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Lymphedema and erysipelas in patients with classic Fabry disease: a retrospective case series

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Abstract

Aim: Fabry disease (FD, OMIM #301500) is a rare, X-linked, lysosomal disorder caused by pathogenic variants in *GLA*; the consequential lack of alpha-galactosidase A activity results in glycosphingolipid accumulation. Although many systemic manifestations of the disease have been documented, the association between FD and erysipelas has not been previously reported.

Methods: We describe 12 patients with Fabry disease and lymphedema of the lower limbs who experienced one or more episodes of erysipelas (with 67 episodes in total).

Results: All 12 patients (ten males and two females) had classic FD. One of the females had highly skewed X chromosome inactivation, silencing the wild-type *GLA* allele. Lymphedema of the lower legs (in 10 out of 11 patients with data) was notable in the patients who experienced erysipelas.

Conclusion: The characteristics of this case series suggest that clinicians should be aware of the risk of erysipelas in patients with FD-associated lower limb lymphedema and should seek to prevent or promptly treat skin wounds



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or infections in this setting.

Keywords: Fabry disease, erysipelas, lymphedema, dermatological manifestations

INTRODUCTION

Fabry disease (FD, OMIM #301500) is an X-linked genetic disorder of glycosphingolipid metabolism caused by a functional deficiency in the lysosomal enzyme alpha-galactosidase A (α -Gal A, EC 3.2.1.22)^[1-3]. The α -Gal A deficiency leads to the widespread deposition of neutral glycosphingolipids (primarily globotriaosylceramide (Gb3) and its deacylated derivative lyso-Gb3) in lysosomes and fluids throughout the body. The FD phenotype can be classified as classic or non-classic (also known as later-onset)^[4]. Patients with classic FD have little or no residual α -Gal A activity and generally start to experience the signs and symptoms of the disease, such as neuropathic pain^[5], gastrointestinal problems, hypohidrosis, and angiokeratoma in early childhood^[6]. The long-term manifestations of FD include proteinuric chronic kidney disease (CKD)^[7], hypertrophic cardiomyopathy with cardiac arrhythmia^[8], hearing loss^[9], and stroke^[10]. In some patients with FD, the Gb₃ deposits disrupt the microlymphatic network and ultimately produce lymphedema^[11]. Lymphography can differentiate the typical angiopathy seen in FD patients (characterized by obliteration of microvessels and significant caliber changes) from that found in primary lymphedema (typically with intact lymphatic network)^[11,12].

According to data from the Fabry Registry (comprising patients with classic FD and patients with later-onset FD), the estimated prevalence of lymphedema in FD was 16.5% overall, 21.7% in males, and 12.7% in women, with no report of erysipelas^[13]. Dermatological manifestations in FD were also reported using data from the Fabry Outcome Survey (FOS). In a cohort of 4,484 patients from 144 centers across 26 countries, 78% of males and 50% of females had at least one skin abnormality, the most frequent being angiokeratoma (in 67% males and 36% females), hypohidrosis (53% males, 28% females), telangiectasia (23% males, 9% females) and lymphedema (16% males, 6% females). There was no mention of erysipelas^[14].

Patients with later-onset FD have some residual α -Gal A activity and thus less severe signs and symptoms. The heart is often the only organ affected, although cardiac involvement may nevertheless be severe^[15].

FD phenotypes are well characterized in males but less so in heterozygous females, in whom X chromosome inactivation leads to greater variability in disease severity^[1].

Erysipelas is a bacterial infection of the superficial layer of the skin, including the lymphatic vessels in the upper dermis. The disease is usually considered to be a subtype of cellulitis. In Europe, the estimated incidence of erysipelas is 190-240 per 100,000 inhabitants per year^[16,17]. Breaks in the skin serve as entry points for bacterial invasion. The causative agent is usually a group A β -hemolytic *Streptococcus*, more rarely a group B, C, or G *Streptococcus*, and very occasionally *Staphylococcus aureus*. The diagnosis of erysipelas is clinical; the disease manifests itself as a raised, well-demarcated, erythematous, tender, warm plaque. Erysipelas has to be differentiated from autoinflammatory diseases^[18]. Patients may also experience systemic signs and symptoms like fever, chills, malaise, and regional lymphadenopathy. If the erysipelas is not treated promptly, the complications may include necrotizing fasciitis, thrombophlebitis, gangrene, and metastatic infection. A number of risk factors for the incidence or recurrence of erysipelas have been identified: these may be local (e.g., lymphedema, venous insufficiency, etc.)^[19] or general^[20-25].

