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CASE REPORT
Other

A case report of *RASA1*-associated inherited lymphoedema with recurrent life-threatening lymphangitis

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Background Most cases of lymphoedema are secondary to other causes, while cases of primary lymphoedema, in particular that of congenital origin, are uncommon. Limited genetic disorders are so far known to be associated with lymphatic malformation including mutations in *RASA1*. This clinical case highlights the possible complications of *RASA1*-associated lymphatic malformation in a female suffering from recurrent life-threatening septic lymphangitis.

Case summary A 23-year-old female patient presented with congenital lymphoedema of the lower right extremity. At the age of eight, she first suffered from an episode of lymphangitis. Thereafter, she developed recurrent episodes of lymphangitis predominately occurring during menstruation and culminating into severe and life-threatening septicaemias. Due to the menstrual association, endometriosis was suspected but could not be confirmed. Furthermore, angiography could not detect any sign of arteriovenous fistula. Single-Photon-Emission-Computed-Tomography confirmed absent major lymphatics of the right leg with severely impaired and prolonged dermal lymphatic backflow. Genetic testing identified a disease-causing variant in the *RASA1* gene.

Discussion To our knowledge, this is the first case of recurrent septic lymphangitis with close relation to menstruation in a female with *RASA1*-associated lymphatic malformation. Due to the possible *de novo* or somatic origin of a pathogenic variant, a genetic disease should be considered in spite of an unremarkable family history or a localized lymphoedema. Although there is no curative therapy available yet, the knowledge of the underlying genetic defect is important for interdisciplinary patient care and might be crucial for individual molecular therapies in the future.

Keywords *RASA1* • Lymphoedema • Menstruation • Infection • Case report

ESC Curriculum 2.1 Imaging modalities • 2.5 Nuclear techniques

Learning points

- Recurrent and menstruation-related infections of localized lymphoedema might occur based on lymphatic malformation
- Genetic testing should be considered in primary lymphoedema, even in case of localized lymphoedema and unremarkable family history due to the possibility of *de novo* or somatic variants

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Introduction

Lymphoedema is a state of tissue swelling due to lymphatic dysfunction that can be caused by a plethora of disorders. Dependent on the origin, it can be divided into primary (inborn) and secondary (acquired) lymphoedema. Secondary lymphoedema is much more common and accounts for more than 80% of all cases.[1] Primary and particular congenital lymphoedema, however, is uncommon with an estimated prevalence of about 1:8000 live births.[2]

Primary lymphoedema can be clinically categorized according to the age of onset and its syndromic appearance. Non-syndromic congenital lymphoedema is usually diagnosed within the first months of life (e.g. in Milroy's disease). Lymphoedema of the lower limbs and with late onset is called 'Meige disease' with an unknown molecular origin until today.[3] Lymphoedema with limb overgrowth has been described as Klippel–Trenaunay syndrome when presenting with capillary-venous and sometimes lymphatic malformation and as Parkes–Weber syndrome when being associated with arteriovenous malformation.[4] Moreover, there are rare single gene defects that are specifically associated with lymphatic malformation. To date, there are nine types of inborn lymphatic malformation and their disease-causing genes listed in the Online Mendelian Inheritance in Man (OMIM) database (lymphatic malformation type 1–9, last accessed: 06/21). They are usually caused by germline mutations, which means that the disease-causing variant can be identified in each tissue. Localized lymphoedema, however, can also be caused by somatic mutations[5] or a somatic second hit[6] in the affected region. The mentioned Klippel–Trenaunay syndrome, for example, can be caused by pathogenic variants in the *PIK3CA* gene[5] while Parkes–Weber syndrome can be associated with variants in *RASA1*.[7]

While secondary lymphoedema can be caused by local infections, primary lymphoedema can also lead to secondary infections in the affected region.[8] In this study, we present a rare case of congenital *RASA1*-associated lymphatic malformation leading to recurrent episodes of life-threatening septic lymphangitis in a female patient.

Timeline

Presentation	Presentation witd an inborn lymphoedema and fulminant erysipelas in tde right lower extremity, septicaemia, and multiple cutaneous capillary malformations. Reported association between tde occurrence of erysipelas and tde patient's menstruation in tde past. Rapid recovery witd tde use of penicillin. Confirmation of tde lymphoedema by magnetic resonance angiography.
Month 1	Recurrence of the erysipelas. Revelation of absent major lymphatics of the right leg with severely impaired and prolonged dermal lymphatic backflow by Single-Photon-Emission-Computed-Tomography.
Month 10	Genetic testing identified the heterozygous pathogenic variant c.2600delC, p.(Pro867Hisfs*4) in *RASA1* (NM_002890.3).

Case presentation

A 23-year-old female patient presented with lymphoedema of the right leg, in which she rapidly developed erysipelas with a fever up to 39.5°C. Laboratory testing at admission revealed a severe leucocytosis (18.62×10^9 g/L, reference: $4.0–9.0 \times 10^9$ g/L) with leftward shift, a high C-reactive protein (12.1 mg/dL, reference: <0.5 mg/dL), and increased procalcitonin (13.2 ng/mL, reference: <0.1 ng/mL).

