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Cardiac involvement of Gorlin-Goltz syndrome: new light among the shadows of an old congenital disorder

Mihail Celeski,[1,2] Andrea Segreti,[1-3] Annunziata Nusca,[1,2] Giuseppe Di Gioia,[3,4] Raffaele Rinaldi,[1,2] Gian Paolo Ussia,[1,2] Francesco Grigioni[1,2]

[1]Fondazione Policlinico Universitario Campus Bio-Medico, Rome; [2]Unit of Cardiovascular Sciences, Department of Medicine and Surgery, Università Campus Bio-Medico di Roma; [3]Department of Movement, Human and Health Sciences, University of Rome "Foro Italico"; [4]Institute of Sports Medicine and Science, Italian National Olympic Committee, Rome, Italy

Correspondence: Andrea Segreti, Fondazione Policlinico Universitario Campus Bio-Medico, Via Alvaro del Portillo 200, 00128, Rome, Italy.
E-mail: a.segreti@policlinicocampus.it

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Abstract

Mutations in the *PTCH1*, *PTCH2*, or *SUFU* genes cause the hereditary, autosomal dominant Gorlin-Goltz syndrome (GGS), which is characterized by high penetrance and variable expressivity. Although its clinical manifestations are primarily marked by multiple basal cell carcinomas, other endocrine, neurological, ophthalmologic, genital, and respiratory alterations have been reported in the literature. Despite the association with cardiac fibromas, cardiovascular involvement is rarely reported. Here, we present a case of a patient with myocarditis of unknown origin, later diagnosed with GGS. We discuss the potential underlying mechanisms of this association, emphasizing the importance of recognizing cardiac manifestations in GGS individuals.

Key words: Gorlin-Goltz syndrome, basal cell naevus syndrome, myocarditis, myocardial injury, cardiovascular screening.

Introduction

Gorlin-Goltz syndrome (GGS) is a hereditary autosomal dominant condition with high penetrance and variable expressivity, resulting from mutations in the genes patched-1 (PTCH1), patched-2 (PTCH2) or suppressor of fused (SUFU) [1]. Multiple basal cell carcinomas, keratocystic odontogenic tumors, and bifid ribs are some of the primary characteristics required for diagnosis. Additional endocrine, neurological, ophthalmologic, and respiratory changes can occur with variable manifestations [1]. However, cardiac disorders in patients with GGS are rarely reported in the literature.

Case Report

A 43-year-old female, with no cardiovascular (CV) risk factors or prior CV disease history, was admitted to the emergency department for persistent chest pain. Her medical history included the removal of multiple basaliomas, treatment with sonic-hedgehog (SHH) inhibitors, edentulism at a young age, microcytic anemia and a previous gastric bypass. On admission, her blood pressure was 110/60 mmHg, heart rate was 70 bpm, peripheral oxygen saturation was 99% on room air, and body temperature was 36.5 °C. Physical examination revealed no signs of fluid overload, no ankle swelling, and no heart murmurs on auscultation.

An electrocardiogram (EKG) showed sinus rhythm, no conduction disorders and non-specific repolarization abnormalities. Routine laboratory tests were mostly normal, with hemoglobin at 13.5 g/dl, leukocyte count of 7000/uL and creatinine at 0.53 mg/dl. However, C reactive protein (CRP) was mildly elevated at 3.5 mg/dl, and highly sensitive cardiac troponin I (hs-cTnI) was elevated at 554 pg/ml, increasing to 813 ng/ml and then decreasing to 293 ng/ml.

A trans-thoracic echocardiography (TTE) revealed a left ventricle with normal dimensions and parietal thickness, preserved systolic function, no wall motion abnormalities, and a mild 3 mm pericardial effusion (Figure 1A). Coronary angiography showed no significant coronary artery stenosis (Figure 1B).

Cardiac magnetic resonance (CMR) imaging showed hypokinesia of the left mid-ventricular lateral wall, mildly reduced global systolic function (EF 49%), and mid-apical anterior and lateral wall hyperintensity with shaded late gadolinium enhancement (LGE) in the antero-lateral segments (Figure 1C). A diagnosis of myopericarditis was made, and the patient was treated with ibuprofen 600 mg and colchicine therapy 0.5 mg. Antinuclear antibodies (ANA), extractable nuclear antigen antibodies, viral antibodies/ antigens virus panel, blood cultures for bacteria and fungi, and toxicology screening were negative. Due to gastrointestinal side effects, treatment was switched to indomethacin 50 mg twice a day. Steroid therapy with

prednisone 30 mg was eventually added, resulting in clinical improvement and a reduction in CRP levels.