To the best of our knowledge, there are no literature data on erysipelas in patients with FD^[26]. In the present study, we report on a case series of 12 patients with FD having experienced at least one episode of erysipelas and delineate demographics, biological and clinical data extracted from those patients' medical records.

PATIENTS AND METHODS

Subjects

In a retrospective, descriptive, observational case series, we analyzed the medical records of all individuals who experienced at least one episode of erysipelas among a cohort of 223 consecutive patients with FD followed at the French Referral Center for Fabry disease (www.centre-geneo.com) from January 1st, 2007, to March 31st, 2024. All patients with a confirmed pathogenic variant in the *GLA* gene (classic form: $n = 176$, later-onset form: $n = 47$) and one or more documented episodes of physician-diagnosed erysipelas were included.

Data collection and analysis

The data were collected from the patients' hospital records and, when necessary, during additional phone interviews with patients. Data on demographic variables (including sex, age at first erysipelas episode and, when applicable, age at death), FD (patient's phenotype, main signs and symptoms, *GLA* variant, and alpha-galactosidase activity), the characteristics of erysipelas (the date of the first episode, number of episodes, and associated complications), and potential contributory or triggering factors (including the known risk factors for erysipelas, and comorbidities) were collected.

RESULTS

Our retrospective analysis showed that 12 (all unrelated) of the 223 patients with FD followed-up at our referral center for FD and lysosomal storage disorders had experienced at least one episode of erysipelas (total number $n = 67$) during the study period [Table 1].

Patient (P) #1: A male patient (currently aged 43) was diagnosed with FD at the age of 23, during family screening. He developed a first episode of left leg erysipelas at the age of 27. There were no known contributory or triggering factors. A standard 7-day course of oral antibiotics led to the complete resolution of the infection. In the following 2 years, the patient experienced three additional episodes of erysipelas - all recurring on the left leg. The patient was given advice on hygiene. At the patient's last follow-up (at the age of 43), the erysipelas had not recurred. In the meantime, the patient had been diagnosed with stage G2A3 CKD (according to the Kidney Disease Improving Global Outcomes (KDIGO) classification), an aortic sinus of Valsalva aneurysm, frequent supraventricular extrasystoles (SVES), and lymphedema.

P#2: A male patient (currently aged 42 and diagnosed with FD at the age of 32 years, due to the presence of angiokeratomas) developed an initial episode of lower limb erysipelas at the age of 39. There were no known precipitating factors. Antibiotic treatment (oral amoxicillin, 1 g 3 times per day for 7 days) resolved the condition, and there were no complications. Erysipelas had not recurred by the time of the last follow-up. P#2 currently has stage G2A2 CKD, early signs of hypertrophic cardiomyopathy (HCM), persistent sinus bradycardia, left hearing loss and tinnitus, *cornea verticillata*, and retinal vascular tortuosity.

P#3: A male patient (currently aged 59) had been diagnosed with FD in childhood, during family screening. At the age of 40, he experienced a first episode of left leg erysipelas. There were no known precipitating factors. The condition recurred on the left forearm at the age of 49. In both instances, the infections resolved with oral antibiotic treatment without complications. The patient was given advice on hygiene, and erysipelas had not recurred by the time of the last follow-up. P#3 had suffered a stroke at the age of 34 and

Table 1. Summary of the characteristics of the 12 patients, with a focus on the existing signs and symptoms prior to the first episode of erysipelas

[illegible]

Compromised integrity of the skin barrier	No	No	No	NA	No	Plantar hyperkeratosis	Pruritus	Severe lymphedema	Intertrigo	Mycosis	Mycosis	No
Venous disease	No	No	No	Previous vein stripping	Varicose veins	Chronic dermohypodermatitis	No	Bilateral saphenectomy	No	No	No	No
Obesity	No	No	Yes	No	Yes	No	Yes	No	No	No	No	No
Diabetes mellitus	No	No	No	No	No	No	No	No	No	No	No	No

P: Patient; M: male; F: female; FD: Fabry disease; NA: not available; lyso-Gb3: globotriaosylsphingosine; ERT: enzyme replacement therapy; RD: rhythm disorder; TIA; transient ischemic attack.

four separate transient ischemic attacks (TIAs) between the ages of 34 and 45. He received a kidney transplant at the age of 43, and currently presents with lymphedema, hypohidrosis, HCM with aortic root dilation, bilateral hearing loss, vertigo, tinnitus, intermittent diarrhea, myalgia, cold intolerance, and carpal tunnel syndrome.

