EUBREAST

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(EUBREAST-15)

A retrospective / prospective Cohort Study to evaluate the Incidence, Diagnostic Features, Clinical Course and Treatment Strategies in histologically confirmed Idiopathic Granulomatous Mastitis

Study Protocol

Version 1.4
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1. Study administration

Principal Investigators
Prof. Dr. med. Maggie Banys-Paluchowski Vice-Chair of EUBREAST e.V. Head of Breast Cancer Center Head of Center for Familial Breast and Ovarian Cancer Department of Gynecology and Obstetrics University Hospital Schleswig-Holstein Campus Lübeck Lübeck, Germany **Priv.-Doz. Dr. med. Natalia Krawczyk** Leading Senior Physician Department of Gynecology and Obstetrics University Hospital Düsseldorf Düsseldorf, Germany
Steering Board
Dr. Sadaf Alipour Professor of Oncologic Surgery Breast Surgeon- Arash Women's Hospital Deputy of Research- Breast Disease Research Center Tehran University of Medical Sciences Tehran, Iran
Prof. Dr. med. Vesna Bjelic-Radisic Head of the Breast Center and the Department of Senology Helios University Hospital Wuppertal Wuppertal, Germany
Prof. Dr. Jana de Boniface Associate Professor at the Department of Molecular Medicine and Surgery Karolinska Institutet Department of Surgery, Breast Centre Capio St. Göran's Hospital Stockholm, Sweden
Prof. Dr. med. Nina Ditsch

Treasurer of EUBREAST e.V. Head of Breast Cancer Center University Hospital Augsburg Augsburg, Germany
Prof. Maria Luisa Gasparri Treasurer of EUBREAST Italy Department of Gynecology and Obstetrics Ospedale Regionale di Lugano EOC Centro di Senologia della Svizzera Italiana (CSSI), Ente Ospedaliero Cantonale Faculty of Biomedical Sciences, Università della Svizzera Italiana (USI) Lugano, Switzerland
Prof. Oreste Gentilini Chairman of EUBREAST Italy Head of Department of Breast Surgery Ospedale San Raffaele Milan, Italy
Prof. Dr. med. Markus Hahn President of German Society of Ultrasound in Medicine (DEGUM) Head of Experimental Senology Department of Women's Health University Hospital Tübingen Eberhard Karls University of Tübingen Tübingen, Germany
Priv.-Doz. Dr. med. Steffi Hartmann Senior physician Department of Gynecology and Obstetrics University Hospital Rostock Rostock, Germany
Prof. **Dr**. **med. Güldeniz Karadeniz Çakmak** Professor of Surgery Director of Breast and Endocrine Unit Zonguldak BEUN The School of Medicine Kozlu/Zonguldak, Turkey
Prof. Cliona Kirwan Professor of Surgery Clinician Scientist in Surgical Oncology and Consultant Oncoplastic Breast Surgeon

Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester
Manchester, United Kingdom

Prof. Dr. med. Thorsten Kühn
Chairman of EUBREAST e.V.
Department of Gynecology and Obstetrics
University of Ulm
Ulm, Germany

Dr. Yazan Masannat
Consultant Oncoplastic Breast Surgeon
Broomfield Hospital, Mid & South Essex NHS Trust, Chelmsford, Essex, England, UK
Visiting Associate Professor
Anglia Ruskin University, Cambridge, England, United Kingdom

Dr. Rosa Di Micco
Vice-Chair of EUBREAST Italy
Breast Surgery Unit
Ospedale San Raffaele
Milan, Italy

Prof. Dr. med. Annette Lebeau
Senior physician
Institute of Pathology
University Medical Center Hamburg-Eppendorf | UKE
Hamburg, Germany
Group Praxis for Pathology
Lübeck, Germany

International Steering Committee – GRAMAREG-*sono*

Prof. Dr. med. Nina Ditsch
Treasurer of EUBREAST e.V.
Head of Breast Cancer Center
University Hospital Augsburg
Augsburg, Germany