The patient has been affected by the lymphoedema since birth. After having suffered from an infection in the right leg caused by a contaminated blister at the age of eight, she repeatedly evolved similar episodes of erysipelas since adolescence. The infections originated from her right groyne encroaching into the lower extremity and partially leading to severe and life-threatening septicaemia. There was also a distinct association between the onset of infection and the onset of her menstruation cycle. Additionally, she developed a deep vein thrombosis within the same leg at the age of 15. Her family history was unremarkable, especially in regard to inherited cardiovascular or lymphatic diseases.

With the use of intravenous penicillin (6 g ampicillin/3 g sulbactam per day), her fever defervesced and there was a rapid decline in her inflammatory markers over the next 5 days. After 1 week, clinical inspection showed the underlying enlargement of the right extremity due to the lymphoedema with no remaining sign of infection (*Figure 1A*). Close inspection of the skin revealed multiple cutaneous capillary malformations of the fingers, right elbow, and right thigh (*Figure 1B*). Because of the close association between the onset of infections and her menstruation endometriosis was suspected. However, clinical work-up including referral to the Department of Gynaecology and Obstetrics for consultation and pelvic magnetic resonance imaging did not confirm the suspected diagnosis. Moreover, arteriovenous fistulae within the right lower extremity, pathognomonic for Parkes–Weber syndrome, were angiographically excluded. Absence of major lymphatics of the right leg with consecutively severely impaired and prolonged dermal lymphatic backflow could be visualized by Single-Photon-Emission-Computed-Tomography using Tc99m-Nanocoll as tracer. In contrast, the left leg demonstrated normal lymphatic drainage via the major lymph duct (*Figure 1C*). The patient was discharged with a long-term prophylactic antibiotic therapy of phenoxymethylpenicillin (2×10^6 international units per day) as well as recommendation for decongestive lymphatic therapy and consequent skin care. Future autologous lymph node transplantation as a possible treatment option will be discussed with the patient at a dedicated surgical institution.

DNA analysis by next-generation sequencing identified the heterozygous frameshift variant c.2600delC, p.(Pro867Hisfs*4) in *RASA1* (NM_002890.3) in DNA isolated from blood lymphocytes (*Figure 1D*). The variant was confirmed by Sanger sequencing in a buccal swap. Genetic testing of the patient's parents was recommended but declined at that point in time. Since cerebral arteriovenous malformations were reported in patients with mutations in *RASA1*,[7] vascular anomalies were excluded by magnetic resonance angiography.

