SERVIZIO SANITARIO REGIONALE
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Istituto Ortopedico Rizzoli di Bologna
Istituto di Ricovero e Cura a Carattere Scientifico

"Giant Cell Tumor of the bone in patients under 15 years old: a single institution case-series"

Study code	**Pediatric GCTB**
Sponsor's Name and Address:	Istituto Ortopedico Rizzoli Via di Barbiano 1/10 40136 Bologna Italy
Study Number/Version/Date:	Vers 1.0 03 Apr 2019
Coordinating Center:	IRCCS Istituto Ortopedico Rizzoli Pathology Unit Via Pupilli 1 40136 Bologna, Italy
Coordinating Investigator and address:	Marco Gambarotti MD Phone: 051-6366.652 Email: marco.gambarotti@ior.it
Methodology:	Experimental study with biological material (Single insitution case series review of clinical and histological data)
Type:	Academic
Founding:	None
Principal Investigator Signature	I confirm that I've read this protocol and I accept to run the study in compliance with what is stated in the protocol and with the ICh-GCP and all applicable law Marco Gambarotti MD Firma

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BACKGROUND

Giant cell tumor of the bone (GCTB) is a locally aggressive tumor composed by oval to spindle cells, with a monomorphic appearance with multinucleated giant cells (osteoclast-like) uniformly distributed.

GCTB is around 4% of primary bone tumors, and it occur mostly in skeletally mature patients (between 20 and 55 years old). However, sporadic GCTB has been reported in older patients, as well as in the first two decades.

GCTB is generally located in the epiphysis of the long bones, especially the distal femur, proximal tibia and distal radius; contrary it is uncommon in short tubular bones of the hands and feet.

GCTBs are a part of a group of lesions, that could be traditionally divided into true neoplastic and those with a reactive nature. Especially in young patients, it is important to differentiate the true neoplastic from giant cell reparative granuloma, because these two categories could present some overlapping morphological features. In this cases correlation with clinical and radiological features is crucial. Moreover, the minority of these lesions can develop a secondary malignant transformation and sporadic case may give distant metastasis. Multifocal metachronous and/or synchronous cases are rare, as well as GCTB can be observed in a specific setting of Paget's disease.

Radiologically, GCTB has characteristic and diagnostic features, especially in adult patients and in common site. It appears as a well-defined bordered, eccentric, lytic, subchondral lesion that involves epiphysis and metaphysis with the typical "soap bubble" appearance; while the bone cortex is expanded and could be focally destroyed. Usually, borders do not showed margins of sclerosis or trabeculation.

Microscopically, mononuclear, spindle-shaped to intermediate-sized oval cells are uniformly dispersed with multinuclear, giant cells (osteoclast-like). Mononuclear cell could be elongated or spindle, with plum nuclei, the mitotic rate of these mononuclear stromal cells can be quite high, but no atypical one is seen. The classic setting of GCTB is modified by a secondary reactive proliferation of fibro-histiocytic tissue, areas of hemorrhage, necrosis and secondary aneurysmal bone cyst-like formation. Malignant transformation has been reported in few cases; however, lung metastasis has been found also in morphological benign cases [.

Differential diagnosis is giant cell reparative granuloma and other possible reactive giant cell lesion (brown tumor of hyperparathyroidism). Recently, driver mutations in the two histone 3.3 (H3.3) genes, H3F3A has been identified in 92% GCTB [Behjati S, 2013] and giant cell sarcomas secondary to GCTB. In addition, the diagnostic value was evaluated in order to differentiate giant cell lesions (aneurysmal bone cyst, nonossifying fibroma, giant cell granuloma, and osteoclast-rich malignant bone tumors) from true GCTB. H3F3A immunohistochemical expression has been demonstrated in 97.8% and mutations has been demonstrated to be essential feature of GCTB that improve pathological evaluation especially in borderline lesions with a not clear cut clinical and radiological contest. Rare case of GCTB have been reported in young patients. A recent Serie reviewed 63 patients under 18 years old, and only 5 TCG harbored H3F3A mutations, confirmed by PCR analysis

OBJECTIVE OF THE STUDY

Primary Objective

Primary objective is to present our series of GCTB, with its clinical, histological, immunohistochemical and/or molecular characteristics of these tumors, in order to collect the largest pediatric series.

Secondary Objective

Secondary objective is to reproduce and confirm the results of H3F3A immunohistochemical expression from the study of Amary et al. 2017 on our series of pediatric GCTB under 15 years old.