Prof. Dr. med. Markus Hahn
President of German Society of Ultrasound in Medicine (DEGUM)
Head of Experimental Senology
Department of Women's Health
University Hospital Tübingen

Eberhard Karls University of Tübingen Tübingen, Germany
Priv.-Doz. Dr. med. Steffi Hartmann Senior physician Department of Gynecology and Obstetrics University Hospital Rostock Rostock, Germany
Prof. Dr. med. Thorsten Kühn Chairman of EUBREAST e.V. Department of Gynecology and Obstetrics University of Ulm Ulm, Germany
Dr. Rosa Di Micco Vice-Chair of EUBREAST Italy Breast Surgery Unit Ospedale San Raffaele Milan, Italy

Data management

EUBREAST (European Breast Cancer Research Association of Surgical Trialists) e.V. Chairman: Prof. Dr. med. Thorsten Kühn Esslingen, Germany

2. Glossary and Abbreviations

IGM	Idiopathic Granulomatous mastitis
MRI	Magnetic resonance imaging
CNGM	Cystic neutrophilic granulomatous mastitis

3. Rationale

Idiopathic granulomatous mastitis (IGM) is a benign inflammatory condition of the breast first described by Kessler and Wolloch in 1972 [1]. The etiology of IGM is largely unknown due to its rare occurrence with an estimated prevalence of 2.4 per 100,000 women aged 20-40 years [2, 3]. Valid data on the prevalence of IGM in Europe are lacking. However, the incidence in the low-income countries appears to be higher compared to western Europe [4], [5], [6]. Since only case reports and small case series of IGM have been so far reported in the literature, our knowledge on risk factors, clinical course of disease, therapeutic management, and clinical outcomes is very limited. Based on the published cases, IGM is considered to predominantly occur in women of childbearing age, mostly parous and more frequently of non-white ethnicity [2, 7-10].

The local symptoms of IGM are mostly severe, lasting up to many weeks or months, causing strong pain and often mimicking inflammatory breast cancer (Fig 1). Diagnosis can be confirmed only by histological evaluation, usually using core needle biopsy. The patients commonly develop recurrent breast abscesses, which do not improve on antibacterial medication and often require repeat incisions or drainages. The degree of suffering of IGM patients is therefore very high.

IGM needs to be differentiated from granulomatous inflammation of the breast that can appear in duct ectasia, as a reaction to foreign material, or in association with specific infections (e.g., mycobacteria, fungi, parasites) as well as in the course of systemic granulomatous diseases such as sarcoidosis. Further, cystic neutrophilic granulomatous mastitis (CNGM) was recently described as a specific form of granulomatous inflammation of the breast linked to infection with *Corynebacterium* species. However, it has not be fully clarified whether CNGM represents a distinct entity or rather a subtype of IGM [11].