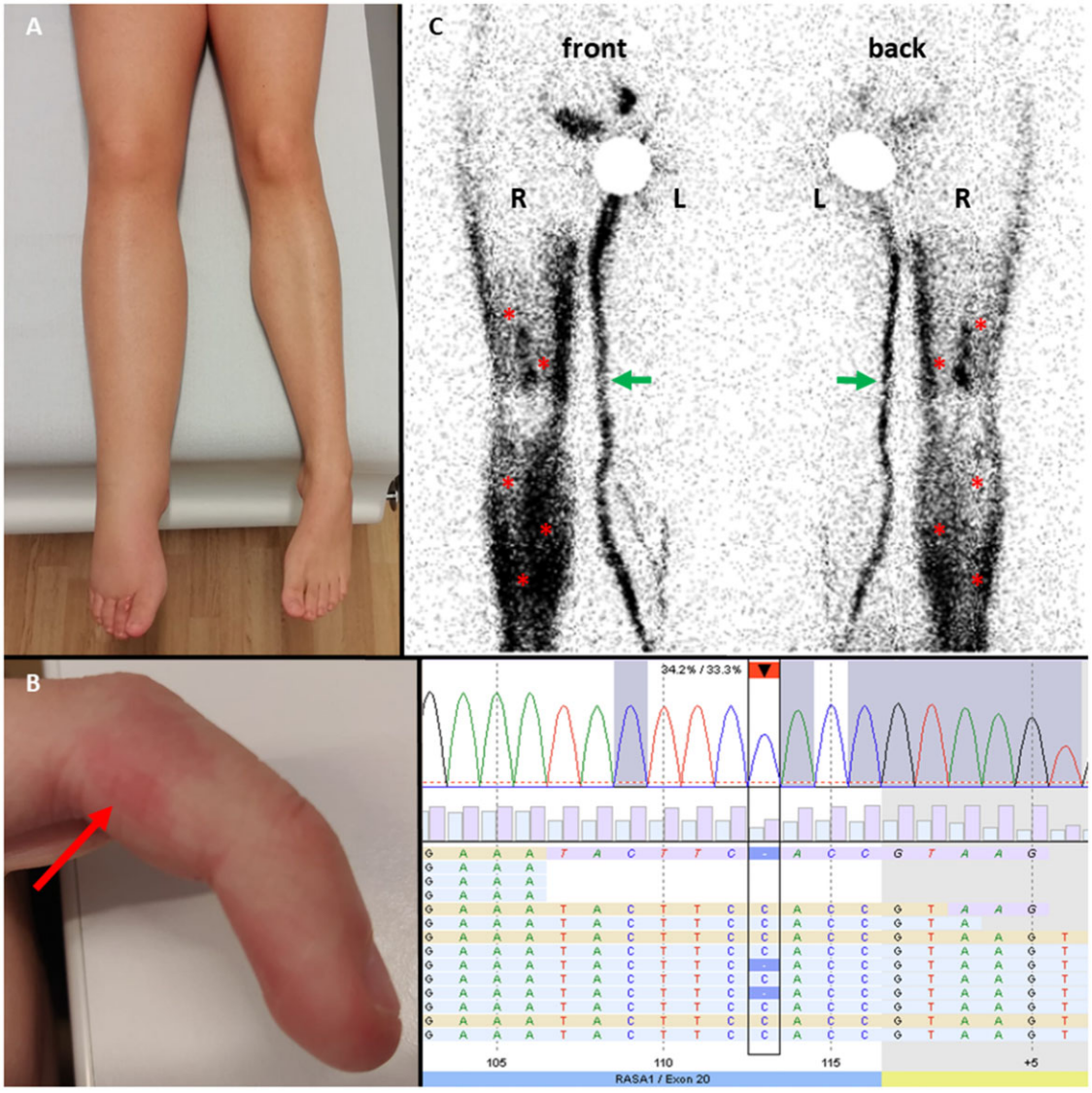

Figure 1 Performed examinations and genetic sequencing. (*A*) Underlying primary congenital lymphoedema of the right lower extremity after successful antibiotic treatment. (*B*) Concomitant capillary malformation on the left forefinger ('port wine stain', red →). (*C*) Single-Photon-Emission-Computed-Tomography demonstrated absent major lymphatics within the right leg with severely impaired and prolonged dermal lymphatic backflow (red *) while the left leg showed normal drainage via the major lymph duct (green →). (*D*) Next-generation sequencing revealed the single base pair deletion c.2600delC in *RASA1* (NM_002890.3) leading to an expected truncated protein.

Discussion

RASA1 encodes the Ras GTPase-activating protein 1 that inhibits the RAS signalling pathway.[9] Next to Parkes–Weber syndrome, pathogenic variants in this gene can be associated with the 'Capillary Malformation-Arteriovenous Malformation Syndrome Type 1' (OMIM #608354). This is a rare genetic condition (prevalence: 1:20 000) that usually affects blood vessels leading to capillary enlargement ('port wine stains').[10] Additionally, localized lymphoedema caused by a somatic second hit in *RASA1* inducing lymphatic malformation has been reported in isolated cases.[6,11] However, life-threatening infections associated with a female patient's menstruation have not been described before. Lymphatic fistulae within the pelvic region due to the lymphatic malformation could explain these recurrent infections. Ascending bacteria through such fistulae during menstruation and the following spread along the retained lymph channels in the right leg might potentially lead to the rapid and cycle-dependent infections.

Autologous lymph node transplantation is a possible surgical treatment for resistant lymphoedema. Some primary lymphoedema may benefit from autologous lymph node transplantation[12] as well as lymphoedema at an advanced stage.[13] However, there are possible complications including iatrogenic lymphoedema at the donor site,[13] which should be discussed with the patient. In particular, there is a lack of data concerning the chances of success in patients with

primary lymphoedema caused by *RASA1*-associated lymphatic malformation.

The patient's parents have not yet been tested for the variant. It cannot be excluded clinically that the variant was inherited by one of the parents because of the disease's broad expressivity even in one family with the same mutation.[6] The phenotypic spectrum reaches from isolated capillary malformations to fatal hydrops fetalis.[14] Nevertheless, a *de novo* origin of the variant in the patient should also be considered since about 30% of the pathogenic variants in *RASA1* were reported to be *de novo* at all.[7] Parkes–Weber syndrome due to a mosaic mutation in *RASA1* has also been reported[15] although there is no sign of mosaicism in our patient. There is a chance of 50% for the patient's offspring to inherit the pathogenic variant. However, the already mentioned variable expressivity[6] makes genetic counselling in regard to prenatal and even pre-implantation genetic diagnosis a difficult task.

In this case of primary congenital lymphoedema associated with recurrent severe infectious complications, we demonstrate the identification of a rare disease-causing variant in *RASA1* as the underlying pathology. Although there is no curative therapy available yet, the knowledge of the underlying genetic defect is important for interdisciplinary patient care and might be crucial for individual molecular therapies in the future.

Lead author biography

Dominik Westphal studied medicine at the Justus Liebig University Gießen, Germany. He is a geneticist specializing in cardiogenetics and currently works at the Institute of Human Genetics as well as the Department of Internal Medicine I at the Klinikum rechts der Isar (Technical University of Munich).

Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports* online.

Data availability

Data available on request.

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Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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