P#4: This male patient had been diagnosed with FD at the age of 63, in the context of end-stage renal disease (ESRD). The patient presented a chronic lower limb venous disorder, hypohidrosis, heat intolerance, hearing loss, chronic diarrhea, and HCM when he experienced his first episode of erysipelas (in the lower limb) at the age of 61. The infection resolved with antibiotic treatment, and there were no complications. The patient's ESRD prompted the initiation of hemodialysis. He developed atrial fibrillation (AF) and ventricular arrhythmia, which led to the implantation of a cardioverter-defibrillator. P#4 died from a stroke at the age of 68.

P#5: A male patient (currently aged 44) was diagnosed with FD at 18 years of age, after the observation of multiple angiokeratomas. He subsequently developed lymphedema, hypohidrosis, HCM, and CKD. At 38 years of age, the patient developed erysipelas of the right hand that required surgical drainage and antibiotic treatment. There were no sequelae. No recurrence of erysipelas was observed at the last follow-up. He currently has CKD stage G3bA2, HCM, first-degree atrioventricular block, tinnitus, heat intolerance, intermittent abdominal pain, and chronic diarrhea.

P#6: This male patient was diagnosed with FD at 42 years of age, in the context of ESRD. He had already experienced a first episode of erysipelas of the lower limb 3 years before the diagnosis of FD, and three recurrences were observed after the diagnosis of FD. P#6 had severe lymphedema of the lower limbs and feet, hypohidrosis, and toe web intertrigo. All the episodes resolved with antibiotic treatment, and there were no complications. The fourth episode of erysipelas was the last observed. The patient also suffered from HCM, atrial fibrillation, diffuse cerebral subcortical atrophy, heat intolerance, and osteopenia. P#6 received a kidney transplant at the age of 51 and died at the age of 68 after a cerebral thrombotic event.

P#7: A female patient was diagnosed with FD at the age of 64, following the discovery of left ventricular hypertrophy. A pacemaker had been implanted for AF and symptomatic bradycardia. Her brain MRI showed numerous white matter lesions. She was diagnosed with stage G3bA3 CKD, lymphedema, hypohidrosis,

and diarrhea and complained of abdominal pain. At the age of 65, she experienced an acute exacerbation of congestive heart failure following a severe, disseminated *Staphylococcus aureus* infection that had seeded from an episode of erysipelas. No previous episodes of erysipelas had been reported. The patient died 8 months later of heart failure.

P#8: A male patient (currently aged 54) was diagnosed with FD at the age of 50, following the sudden onset of bilateral deafness. He also suffered from HCM, stage G3aA2 CKD, atrial fibrillation, New York Heart Association (NYHA) class 2 heart failure, chronic asthenia, severe lymphedema of the right lower limb with positive Stemmer's sign, and hypohidrosis. The patient reported multiple ($n = 44$) episodes of lower limb erysipelas (starting at the age of 33) and previous bilateral vein stripping. All infectious episodes resolved with antibiotic treatment, and there were no complications. Despite the initiation of enzyme replacement therapy (ERT), P#8 has experienced a further seven episodes in the last four years. Prophylaxis with oral phenoxymethylpenicillin (1,000,000 IU, two times a day) was initiated in 2024 for the prevention of recurrent erysipelas as per French national guidelines^[27]. Temporary interruption of oral phenoxymethylpenicillin recently resulted in the occurrence of another episode of erysipelas upon 48 hours of prophylaxis discontinuation by the patient [Figure 1].

P#9: A male patient (currently aged 50) was diagnosed with FD at the age of 43, in the context of family screening. He had CKD stage G2A2, HCM, a short PR interval, abdominal pain, frequent diarrhea, lymphedema, and hypohidrosis. Around the time of diagnosis, the patient experienced 3 episodes of erysipelas of the right leg; toe web intertrigo was the likely starting point. Erysipelas in the right leg recurred when the patient was 47. The infection resolved with oral antibiotic treatment, in the absence of complications. No other recurrence was noted at the last follow-up. At the age of 43, the patient experienced a TIA and a sudden but transient episode of hearing loss.