During hospitalization, the patient developed new-onset paresthesia, lumbar pain, and weakness in the left lower limb. A cerebral and lumbar magnetic resonance imaging showed a focal area of T2-flair hyperintensity and diffusion restriction in the right parietal region, consistent with a new ischemic lesion. There was also cerebellar dysmorphism, including hypoplasia of the vermis and left cerebellar hemisphere, with loss of substance in continuity with the IV ventricle, suggesting a "cerebellar cleft." Additionally, calcifications of the falx cerebri and multiple disc protrusions with mild cervical and lumbar vertebral dysmorphisms were noted. Electromyography showed no significant findings. Considering the history of multiple basaliomas, SHH inhibitors treatment, early edentulism due to odontogenic tumors, falx cerebri calcifications, cerebellar cleft, and unexplained cardiac changes, genetic counseling was requested. Gorlin-Goltz syndrome was suspected, and genetic testing was performed. Follow-up genetic testing confirmed a PTCH1 gene mutation on chromosome 9, establishing the diagnosis of GGS. At discharge, the patient was asymptomatic, and follow-up TTE showed mild left ventricular dilation with preserved systolic function.

Discussion

GGS, also known as basal cell nevus syndrome (BCNS), is an autosomal dominant familial cancer syndrome with an estimated prevalence ranging from 1:30000 to 1:250000 [1]. It is typically caused by a mutation in the tumor suppressor gene PTCH1, located on chromosome 9q [1]. PTCH encodes a transmembrane receptor protein that recognizes signaling proteins of the SHH family. Homozygous suppression of the PTCH promotes cell proliferation, tumorigenesis, and the formation of basal cell carcinomas and other neoplasms, including cardiac fibromas [1,2]. GGS is a multisystem disorder affecting various organs, although multiple basal cell carcinomas are the hallmark feature. Diagnosis of GGS requires the presence of two major or one major and two minor clinical criteria [1], as shown in Table 1. Our patient met two major criteria: multiple basal cell carcinomas at young age and calcification of the falx cerebri. Additionally, a PTCH1 gene mutation confirmed the diagnosis. The cardiac manifestations of GGS are not well understood. About 3-5% of those affected by GGS develop cardiac fibromas [1,3]. Indeed, fibromas are the most common cardiac presentation among GGS patients. While cardiac fibromas typically manifest during childhood, there have been reports of late-onset cardiac tumors with symptomatic presentations [4]. Cardiac fibroma may cause conduction delays, arrhythmias, or heart failure if they cause ventricular outflow obstructions [1].

There are relatively few cases of GGS patients presenting with arrhythmias. However, Ritter et al. described a case of a six-year-old child with GGS who experienced ventricular tachycardia and was later diagnosed with a cardiac fibroma in the left ventricle [3]. GGS patients, particularly those with cardiac fibromas, maybe more susceptible to arrhythmias, as the increased fibrous tissue can create microcircuits that serve as a substrate for ventricular arrhythmias. On the other hand, only one case has been reported in the literature, reporting a GGS patient with dilated cardiomyopathy, reduced global systolic function, and a heart failure [5].

To the best of our knowledge, this is the first report of myocarditis of unknown origin in a patient with GGS. After the patient was admitted to the emergency department for chest pain and increase of hs-cTnI, coronary angiography excluded ischemic origin of the chest pain. CMR provided additional information supporting the diagnosing of myopericarditis [6]. Subsequent neurological manifestations paved the way for the diagnosis of GGS, as previously described. Further laboratory evaluations ruled out infectious, toxic, and autoimmune disease. Additionally, corticosteroids therapy led to significant clinical improvement. Based on the patient's history and presentation, we proposed three potential hypotheses linking GGS and myocarditis.