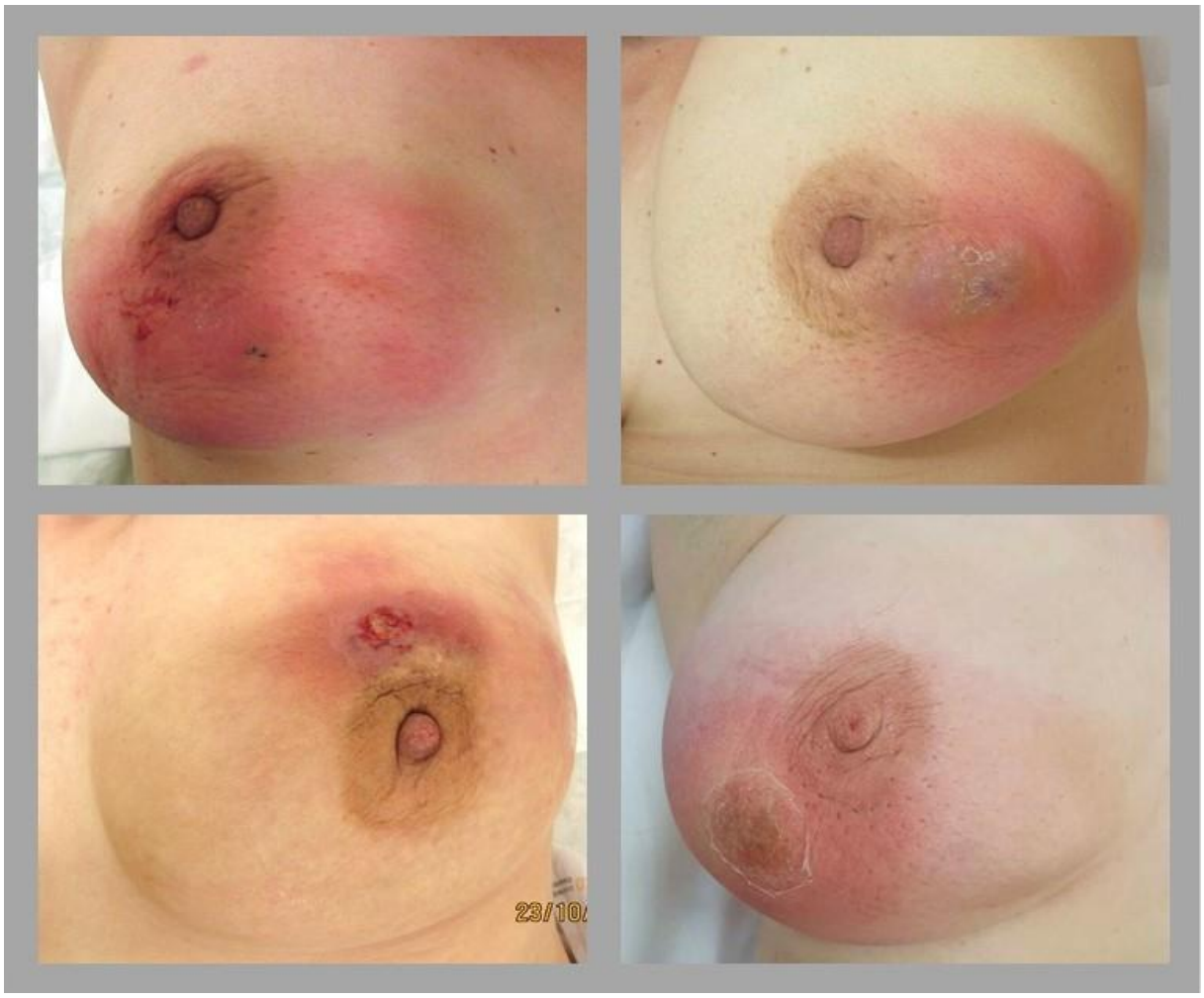


Figure 1. Clinical examples of idiopathic granulomatous mastitis.

Treatments strategies including high-dose steroids, immunosuppressive agents, bromocriptine, antibiotics, and surgical resection or even mastectomy have been described in the published cases [10, 12-14]. However, no evidence-based treatment recommendations are available to date.

GRAMAREG will be the first registry for patients with histologically confirmed idiopathic granulomatous mastitis in Europe with an aim to systematically evaluate this uncommon disease and its management as well patient outcomes (duration of symptoms and recurrence rate).

4. Methods

4.1. Study design

Investigator-initiated non-interventional observational international prospective / retrospective cohort study

4.2. Aims and objectives

Primary outcomes:

- Proportion of patients presenting with specific symptoms (e.g., pain, redness, palpable mass)
- Duration of symptoms depending on treatment strategy

Secondary outcomes:

- Type and duration of systemic treatment
- Number of surgeries, if performed
- Recurrence rate
- Risk factors associated with recurrence
- Time between first symptoms occurring and first histological confirmation
- Presentation on breast imaging (mammography, sonography, MRI, if performed)

The analysis of outcomes regarding diagnostics and ultrasound will be performed by the International Steering Committee GRAMAREG-*sono*.

