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CASE REPORT

Skin infections caused by *Mycobacterium chelonae*: Underestimated, especially in immunocompromised patients

Celine De Krock[1] | **Otto Van de gaer**[2] | **Emmanuel André**[2,3] | **Jan Leo Lenaerts**[4,5] | **Patrick Verschueren**[4,6] | **Paul De Munter**[3,7] | **Petra De Haes**[1,3]

[1]Department of Dermatology, University Hospitals Leuven, Leuven, Belgium

[2]Clinical Department of Laboratory Medicine, University Hospitals Leuven, Leuven, Belgium

[3]Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium

[4]Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium

[5]Department of Rheumatology, Reuma instituut Hasselt, Hasselt, Belgium

[6]Department of Development and Regeneration, Skeletal Biology and Engineering Research Centre, KU Leuven, Leuven, Belgium

[7]Department of General Internal Medicine, University Hospitals Leuven, Leuven, Belgium

Correspondence
Celine De Krock, Herestraat 49, 3000 Leuven Belgium.
Email: celine_dekrock@hotmail.com

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Abstract

Mycobacterium chelonae infections are rare but significant in immunocompromised patients, often leading to delayed diagnosis due to a specific clinical signs and the difficulty to culture and identify the causative agent with conventional laboratory techniques. We report a case series of five patients presenting with cutaneous infection due to *M. chelonae*. An extensive review of the literature was accomplished to provide summary data on the clinical presentation, diagnostic methods and treatment options for these infections. Four out of five patients were receiving immunosuppressive treatments. All patients presented after a prolonged history of painful lesions on the extremities. Sampling and definitive diagnosis implied repeated tissue biopsies and a combination of mycobacterial tests. All patients received a combination of antibiotics comprising a macrolide and achieved complete healing of the skin lesions after 4–12 months. Our case report aims to increase awareness of skin infections caused by *M. chelonae* and emphasises the importance of early implementation of mycobacterial cultures in the diagnosis of painful ulcerations on the extremities that do not improve to standard systemic antibiotics.

KEYWORDS
atypical mycobacterium infection, immunosuppression, *Mycobacterium chelonae*, skin infection

INTRODUCTION

Mycobacterium chelonae is one of the most common nontuberculous mycobacteria (NTM), and is classified among rapidly growing mycobacteria, as their growth is usually observed after 3–7 days of incubation.[1] NTMs are ubiquitous in the environment and have been isolated from soil, water and natural water supplies. Due to genomic and metabolic similarities, *M. chelonae* has long been grouped together with *Mycobacterium abscessus*, within a so-called *M. chelonae–abscessus* complex.[2,3] The incidence of skin infections caused by NTMs tends to

increase and varies between 0.9 and 7.2 cases per 100,000 persons per year. This increase can be partly explained due to diagnostic advances, increased awareness and a larger elderly or immunocompromised population.[4,5] Overall prevalence is not known because NTM infections are still inadequately diagnosed and notified in most countries.

M. chelonae is regularly associated with localized cutaneous and soft tissue infections. Disseminated and deep infections are rare. The absence of invasive disease can be explained by the fact that most isolates of *M. chelonae* have an optimal growth temperature of 30–32°C. *M. chelonae infections* often occur in the context of immunosuppression.[1,4,6,7] Skin and soft tissue infection typically occurs after incidental environmental inoculation.[8] Inoculation after surgeries, and cosmetic procedures such as mesotherapy, sclerotherapy, acupuncture and liposuction have also been described.[1,6,7,9]

The diagnosis of such chronic infection typically requires a skin biopsy for histopathology and microbiological processing, including culture on selective media and a reliable identification at the species level.[9,10] There are no universal therapeutic recommendations for *M. chelonae* skin and soft tissue infections. Treatment with multiple antibiotics, comprising a macrolide, prolonged over duration of several months is recommended.

CASE REPORTS

Case 1

A healthy 76-year-old woman presented with progressive, confluent purpuric papulonodular lesions and painful ulcerations on the lower right leg, following minor trauma in Gambia (Figure 1a). Initially, diagnosis of ecthyma gangrenosum was suspected, however classic bacterial wound cultures remained negative and there was no response to multiple antibiotics (minocycline, doxycylin, amoxicillin clavulanic acid). Skin biopsy showed an ulceration reaching the subcutis with a granulomatous inflammation. On tissue biopsy, auramine stain was negative, but mycobacterial growth was seen on NTM agar. Identification of culture using polymerase chain reaction (PCR) revealed the presence of *M. chelonae*. She was hospitalized for 2 weeks and a multidrug treatment (based on susceptibility testing) with oral clarithromycine (500 mg, 2×/day) and intravenous tigecycline (50 mg, 2×/day) was initiated. Lesions improved within a week and resolved completely after 3 months of treatment. Clarithromycin (500 mg, 2×/day) was continued for a year posthospitalization. Follow-up at 4 months showed no recurrence (Figure 1b).

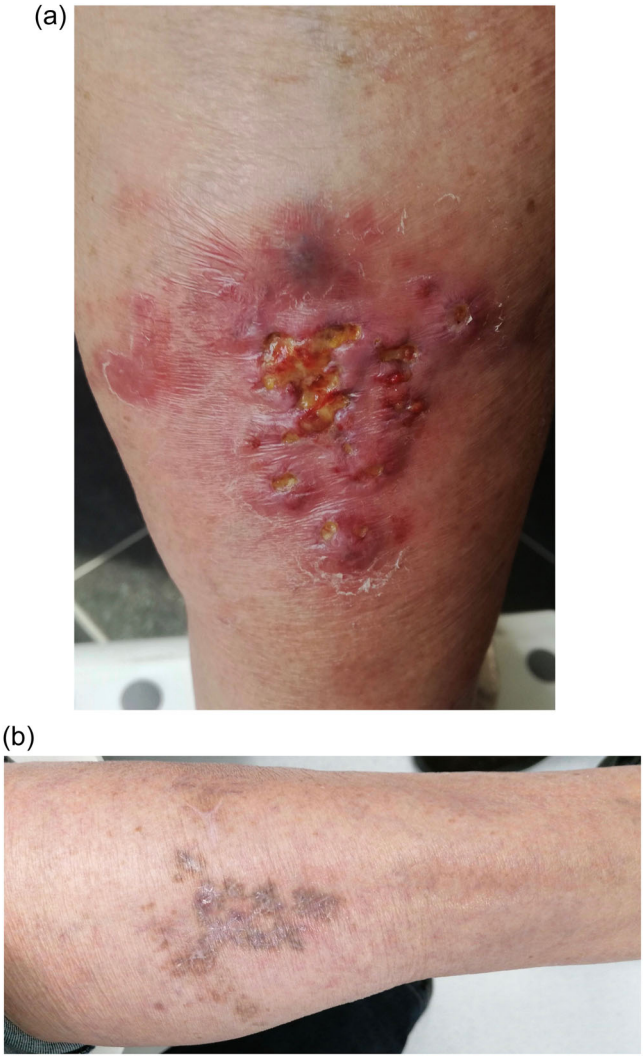

FIGURE 1 Clinical presentation of case 1. (a) Lesions before antibiotic treatment. (b) Lesions 9 months after initiation of antibiotics.

Case 2

A 74-year-old female presented with painful erythematous/purpuric subcutaneous nodules, several pustules and a bulla on the lateral side of the left foot (Figure 2a). Her medical history included: IgA nephritis and systemic lupus erythematous (SLE) with polyarthritis, for which she was taking methotrexate (15 mg/week), prednisone (6 mg/day) and hydroxychloroquine (200 mg/day). Because of the worsening of the lesions after treatment with multiple systemic antibiotics (amoxicillin clavulanic acid, doxycycline, flucloxacillin), the patient was hospitalized for further investigations.

Skin biopsy showed an extensive purulent polynuclear infiltrate with the presence of threadlike structures on Grocott, PAS and Ziehl-Neelsen stain. Classic bacterial and fungal cultures on skin biopsy remained negative, as was the auramine stain. However, both mycobacterial culture and PCR demonstrated the presence of *M. chelonae* on the biopsy. After susceptibility testing, treatment with IV tobramycin (5 mg/kg/day) and po clarithromycin (500 mg 2×/day) were given concurrently during 2 weeks of hospitalization, followed by oral clarithromycin (500 mg 2×/day) monotherapy for 6 months. Methotrexate was discontinued, but prednisone had to be temporarily increased to 10 mg/day to control the underlying SLE with polyarthritis. After the initiation of this treatment, there was a slow, but complete healing of the wounds over 4 weeks (Figure 2c). One year after termination of antibiotics, there was no recurrence of the lesions.

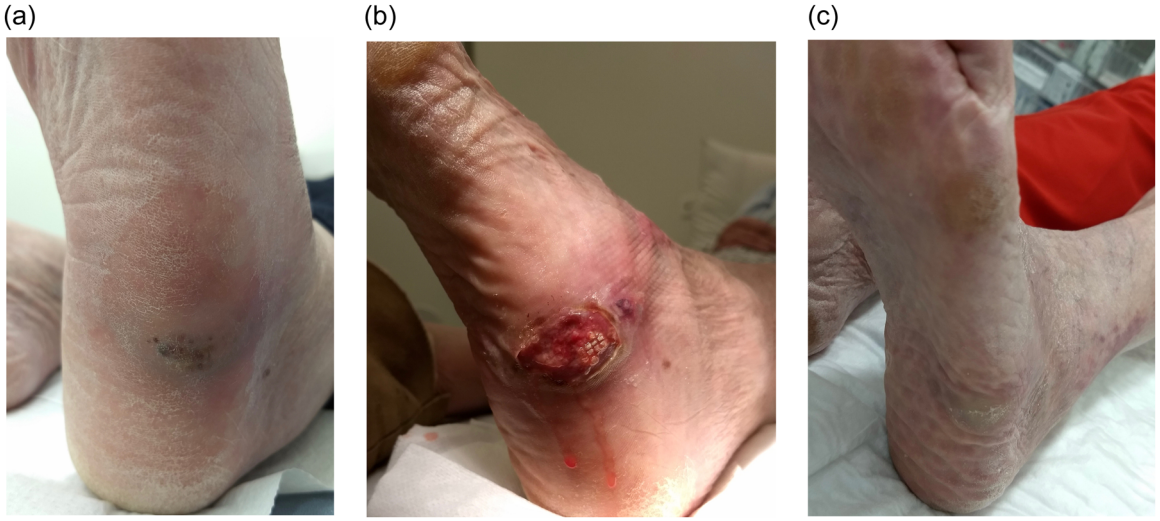

FIGURE 2 Clinical presentation of case 2. (a) Lesions before antibiotic treatment. (b) Lesions 14 days after development of initial lesions. (c) Lesions 1 month after initiation of antibiotics.

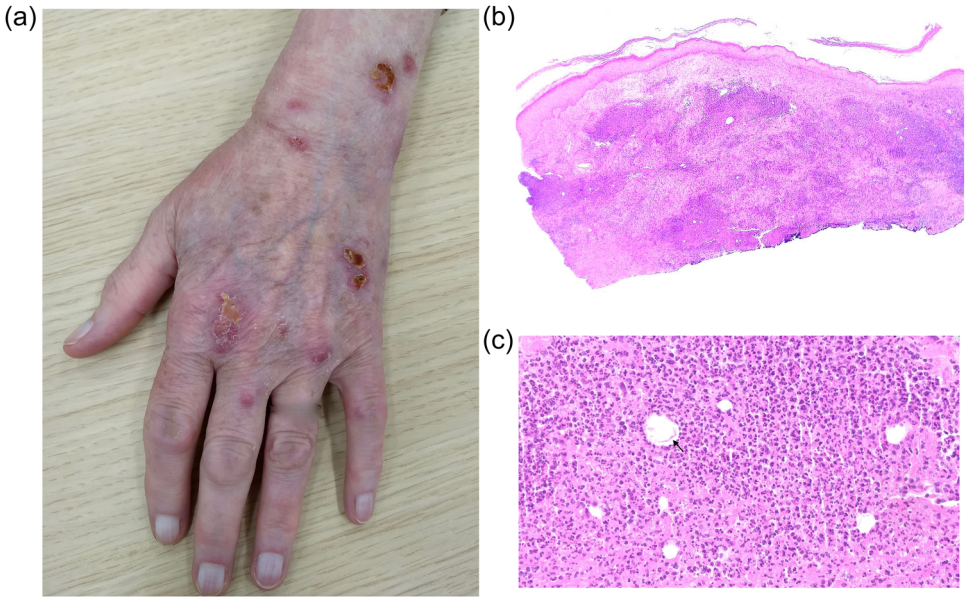

FIGURE 3 Clinical presentation of case 3. (a) