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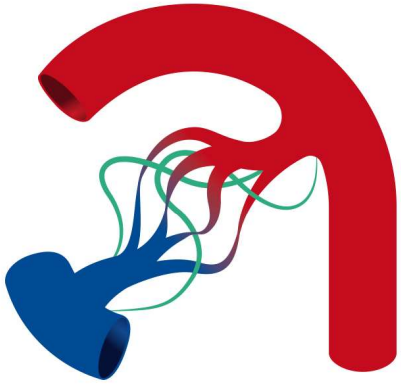
for rare or low prevalence complex diseases

Network Vascular Diseases (VASCERN)



Lymphatic malformation

Final Approved Patient Pathway by the Vascular Anomalies (VASCA) Working Group – 29/04/2020

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Disclaimer

- This document is an opinion statement reflecting strategies put forward by experts and patient representatives involved in the Vascular Anomalies (VASCA) Rare Disease Working Group of VASCERN.
- It is preferable that patients be evaluated in a multidisciplinary center specialized in the diagnosis and management of vascular anomalies.
- This pathway is issued on 29/04/2020 and will be further validated and adjusted as needed.
- Multidisciplinary team should re-evaluate treatment decisions regularly
- Responsibility for care of individual patients remains with the treating physician.

Dieses Dokument wurde am 05.12.2022 von Dr. Friedrich Kapp für das Zentrum für Gefäßfehlbildungen (Uniklinik Freiburg) für das FZSE Freiburg geprüft und kommentiert. Eine gemeinsame Überprüfung und Diskussion wird unabhängig hiervon in VASCA-WG erfolgen.

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Lymphatic malformation Diagnostic Work-Up: Overview

Suspected lymphatic malformation

Possible clinical signs or symptoms :

- Prenatal detection of a cyst
- Onset most often in early childhood
- Gradual swelling of a (subcutaneous) non-solid, non-compressible mass
- Bluish hue on the skin
- Vesicles
- Recurrent lymph leak/oozing/ bleeding
- Frequent skin infections and inflammations in the mass
- Protein loosing enteropathy / pleural- pericardial or abdominal fluid effusion or cysts
- Most often no pain
- Incidental finding
- Edema

- Doppler ultrasound to confirm diagnosis & exclude flow in the lesions
- MRI if diagnosis unclear or prior to surgery or sclerotherapy
- CT if suspicion of bone involvement (Gorham-Stout disease)
- Lymphatic scintigraphy if suspicion of lymphedema
- Mucosal investigation with endoscopy
- Lymphangiography if suspicion of channel type LM or pleural-, pericardial- or peritoneal chylus effusion
- Coagulation work-up (Chronic localized intravascular coagulopathy?) Kasabach-Merritt Phenomenon (KMP)
- Biopsy or FNAC occasionally needed for differential diagnosis *

*__Histology__ is helpful for differential diagnosis : LMs are composed of thin-walled, dilated irregular channels which often appear empty or contain pale eosinophilic amorphous material. Superficial LM may be associated with overlying epidermal hyperplasia and hyperkeratosis. Immunostains for lymphatic markers are helpful in differentiating LM from other malformations. PROX1, VEGFR-3, D2-40 (podoplanin) and LYVE-1 all label lymphatic endothelium.

* __Cytology__ and cyst chemistry is used to rule out cysts of other origin such as pseudocysts from parenchymal organs

Somatic PIK3CA mutation is associated to most LM

- Simple/ Common LM
- LM part of Generalized lymphatic anomaly (GLA) and Kaposiform Lymphangiomatosis (KLA)
- LM in Gorham-Stout disease (GSD)
- Channel type LM
  Kommentar FK 11/2023: akutelle Bezeichnung ist central conducting lymphatic anomaly (CCLA)
- Syndromic (i.e. PROS)
  - Please see pathway for *Syndromic vascular malformations*
- Primary lymphedema
  - Please see pathway from *VASCERN PPL-WG*

LEGEND: Clinical evaluation | Investigations | Treatment | Associated genes | Particular cases

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Lymphatic malformation: Management/Treatment Overview

Common management LM:

All LM

Overall treatment options are:
Watchful waiting ,compression garments, antibiotics, corticosteroids, sclerotherapy, surgery and Sirolimus. The decision must be made within multi-disciplinary teams with good knowledge of all treatment modalities, the treatments must be re-evaluated regularly

In case of signs of infection, always start early with antibiotics. Consider corticosteroids after systemic bacterial infection has been ruled out.

Micro cystic LM
Macro cystic LM
Mixed LM
GLA/KLA
Channel Type

Overall treatment strategy:

- Reduce risk of infections and inflammations
- Treat oozing, bleeding and causes of protein loss
- Reduce risk of compromise of vital function if sudden swelling occurs in the malformation, protect vital functions
- Improve quality of life and treat malformation which give psychosocial burden to the patient

Specialized treatments per type of LM:

Micro cystic LM

- Antibiotics due to recurrent infections.
- Topical corticosteroids
- Surgery if excisable lesions.
- Consider sclerotherapy (Bleomycin)
- Consider Sirolimus

Macro cystic LM
Mixed LM

- Sclerotherapy often first line of treatment: OK-432, Bleomycin, Doxycyclin etc.
- Consider primarily surgery if excision can be made or after more than four attempts of unsatisfactory sclerotherapy sessions