P#10: A male patient was diagnosed with FD at the age of 48, in the context of family screening. He had experienced two episodes of erysipelas at the age of 35. The infections resolved with oral antibiotic treatment without complications. No other recurrence of erysipelas was documented at the last follow-up. The patient experienced two TIAs and a subtentorial hemorrhage and also presented HCM, ischemic cardiomyopathy, chronic asthenia, lymphedema, and hypohidrosis. Chronic kidney disease progressed to ESRD, and the patient received a kidney transplant (followed by a cytomegalovirus infection) at the age of 51. He died at the age of 56 with multiple comorbidities and the exact cause of death was not determined.

P#11: A female patient was diagnosed with FD at the age of 29, during family screening. Her X-chromosome inactivation profile was highly skewed (0% / 100%), with the wild-type *GLA* allele fully silenced. She had CKD, non-sustained supraventricular tachycardia, *cornea verticillata*, hearing loss, vertigo, osteopenia, lymphedema of the lower limbs, hypohidrosis, and asthma. At the age of 41, she developed lower limb erysipelas; the likely origin was toe web intertrigo and mycosis. The infections resolved with antibiotic and antifungal treatment and did not recur or result in any complications. No recurrences of erysipelas were documented at the last follow-up. The patient (currently aged 48) has developed left HCM with right bundle branch block and ESRD requiring hemodialysis.

P#12: A 55-year-old male patient was diagnosed with FD at the age of 44 by next-generation sequencing (genes panel) for hypertrophic cardiomyopathy. He had two strokes at age 45 and 47 while on enzyme replacement therapy (agalsidase beta) with neutralizing antibodies. He was switched to pharmacological chaperone therapy due to the theoretical amenability of his *GLA* variant (p.N34H). However, progressive kidney deterioration reaching CKD stage 4 on migalastat therapy prompted the reverse switch to enzyme

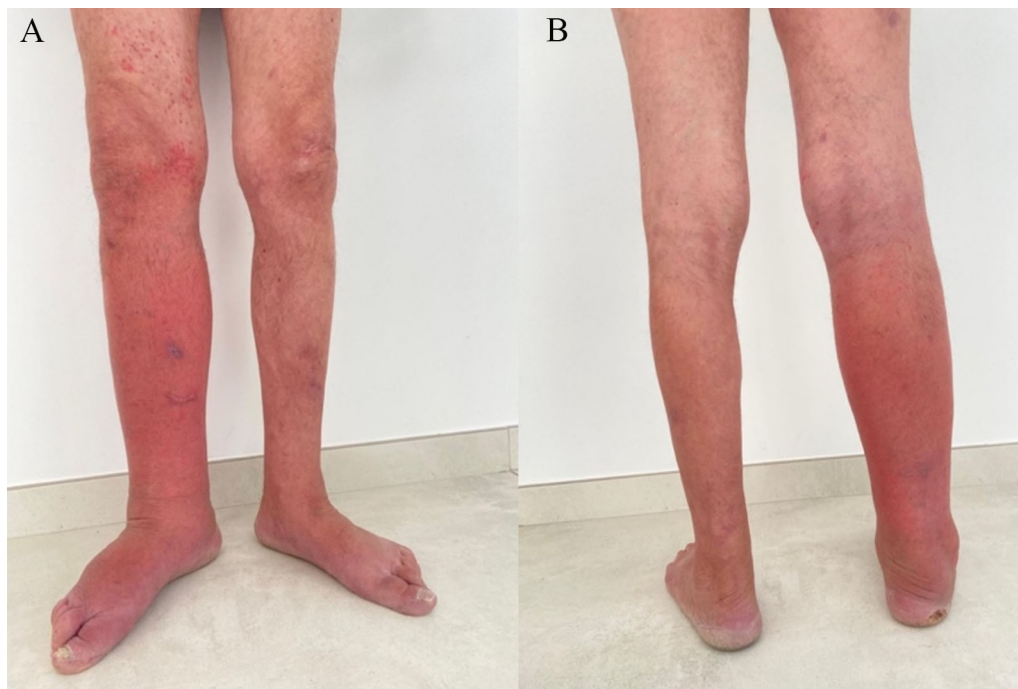


Figure 1. Episode of erysipelas of the right lower limb in patient #8 (a, anterior view and b, posterior view), which occurred shortly after the patient discontinued prophylaxis with oral phenoxymethylpenicillin (1,000,000 IU, two times a day) initiated for the prevention of recurrent erysipelas. The patient keeps track of all his erysipelas episodes and reported this one to be the forty-fourth. Written permission for publishing the figures was obtained from the patient.

replacement (agalsidase alfa). The patient condition has been stable on agalsidase alfa with the exception of two episodes of erysipelas of the right lower limb on which he has moderate lymphedema. He was successfully treated with amoxicillin.

All of the 12 patients (10 males and 2 females) were French. The age on inclusion ranged from 42 to 59 years (mean \pm standard deviation (SD): 50 ± 6.4). Four patients died; the age at death ranged from 56 to 68 years (mean \pm SD: 63 ± 5.7); none of the deaths was related to erysipelas. All patients had a confirmed molecular diagnosis of FD (7 missense, 2 nonsense, 1 frameshift, 1 indel, and 1 splice-site *GLA* variant). All male patients had classic FD and extremely low ($< 1.5\%$) residual levels of α -galactosidase activity. The two female patients show various manifestations of FD: P#7 had a residual level of α -galactosidase activity ($1.5 \mu\text{mol/h/mg}$, when the norm is > 2.0), a variety of signs and symptoms of classic FD, but late initiation of ERT. P#11 has classic FD with a highly skewed X-inactivation profile with complete silencing of the wild-type allele in four tissues^[15], no residual α -galactosidase activity and multisystem clinical involvement.

All the patients underwent probabilistic antibiotic treatment, but microbiological confirmation was not obtained for most patients. Erysipelas is a clinical diagnosis [Figure 1] and current recommendations do not call for obligate confirmation of the group A beta-hemolytic streptococcal infection in clinical practice since the worldwide dominance of this germ has been documented in the medical literature.

The most frequently observed manifestations of FD before the onset of erysipelas were lymphedema (in 10 of the 11 patients with data) [Figure 2], hypohidrosis/anhidrosis (10 out of 12), proteinuria (in all 12), CKD (10 out of 12), rhythm disorder (10 out of 12), hypertrophic cardiomyopathy (9 out of 12), and angiokeratoma (8 out of 12). The mean \pm SD age at the time of the first episode of erysipelas was 42.7 ± 11.4



Figure 2. Severe lymphedema of the lower limbs (a, anterior view and b, left lateral view) in a female patient heterozygote for FD with highly skewed X-chromosome inactivation profile (100% / 0%) favoring the silencing of the wild-type *GLA* allele. Written permission for publishing the figures was obtained from the patient.

(range: 27-65), and most of the episodes affected the lower limbs (11 out of 12). There were no complications of erysipelas except for P#7 (disseminated infection during the second episode of erysipelas). When considering potential risk factors for erysipelas, ten patients had lymphedema, three patients were overweight, three had varicose veins, two had mycosis, and two had toe web intertrigo. The two youngest patients at the time of the first episode of erysipelas (P#1 and P#2) had no known risk factors.

DISCUSSION

Our results constitute the first report on a series of cases of erysipelas in patients with Fabry-disease-associated lower limb lymphedema. In a cohort of 223 patients with confirmed FD being followed up at our national referral center, 12 (10 of whom had lower limb lymphedema) experienced one or more episodes of erysipelas (giving a total of 67 episodes). The association between erysipelas and FD had not been previously reported in the literature.

Clinical implications

The occurrence of erysipelas in a patient with FD has significant clinical implications. Firstly, patients may be vulnerable to the infectious sequelae of erysipelas: antibiotic therapy and wound care treatments must therefore be implemented judiciously while taking account of FD-associated comorbidities and potential drug interactions. Secondly, the recurrent nature of erysipelas described in the literature and observed in 7 of the 12 patients of this case series underscores the need for preventive measures and close monitoring, particularly when lower limb lymphedema is present^[28]. Proactive measures (including prompt recognition of intertrigo or skin wound, early initiation of oral antibiotic therapy, skin hygiene education, and diligent wound care) are paramount in optimizing clinical outcomes and minimizing the impact of erysipelas on FD progression.