Firstly, GGS may elicit an immune response resembling delayed-type hypersensitivity, characterized by tumor antigen recognition and a subsequent cell-mediated response. There may be a persistent immune process characterized by a balance between local immune stimulation and immunosuppression, mediated by regulatory T-cells (T-regs) and inhibitory cytokines such as IL10 and TGFβ [7]. In our patient, myocardial damage could be secondary to abnormal immune process associated with SHH pathway alterations in GGS. Second, SHH signaling can induce PD-L1 (an immune-checkpoint protein) expression in cells. Combining immune checkpoint inhibitors with SHH inhibitors may improve cancer therapy outcomes [8]. However, it is well-documented that immune checkpoint inhibitors can cause autoimmune-related side effects, including myocarditis [9]. Since our patient was treated with SHH inhibitor, it is possible that immune-mediate myocardial damage may have occurred via mechanisms similar to those seen with immune checkpoint inhibitors. Lastly, mutations in genes encoding desmosomal proteins, such as desmogelin 2, may be present in some GGS patients [10]. Although these mutations are not essential for diagnosis, they are rarely tested in such cases. Desmosomal alterations can contribute to the development of dilated cardiomyopathy, arrhythmogenic cardiomyopathy, or even increase the risk of myocarditis [11]. Thus, a potential causal association between desmosomal mutations and myocarditis in GGS patients should be further investigated through clinical and in vitro studies.

Although myocardial inflammation may be part of the cardiac spectrum in GGS, its exact role remains unclear. We recommend careful evaluation and a specific diagnostic plan for GGS patients presenting with cardiovascular symptoms of unknown origin (Figure 2). Due to the rarity of the syndrome, large-scale clinical trials addressing the optimal therapeutic strategies and management of GGS patients are lacking. Therefore, an interprofessional approach is necessary to ensure accurate diagnosis and appropriate management.

Conclusions

Cardiac muscle damage and inflammation may be part of the spectrum of clinical manifestations in GGS. It remains unclear whether mutations in PTCH-1 and the associated changes in the PTCH1-Sonic Hedgehog pathway, which plays a critical role in early development, contribute to cardiac injury either directly or indirectly. Individuals with GGS, as well as their family members, should be informed of the importance of genetic counseling. Furthermore, echocardiography and cardiological assessment, including CMR, should be considered as part of routine management and family screening for GGS patients. To establish a molecular and pathophysiological connection between cardiac manifestations and GGS, further investigation is required.

References

1. Verkouteren BJA, Cosgun B, Reinders MGHC, et al. A guideline for the clinical management of basal cell naevus syndrome (Gorlin-Goltz syndrome). Br J Dermatol 2022;186:215-26.
2. Wilke PI, Biermann D, Grafmann M, et al. Siblings with Gorlin-Goltz syndrome associated with cardiac tumors: a case report and review of literature. Orphanet J Rare Dis 2023;18:178.
3. Ritter AL, Granquist EJ, Iyer VR, Izumi K. Cardiac fibroma with ventricular tachycardia: an unusual clinical presentation of nevoid basal cell carcinoma syndrome. Mol Syndromol 2018;9:219-23.
4. Kluger N, Marco-Baertich I, Guillot B. Late onset of cardiac tumour in naevoid Basal cell carcinoma (Gorlin) syndrome. Acta Derm Venereol 2007;87:272-3.
5. Herceg S, Dilber D, Šarić D, et al. 190 left ventricle cardiac fibroma in a patient with gorlin – goltz syndrome. Arch Dis Childhood 2021;106:A80-1.
6. Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European

Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34:2636-48, 2648a-2648d.
7. Gambini D, Passoni E, Nazzaro G, et al. Basal cell carcinoma and hedgehog pathway inhibitors: focus on immune response. Front Med 2022;9:893063.
8. Gampala S, Yang JY. Hedgehog pathway inhibitors against tumor microenvironment. Cells 2021;10:3135.
9. Zotova L. Immune checkpoint inhibitors-related myocarditis: a review of reported clinical cases. Diagnostics 2023;13:1243.
10. Lupu M, Caruntu C, Ghita MA, et al. Gene expression and proteome analysis as sources of biomarkers in basal cell carcinoma. Dis Markers 2016;2016:9831237.
11. Ammirati E, Raimondi F, Piriou N, et al. Acute myocarditis associated with desmosomal gene variants. JACC Heart Fail 2022;10:714-27.