STUDY DESIGN

This is single institution cases series review of histological and clinical data

POPULATION

Inclusion criteria

1) Male and female patients under 15 years old treated at Rizzoli Institute from 01 January 1982 to 31 December 2018.
2) Diagnosis of GCTB, aneurysmatic bone cysts with solid features and giant cell reparative granuloma.
3) Histological slides/formalin-fixed paraffin-embedded tissue tumor (FFPE) blocks from archive available to perform the histology analysis
4) Written informed consent prior to any study-specific analysis and/or data collection

Exclusion criteria

1) Patients with histological diagnosis different from diagnosis of giant cell tumor, aneurysmatic bone cysts with solid features, and giant cell reparative granuloma.

2) Patients with no available material for additional immunohistochemical and molecular analysis

MATERIAL AND METHODS

We will retrieve from the archives of the Rizzoli Institute all the cases with a histological diagnosis of GCTB, aneurysmatic bone cysts with solid features, and giant cell reparative granuloma. By reviewing our database, we aspect to find approximately 50 cases We will review all the medical records, radiological imaging, and histological slides of all of these cases. In all cases with enough available material, immunohistochemistry will be performed on FFPE material. Histone 3.3 (H3.3) genes, H3F3A and mutation will be analyzed with immunohistochemistry and/or by allele specific-PCR analysis.

STATISTICS

To the case series will be applied a descriptive statistic.

ENROLLMENT PROCEDURE

Patients considered eligible will be included in the study, after providing a written informed consent.

DATA COLLECTION

Clinical data will be retrieved by patient charts.

A protocol-specific CRF reporting the results of the review will be provided.

A CRF is required and should be completed for each included subject.

ETHICS AND QUALITY ASSURANCE

The clinical trial protocol and its documents will be sent before initiating the study to the competent Authorities and Ethics Committees of each participating country for its approval.

The responsible investigator will ensure that this study is conducted in agreement with either the most updated Declaration of Helsinki and all the international and local laws that apply to clinical trials and to patient protection.

The protocol has been written, and the study will be conducted according to the principles of the ICH Harmonized Tripartite Guideline for Good Clinical Practice

(ref: http://www.emea.eu.int/pdfs/human/ich/013595en.pdf).

INFORMED CONSENT

All patients will be informed, by the investigator, of the aims of the study, the possible risks and benefits that will derive from the study participation.

The Investigator must clearly inform that the patient is free to refuse participation in the study and that can withdraw consent at any time and for any reason.

They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

The informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

The Investigator must also sign the Informed Consent form and will keep the original at the site and a copy of the original must be handed to the patient.

The competent ethics committee for each Institution participating to the study must validate local informed consent documents before the study can be opened. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the study whenever he/she wants. This will not prejudice the patient's subsequent care.

Due to the high incidence of mortality of the disease under investigation, it would be possible that some potential eligible subjects will be deceased.

GENERAL PRINCIPLES FOR HUMAN BIOLOGICAL MATERIAL (HBM) COLLECTION

Human biological material (HBM) collection involves the collection and storage of biological material, residual biological material or derivatives in compliance with ethical and technical requirements.

Biological material (FFPE blocks of tumor sample) are already stored in the archive of the Istituto Ortopedico Rizzoli, Pathology Department.

The biological material will be used and stored according with the sample characteristic and applicable regulation.

- The Istituto Ortopedico Rizzoli will have a designated person responsible for collection and will act as a communication point
- The collected HBM should be documented, i.e. the amount remaining and its location. act as a communication point

CONFIDENTIALITY

In order to ensure confidentiality of clinical trial data as disposed the national and European applicable regulation, data will be only accessible for the trial Sponsor and its designees, for monitoring/auditing procedures, the Investigator and collaborators, the Ethics Committee of each corresponding site and the Health Authority.

Investigator and the Institution will allow access to data and source documentation for monitoring, auditing, Ethic Committee revision and inspections of Health Authority, but maintaining at all times subject personal data confidentiality as specified in the "Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995".

The Investigator must guarantee that patient anonymity is kept at all times and their identity must be protected from unauthorized persons and institutions.

All patients included in the study will be identified with a numeric code, so that no identifiable personal data will be collected (pseudo anonymization)

The Investigator must have and conserve a patients' inclusion registry where it figures the personal data of the patient: name, surname, address and corresponding identification code into the study, this register will be kept on the Investigator File.

PUBBLICATION OF RESULTS

The results from this study will be published or shown at scientific conferences. The final publication of the study results will be written by the Principal Investigator.

SPONSOR ROLE AND RESPONSIBILITY

The sponsor is the sole owner of the data and is responsible of all the clinical trial activities from study design, development, data collection, management, analysis, interpretation of data, writing and the decision to submit the report for publication written by the Principal Investigator,

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