact cause of this disease is unknown and its severity unpredictable: the disorder can potentially cause disfigurement or functional disability. For this reason an understanding of the pathological process is pivotal to ensure the adoption of the most appropriate management strategy.

Gorham-Stout disease

Over the previous 10 years, a 46 years old female retired teacher had an evolving right parietal bony defect and episodic headaches associated with other unspecific symptoms like a burning sensation in the ipselateral temporal region and blurred vision. Other than that, her previous medical history was insignificant and negative for previous traumas. The headache had been diagnosed as migraine, and treated symptomatically; nonetheless her complaints progressed over time, eventually leading to the attention of her family doctor for a transitory episode of left upper limb numbness. On clinical examination there

was a palpable skull defect, without any obvious neurological deficit.

Computed tomography (CT) and magnetic resonance imaging (MRI) brain confirmed two major areas of bone resorption, with possible infiltration of the dura mater (Figure 1). All blood tests (including full blood count, inflammatory markers, parathyroid hormone and calcium, myeloma screening) resulted negative; furthermore, a cerebrospinal fluid sample was sent for physico-chemical and cytological analysis which was unremarkable.

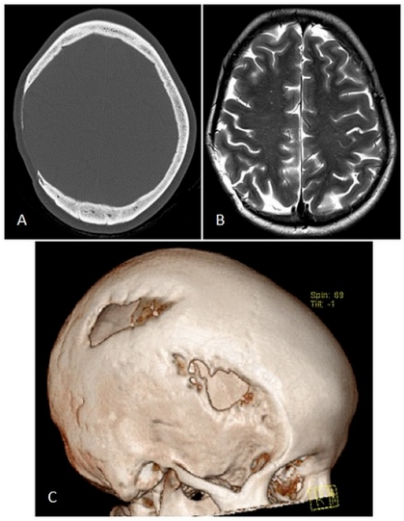

Figure 1. Initial neuroradiological investigations (A: axial CT head; B: axial T2-weighted brain MRI; C: 3D reconstruction of CT head with bone window). The images show two osteolytic lesions in the right frontoparietal region without evidence of fractures, inflammation or neoplastic growth. The underlying brain parenchyma appears otherwise unremarkable.

Several aetiologies, relevant to the abovementioned presenting symptoms and clinical scenarios, were considered in the differential diagnosis to guide our investigations: benign and malignant diploic lesions (eosinophylic granuloma of the skull, myeloma, lytic metastasis from unknown primary tumour, etc), osteomyelitis, and idiopathic osteolysis or GSD. Given the negative results obtained with the routine CT/MRI scans and laboratory tests, to clarify the nature of the skull lesion a ^{18}F-FDG total body PET scan was performed. This ruled out a possible malignant or infective nature of the disease, while raising the suspicion of idiopathic osteolysis. Surgical excision of the parietal bone with biopsy of the adjacent skeletal muscle eventually confirmed this suspicion (Figure 2). A cosmetic cranioplasty and adjuvant bisphosphonates treatment ensured a satisfactory functional outcome.

Discussion

Gorham-Stout disease which is also known as idiopathic osteolysis type IV (Table 1) might be triggered by a traumatic or metabolic event, resulting in an impaired blood supply to the bone [4]. The leading theories point at the unbalance between the activities of osteoblasts and osteoclasts to explain this isolated but progressive bone resorption [5-7].

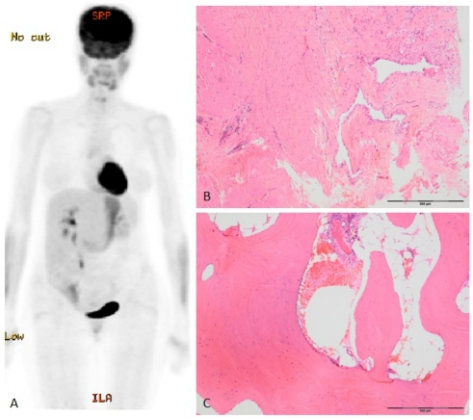

Figure 2. Nuclear medicine and histological studies (A: ^{18}F-FDG PET scan; B and C: histopathology specimens-haematoxylin & eosin staining). No pathological uptake of the radiotracer is noticed anywhere in the body suggesting an idiopathic osteolysis (A). Diagnosis of GSD is confirmed by the congestive vascular proliferates intermixed with fibrous connective tissue, along with mild infiltration of lymphocytes and plasma cells (B), and the remarkable enlargement of blood vessels ©

This disease seems to affect females more often, like in our case; and the reports available so far suggest that this condition occurs mostly in children and young adults (less than 40 years of age). Any bone can be affected, and the skull has been rarely described as a site of GSD, mostly with involvement of the petrous region of the temporal bone. Our case represents one of the few GSD (less than 10 cases described in the literature) localized in the calvaria reported so far. Painful osteolytic lesions represent challenging diagnostic and therapeutic scenarios. In our case, the persistent migraine ipselateral to the focus of parietal resorption could have been a misinterpretation of the early symptoms of the disease: possibly related to local release of inflammatory cytokines [5]. Since clinicians dealing with a new diagnosis of osteolysis need to rule out malignancies and infective lesions, nuclear medicine should be considered early in the investigation protocols: these may include bone scintigraphy and total body PET scan [8-10]. Of note, ^{18}F-FDG is a radiolabelled glucose analog suitable for PET imaging which enters cells via glucose membrane transporters, reflecting metabolic activity and therefore extremely useful to demonstrate or rule out any increase in metabolism which might indicate a neoplastic or infective pathology [11].