Table 1. **Clinical manifestations and criteria for diagnosing Gorlin-Goltz syndrome.**

System	Major criteria°	Minor criteria	Non criteria
Skin	1. BCCs prior to age 20 years or multiple BCCs 2. Palmar or plantar pitting		Facial milia,epidermal cysts
Stomatological system	1. Odontogenic keratocysts prior to 20 years		
Skeletal system and dysmorphisms		1. Rib anomalies (bifid/fused/splayed) 2. Macrocephaly 3. Cleft/lip palate 4. Vertebral anomalies/ kyphoscoliosis/ short fourth metacarpals/ postaxial polydactyly	Abnormal skull formation, spina bifida occulta, prengel deformity, bone cysts, pectus deformity, mandibular prognathism, facial asymmetry, synophrys, epicanthus
Central nervous system	1. Lamellar calcification of the falx cerebri 2. Medulloblastoma (desmoplastic variant)		Tentory cerebelli calcification, 'spotted' meningeal calcification, complete or partial bridging of the sella turcica, meningioma
Family	First-degree relative with GGS		
Ocular		1. Strabismus/ hypertelorism /congenital cataracts/ glaucoma/ coloboma	Nystagmus, iris transillumination defects, myelinated nerve fibres, epiretinal membranes, macular hole, retinal hamartomas
Gastroenteric system		1. Lymphomesenteric cysts	
Genitourinary system		1. Ovarian fibroma	Ovarian cysts; ovarian calcifications; hypogonadotropic hypogonadism, horseshoe kidney, L-shaped kidney, unilateral renal agenesis, renal cysts, duplication of the renal pelvis and ureter
Cardiovascular system		1. Cardiac fibromas	Arrythmias, heart failure, myocardial damage

°Diagnosis of Gorlin Goltz Syndrome requires the presence of two major criteria, one major criterion and genetic confirmation or one major and two minor clinical criteria. BCCs, basal cell carcinomas.