4.3. Inclusion and exclusion criteria

Inclusion criteria

- Histologically confirmed idiopathic granulomatous mastitis or cystic neutrophilic granulomatous mastitis by the local pathology (minimally invasive biopsy or histological confirmation on surgical specimen) after 01.01.2015
- Female / male patients ≥ 18 years old
- Signed informed consent form for all patients that are included in the prospective part of the study (presentation with idiopathic granulomatous mastitis after activation of the study at study site)

Exclusion criteria

- Patients with suspicion of idiopathic granulomatous mastitis but without histological confirmation
- Suspicion of or confirmed secondary granulomatous mastitis due to e.g., tuberculosis, sarcoidosis, fungal and parasitic infection, foreign body

4.4. Registration

This study is based on a database with both retrospective and prospective character.

Retrospective data collection:
Collection and analysis are performed via an anonymized electronic database maintained by EUBREAST e.V. The participating Study Sites commit themselves to identification and documentation of patients with histologically confirmed idiopathic granulomatous mastitis treated during the investigational period at their institution (i.e., between 1st January 2015 and activation of Study Site). No patient identifying information will be disclosed or documented. Data collected during the retrospective phase of the study will be fully anonymous. The retrospective data will not include prospective follow up.

Prospective data collection:
All patients with histologically confirmed idiopathic granulomatous mastitis presenting at the Study Site after activation of the study will be informed about the possible participation in the GRAMAREG registry. The inclusion and exclusion criteria are verified by the investigator and written informed consent is obtained from the patient.

Diagnostic management and treatment should be conducted according to institutional standards. Since the GRAMAREG study in a non-interventional trial, the Study Sites do not deviate from their own institutional protocol at any timepoint.

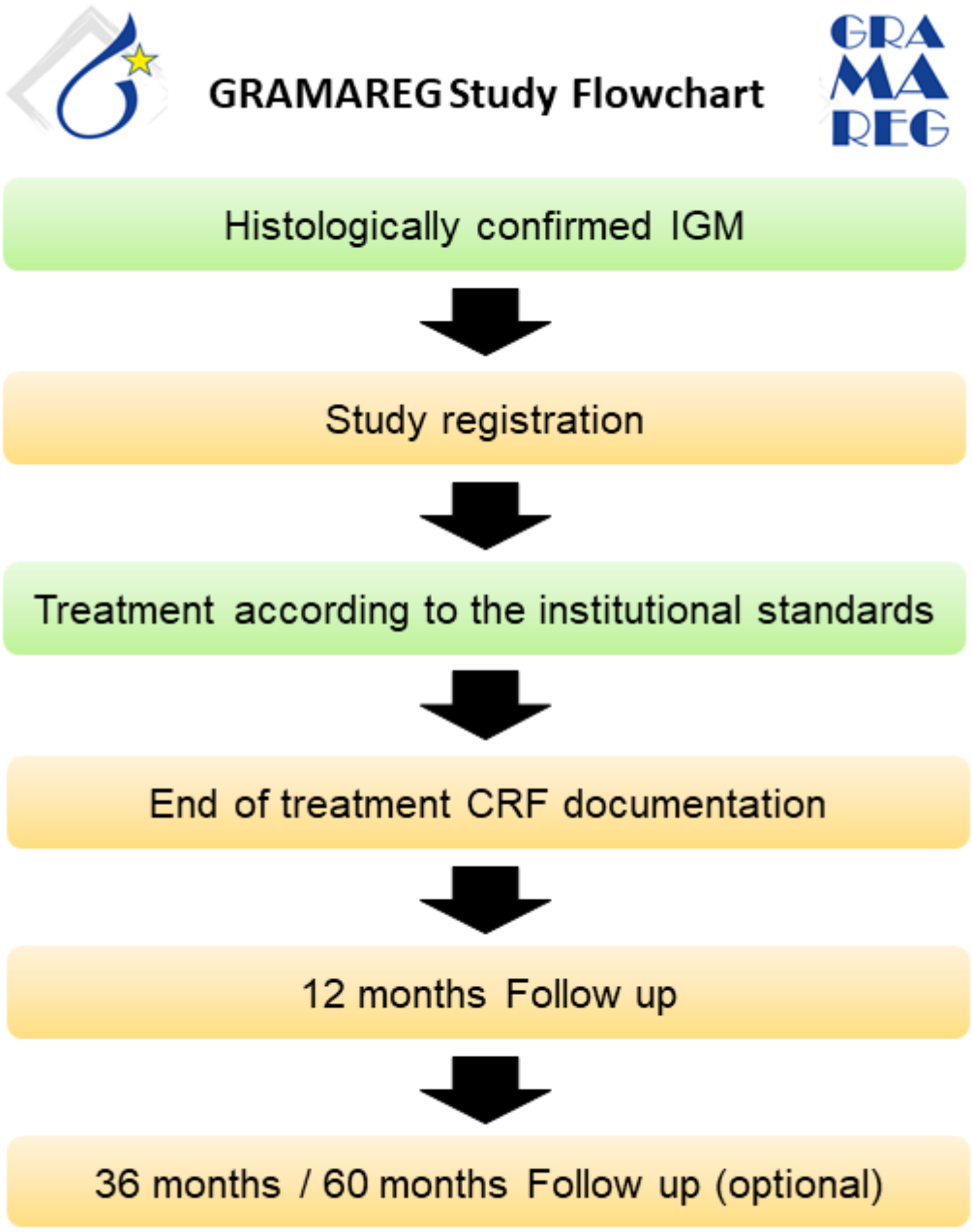
The follow up on patient status is conducted 1, 3 and 5 years after the first diagnosis. In order to collect follow up data the patients will be contacted directly by the study site to evaluate current symptoms (follow up after 1 year) and to document a potential recurrence of IGM (follow up 1, 3 and 5 years after the first diagnosis).