Kommentar FK 11/2023: Doxyclin weitere Option zur Sklerosierung oder Bleomycin-Elektrosklerotherapie (BEST)

GLA/KLA/GSD

- Coagulation work-up prior to treatment. Associated with higher risk of chronic Localized Intravascular Coagulopathy (LIC) and Kasabach Merritt Phenomenon (KMP)
- Consider surgery prior to sclerotherapy when malformation is in contact with vital structures and functions.
- Consider Sirolimus if there are contraindication to other treatments
- Consider MR lymphangiography and embolization treatment

Kommentar FK 11/2023:Kasbach-Merritt-like Phänomen bei KLA beschrieben (KMP nur bei KHE)

Channel Type

- Dietary adjustment to lower chylus circulation
- Consider MR lymphangiography- a new emerging diagnostic tool which opens new treatment options i.e. embolization treatment

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Part A

Lymphatic malformation: Diagnosis, Management and treatment (Simple LM, Common LM)

Suspected lymphatic malformation

1) Ultrasound/ Doppler :
- No flow in cysts?
- Size of cysts?
- Involvement of deeper tissue and relation to vital structures?

2) MRI if suspicion of extension to vital structures and organs, and/or prior to treatment

3) Mucosal investigation with endoscopy if signs of protein losing enteropathy

Localized lesions, limited to the skin, subcutaneous tissue or mucosa

Common Macrocystic LM

Common Microcystic LM

Common Mixed LM

Somatic PIK3CA mutation?

Watchful waiting if no symptoms, no risk of relevant physical complications nor psychosocial impairment

Sclerotherapy, first line of treatment for most LM. OK-432, Bleomycin, Doxycycline depending on cyst type and location.
May require several treatment sessions.

Surgery, If the lesion is considered resectable, part of a debulking procedure or after several (>4 sessions) attempt of insufficient sclerotherapies.

Laser, in cases of oozing vesicles in skin or mucosa

Sirolimus, if other treatment options are considered inadequate.

If signs of local infections / cellulitis or septicemia start with **systemic antibiotics** and, consider short term of **glucocorticoids**

Diffuse and extensive lesions, verified deep extension or fluid /lymph effusions in deep cavities on MRI

See Part B

Therapeutic options, depending on the characteristics of the lesion and the **multidisciplinary team** decision, treatments require **re-evaluation regularly**

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Lymphatic malformation: Management and treatment (Diffuse and extensive LM)

Part B

MRI to evaluate relation to vital structures and organs and prior to surgery or sclerotherapy

Diffuse and extensive lesions, verified deep extension or fluid /lymph effusions in deep cavities on MRI

Kommentar FK 12/2022:
Die Folie bezieht sich größtenteils auf komplexe lymphatische Anomalie. Die Therapiekonzepte sind meist sehr individualisiert.

Generalized Lymphatic Anomaly (GLA)
Mixed- and macro cystic LM not limited to the subcutaneous tissue with deep expansion, lymphatic/chylus leak into pleura, pericardium or the peritoneal cavity

Kaposiform Lymphangiomatosis (KLA)
GLA phenotype associated with coagulation disorder such as Kasabach Merritt Phenomenon (KMP)

Gorham stout disease (GSD),
GLA phenotype with bony involvement

CT for investigation of bony involvement

Channel type LM,
LMs part of the central conducting lymphatic vessels associated with lymphatic shunts or chylus reflux

1) Blood work, with haemostatic/coagulation evaluation
2) Consider MRI lymphangiography to evaluate lymphatic shunts and chylous reflux

Somatic PIK3CA/ germline ARAF/ somatic NRAS mutation?

Always individualized treatments tailored to reduce risk of **life threatening complications, improving life quality** including prevention of **psychosocial impairment.**

Treatment options are:
1) Dietary adjustments to reduce chylus circulation
2) Watchful waiting if no symptoms and no risk of complications to vital functions if sudden swelling occurs.
3) Sclerotherapy if no risk of complications to vital structures, first line of treatment in macrocysts including limited bone cysts.
4) Consider surgery when indication is to protect vital functions if sclerotherapy requires several sessions with high risk of prolonged intensive care.
5) Consider lymphangiography with embolization in case of lymph flow obstruction or lymphatic leakage or chylus reflux
6) Low molecular weight heparin if haemostatic disorder and recurrent bleedings
7) Consider Sirolimus, if surgery or sclerotherapy is not possible or safe.

Kommentar FK 11/2023: genetische Diagnostik anstreben, um eine zielgerichtete Therapie zu ermöglich

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to patients with rare vascular diseases

VASCERN, the European Reference Network on Rare Multisystemic Vascular Diseases, is dedicated to gathering the best expertise in Europe in order to provide accessible cross-border healthcare to patients with rare vascular diseases (an estimated 1.3 million concerned). These include arterial diseases (affecting aorta to small arteries), arterio-venous anomalies, vascular malformations, and lymphatic diseases.

VASCERN currently consists of 30 highly specialised multidisciplinary Healthcare Providers (HCPs) from 11 EU Member States and of various European Patient Organisations and is coordinated in Paris, France.

Through our 5 Rare Disease Working Groups (RDWGs) as well as several thematic WGs and the ePAG – European Patient Advocacy Group, we aim to improve care, promote best practices and guidelines, reinforce research, empower patients, provide training for healthcare professionals and realise the full potential of European cooperation for specialised healthcare by exploiting the latest innovations in medical science and health technologies.

More information available at: https://vascern.eu

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