Underlying mechanisms

The mechanisms underlying the link between FD and erysipelas have yet to be identified. In our series, lymphedema^[29] preceded erysipelas in 11 of the 12 patients with available data. Thus, in retrospect, and given the accumulation of cases, lymphedema appeared to be the key predisposing factor to erysipelas^[30] in patients with FD. We conducted a search within our cohort and identified only seven additional patients with lymphedema who had not experienced erysipelas. Given this small sample size (possibly due to missing data in the context of this retrospective study), our ability to draw definitive conclusions was limited. However, we performed a comparison and found no notable differences in the prevalence of any risk factors. Apart from lymphedema, microvascular dysfunction is a prominent feature of FD and manifests itself through endothelial cell damage, impaired vasomotor regulation, and aberrant angiogenesis^[9,30]. These microvascular perturbations may compromise tissue perfusion and predispose patients with FD to skin damage, bacterial invasion, and thus greater susceptibility to erysipelas. The dysregulation of the immune system in FD (as characterized by aberrant cytokine profiles, impaired leukocyte function, and altered inflammatory responses) may also compromise the host's defenses against bacterial pathogens. Furthermore, the chronic inflammatory state in FD^[31] might exacerbate susceptibility to cutaneous bacterial infections like erysipelas. Hypohidrosis^[13] also compromises the skin barrier and facilitates bacterial invasion. Lastly, the deposition of glycosphingolipids within the vascular endothelium - a hallmark feature of FD^[32] - might exacerbate endothelial dysfunction^[33] and exacerbate a pro-inflammatory milieu conducive to the development of erysipelas or cellulitis.

Anecdotally, patients with hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis (POIKTMP) present with lymphedema, as seen in some patients with FD^[34]. Erysipelas has been documented in approximately 8% of patients with POIKTMP; this suggests that the underlying pathological mechanisms for erysipelas in these two genetic diseases are similar and further highlights the role of lymphedema as a risk factor^[19,27-29].

In contrast, a search of the literature data on other genetic diseases of the skin (including epidermolysis bullosa, ichthyosis, palmoplantar keratoderma, and pseudoxanthoma elasticum) did not identify any reports of an increased prevalence of erysipelas (with the exception of primary lymphedema)^[27]. Similarly, a literature search for erysipelas as a complication of lysosomal storage diseases other than FD did not produce any valid hits.

Impact on disease progression

Recurrent erysipelas might exacerbate the disease burden, including fatigue and poor overall quality of life^[22,35] - particularly in individuals with concomitant renal, cardiac, or neurological manifestations. Prophylaxis or early intervention might reduce the frequency of recurrence of erysipelas in patients with FD.

Limitations

While our study provides valuable insights into the association between FD, lymphedema, and erysipelas, it is not without limitations. First, the retrospective design of the study inherently introduces the possibility of incomplete or missing data for certain parameters, which may affect the comprehensiveness of our analysis. Additionally, the reliance on medical records and patient recall could have led to underreporting or oversight of some cases of erysipelas and lymphedema, potentially influencing the observed prevalence. A second limitation is the absence of a control group comprising patients with lymphedema unrelated to FD. Such a control group would have allowed for comparative statistical analysis, enabling us to evaluate potential differences in the incidence of erysipelas, identify additional risk factors, and assess the severity of complications between FD and non-FD populations. Despite this limitation, the prevalence of erysipelas in

our cohort (12 out of 223 patients, with a total of 67 episodes) appears notably higher than that reported in the general population, suggesting a meaningful association. To further elucidate these findings, future multicenter, prospective studies are warranted.

Conclusion

Our case series shows that patients with FD-associated lymphedema are at risk of erysipelas and sheds light on a previously unrecognized complication of FD. Lower limb lymphedema rather than FD *per se* appears to be the predisposing factor. Awareness of this risk should prompt greater vigilance and proactive management strategies for preventing the occurrence of erysipelas or cellulitis and mitigating their acute symptoms and long-term sequelae^[21,24,36] in patients with FD-associated lymphedema.

DECLARATIONS

Authors' contributions

Conceptualization: Germain DP

Methodology: Germain DP, Vasconcelos AP

Validation: Germain DP, Burlina AP, Vasconcelos AP, Barache L

Formal analysis: Germain DP, Vasconcelos AP

Investigation: Germain DP, Vasconcelos AP, Barache L

Resources: Germain DP

Data curation: Germain DP, Nguyen TT, Vasconcelos AP, Barache L

Writing - original draft: Germain DP

Writing - review and editing: Germain DP

All authors have read and approved the final version of the manuscript.

Availability of data and materials

All data underlying this publication are available in the article. Additional raw data will be made available by the corresponding author upon reasonable request.

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None.

Conflicts of interest

Germain DP is a consultant for Chiesi, Idorsia, Sanofi, and Takeda. The companies were not involved in the study. The remaining authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval and consent to participate

In line with the French legislation on retrospective studies of clinical practice, approval by an institutional review board was not required (<https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000037187498>). The need for patient consent was waived because the study was qualified as non-interventional, according to French legislation (reference: MR004). However, all patients were given written information on the study's objectives and procedures and were free to object to the processing of their personal medical data.

Consent for publication

All patients gave their written, informed consent to the publication of the research results.

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