4.5. Target accrual

Unlimited

4.6. Study duration

Open registry due to the rarity of the disease



5. Data management

This part of the Protocol will discuss the Data Sharing and Data Management policy between two parties: The Provider & The Recipient. The Provider as per this agreement will be the Study Site supplying the dataset in accordance with the Protocol of the study. The Recipient will be EUBREAST e.V. who will collect the data in accordance with the Data Protection policy as set out in this agreement. Study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the server belonging to and managed by EUBREAST.

To register for the study, Study Sites (Providers) will contact the Head of their National Steering Committee to request participation in the Study and access to the online database. Each Study Site will then be designated a Site ID in format: Two-letter Country Code – Site number (e.g., DE-001 for the first German Study Site), which will be used as a prefix for the Patient ID (e.g., DE-001-001 for the first patient recruited at Study Site DE-001). All patients who consent to participation in the Study are recorded in the Subject Identification Log that remains at the study site. This document is the only record containing patient personal data and the corresponding Patient ID. EUBREAST does not have access to the Subject Identification Log at any time. No personal data will be disclosed under the Data Sharing Agreement. No patient identifiable data will be recorded for the purpose of the Study.

For further analysis data are filled in the REDCap-based eCRF by the Study Site. The printed version of CRF (PDF file) is also available. Its use is optional. All data are checked for plausibility through remote monitoring. The Monitors do not have access to patient data and do not visit Study Sites. Are the data insufficient for evaluation of predefined study aims, the Monitor will generate a query and Study Site will be requested to clarify.

REDCap has been disseminated for local use by more than 1,005 academic/non-profit consortium partners in 79 countries. Vanderbilt leads the REDCap Consortium, which currently supports more than 99,000 projects and 128,000 users. More information about the consortium and system security can be found at http://www.projectredcap.org/. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

REDCap is created by Vanderbilt University, with the server hosted by the EUBREAST. REDCap was developed specifically around HIPAA-Security guidelines. Web browser communication to the server is SSL-encrypted by default. All other ports are firewall protected. Data is stored in MySQL databases on a separate server. This server is behind a firewall and can only be accessed from the IP address of the web server. An SSL-tunnel encrypts communication between the web and databases servers. File upload is secured between servers using theWebDAV protocol with SSL. “At rest” encryption is in place on the database server (aes-xts-plain64:sha256 with 512-bit keys). Daily back-ups are made of both servers and stored for two weeks prior to being deleted. Operating security updates are installed automatically. Antivirus software runs to a scheduled protocol on the web server. User passwords are managed directly. Accounts are disabled after 5 failed login attempts. Users are auto logged out after 30 mins of no activity. Daily audit tracking of users is in place with removal of unused user accounts.

5.1. Data Purpose

The Recipient will have access to the Data Set to the extent necessary for the purpose of the Study. The pseudonymized Data Set shall be made available only to the Party responsible for Statistical Analysis. The Data Set will not be disclosed, transferred, or made available to any other third party. Summary Safety data may be transferred to the Manufacturers; however, this will NOT include any personal patient data. The Data Set will be kept confidential, and all reasonable steps will be taken to protect it against accidental or unlawful loss, modification or destruction, or unauthorized access, disclosure, copying, use, misappropriation, or modification. Following study closure, datasets cannot be transferred to any third party without the permission of the Recipient.

The results will be published in an academic publication. The Study Sites will be informed about the publication, and the publications will be uploaded to the EUBREAST website, the link to this publication will be sent to Study Sites. In accordance with customary scientific practice, any publications or presentations made in relation to the results, whether in oral, visual, or written form, the Study Site will be acknowledged as the source of the Data Set (see section “Publication and authorship policy”).

5.2. Data Ownership

The data is submitted by the Provider with the intention of contributing to a combined dataset. Providers can access their Study Site’s complete dataset at any point within the study recruitment period.

6. Publication and authorship policy

All presentations and publications will be made on behalf of the EUBREAST Study Group. Two levels of authorship are proposed based on degree of study participation:

6.1. Named authors

Named authors will be required to meet the International Committee of Medical Journal Editors (ICMJE) criteria (www.icmje.org) for authorship. These will include:

- Principal Investigator and Deputy Principal Investigator
- Members of the Steering Board
- Heads of National Steering Committees representing countries with top recruiter status
- Main statistician

6.2. Acknowledged collaborators

Collaborators will have made a considerable contribution to the study but will not have met the ICMJE criteria for authorship (non-author contributors). These will include:

- Heads of National Steering Committees representing countries without top recruiter status
- Members of National Steering Committees
- Local PIs of active Study Sites who have recruited at least one study participant. Recruitment in this context includes submission of a completed data set. In case a Study Site enrolled more than ten patients, an additional member of the Study Site will act as acknowledged collaborator. In case a Study Site enrolled more than fifty patients, two additional members of the Study Site will act as acknowledged collaborators.

All acknowledged collaborators will be listed as GRAMAREG Study Group.

7. Statistical considerations

Data analysis will be descriptive only.

8. Safety

GRAMAREG is a non-interventional study. All diagnostic and therapeutic procedures will be conducted according to institutional standards in the clinical routine.

9. Funding

Study support is currently applied for.

10. References

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11. Protocol Change Log

Version	Changes
1.4	Members of the Steering Board updated (Prof. Maria Luisa Gasparri, Dr. Rosa Di Micco, Prof. Cliona Kirwan and Dr. Yazan Masannat added) International Steering Committee GRAMAREG-*sono* added Corrected scientific title of Prof. Gentilini Literature updated (Krawczyk et al. Cancers 2024)
1.3	Addition of "diagnostic features" to the study tittle Rationale for inclusion of cystic neutrophilic granulomatous mastitis (CNGM) specified Inclusion criteria expanded to include CNGM Study flow chart corrected
1.2	Members of the Steering Board updated (Prof. Dr. Bjelic-Radisic added) Protocol change log added
1.1	Follow up described in more detail