Recently, fluorine-18-sodiumfloride (^{18}F-NaF) has been proposed as a more bone-specific agent: being deposited on the surface of the hydroxyapatite matrix and leading to formation of fluoroapatite, its bone uptake and retention would reflect an increased blood flow [12]. Vessel proliferation associated with the osteolytic process typical of GSD could be identified with ^{18}F-NaF-PET/CT imaging. Hopefully, research efforts to optimize contrast agents and radiotracers will provide soon alternative ways to obtain complementary and more focused neuroradiology and nuclear medicine diagnosis [13]. For now, coupling information from different set of nuclear medi-

Table 1. *Classification of idiopathic osteolysis*

Class	Aetiology	Type and Onset	Clinical Course
Type I	Hereditary with dominant transmission	Multicentric osteolysis occurring in the first decade (between 2 and 7-year of age).	Children become symptomatic due to spontaneous pain and swelling in the hands and feet. Carpo-tarsal osteolysis occurs over a period of few years; nonetheless the progression ceases normally in adolescence.
Type II	Hereditary with recessive transmission	Multicentric osteolysis occurring in adult life.	Patients suffer from carpo-tarsal osteolysis often followed by the development of severe generalised osteoporosis.
Type IIII	Nonhereditary	Multicentric osteolysis occurring in early childhood.	Usually associated with nephropathy and characterized by proteinuria, gradual disappearance of the carpus, and to a less extent of the tarsal bones. Chronic renal failure and malignant hypertension may be lethal.
Type IV (Gorham Stout Disease)	Nonhereditary	Monocentric osteolysis, occurring at any age.	Osteolysis may involve any part of the skeleton. Patients become become symptomatic due to focal pain and swelling. Hemangiomatous tissue is usually found in the osteolytic region. Gorham Stout Disease may require surgical excision, but overall it has a self limiting course.
Type V (Winchester Syndrome)	Hereditary with autosomal recessive inheritance	Multicentric osteolysis occurring in childhood.	Children suffer from carpo-tarsal osteolysis, skin lesions and corneal clouding. Osteoporosis may follow, nephropathy is not a feature of Winchester Syndrome.

cine investigations could be extremely useful in particularly challenging cases, especially when a biopsy would carry a high surgical risk [11, 12].

Unfortunately, GSD still lacks standard-of-care management protocols: beside the difficulties in reaching a conclusive working diagnosis, the treatment options include radical surgical excision, with or without reconstruction, radiation therapy, steroids, bisphosphanates, and recently immunosuppressant drugs.

Data from the German Cooperative Group on Radiotherapy for Benign Diseases showed that radiation therapy can prevent progression of GSD in 80% of cases [13]. Stereotactic radiosurgery could potentially yield to better and safer clinical results due to the focal delivery of high-radiating doses while sparing the surrounding brain parenchyma [14, 15]. Systemic pharmacological treatment entered the management of GSD only recently: a monotherapy with drugs that inhibit bone resorption, such as bisphosphanates (pamidronate or zoledronic acid), can induce remission or at least delay disease progression [16]. Alternative options include: vitamin D, cisplatin, bleomycin, magnesium, estrogen, fluoride, calcium, vascular endothelial growth factor inhibitor and calcitonin [17].

Future studies will demonstrate whether the use of new drugs (i.e.: the RANK-ligand inhibitor, denosumab; and the mTOR inhibitor, sirolimus) can fully halt the progression of GSD by inhibiting the development of osteoclasts; hence serving as substitutes to surgical resection in selective cases [18].

In conclusion, considering the ^{18}F-FDG PET scan early in the diagnostic protocol for this osteolytic lesion provided useful information to confirm or rule out malignancies and osteomyelitis and a high index of suspicion for GSD. At present three North American studies (NCT02744027, NCT03001180, NCT02399527) registered on ClinicalTrials.gov are actively recruiting patients for diagnostic studies on biomarkers and biosignatures for GSD. Of note, clinicians worldwide can now make use of the International Patient Registry provided by the Lymphangiomatosis & Gorham's Disease Alliance as a powerful tool to participate in the development of future diagnostic and therapeutic clinical trials [19].

The authors declare that they have no conflicts of interest

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