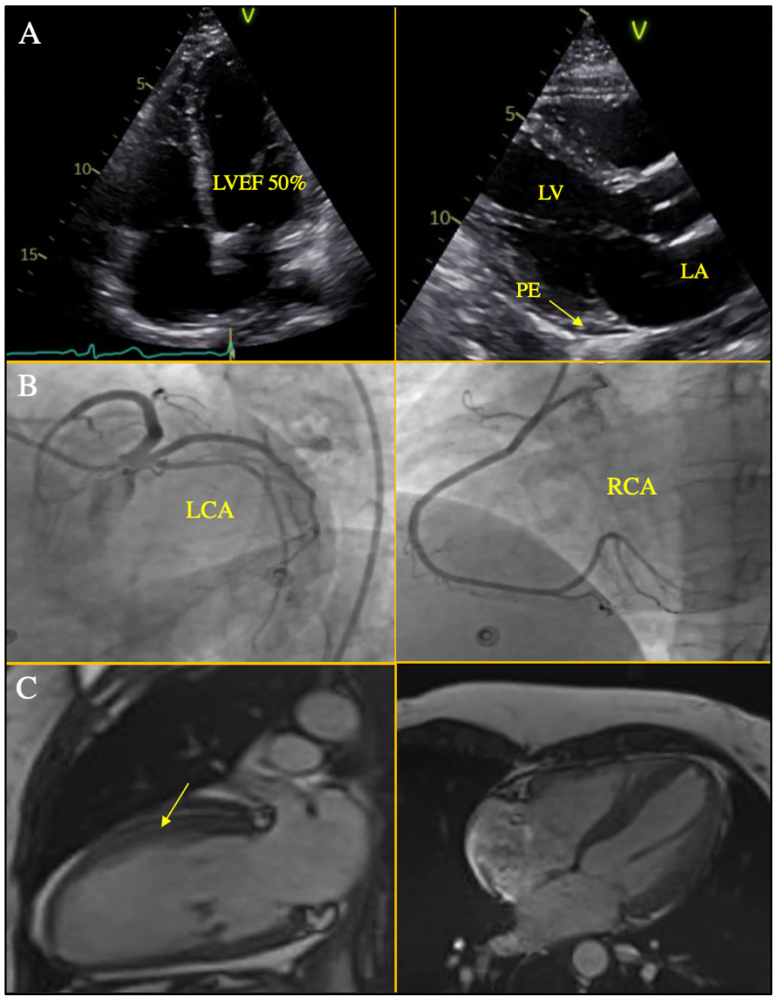

Figure 1. A) Trans-thoracic echocardiography showing preserved left ventricular function, normal atrial and ventricular dimensions, pericardial effusion of 3 mm, no cardiac masses; B) coronary angiography showing no coronary lesions; C) cardiac magnetic resonance showing anterior and lateral wall hyperintensity with presence of shaded late gadolinium enhancement. LA, left atrium; LCA, left coronary artery; LVEF, left ventricular ejection fraction; LV, left ventricle; PE, pericardial effusion; RCA, right coronary artery.

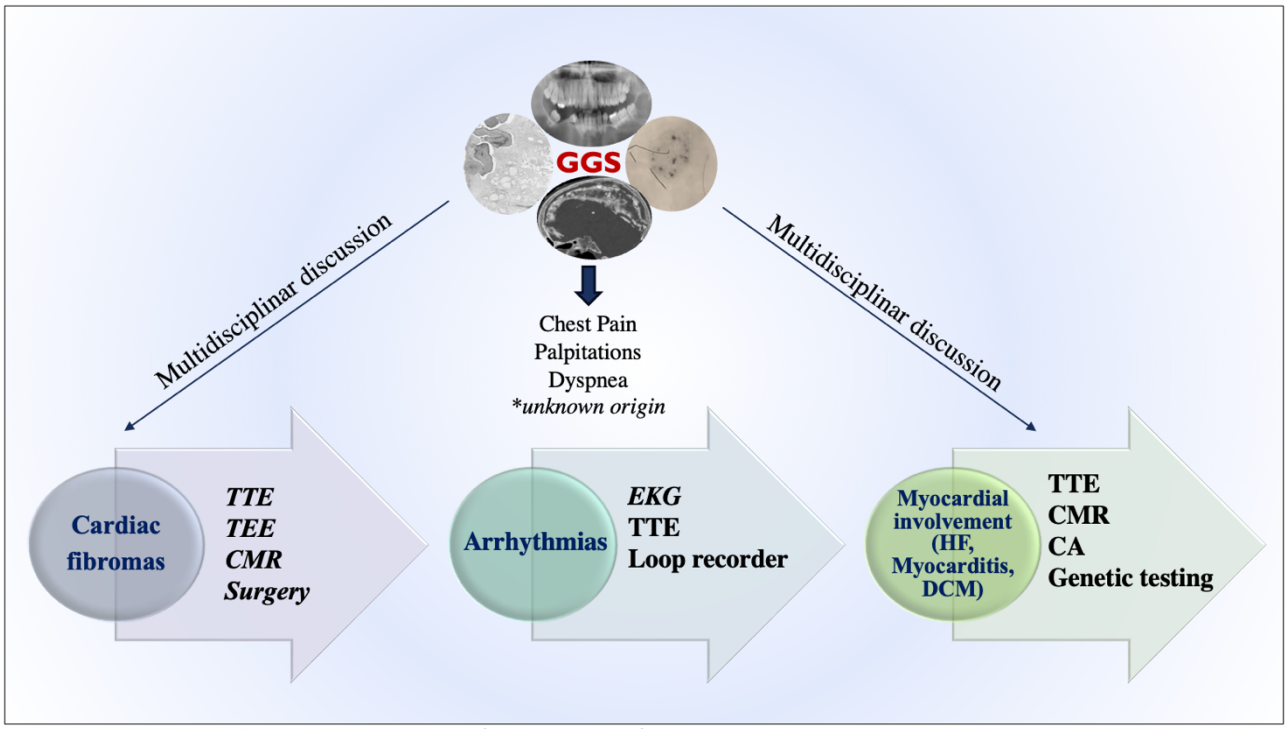

Figure 2. Possible cardiac manifestation of Gorlin-Goltz syndrome and recommended diagnostic methods. CA, coronary angiography; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; GGS, Gorlin-Goltz Syndrome; HF, heart failure; TEE, trans-esophageal echocardiography; TTE, trans-thoracic echocardiography.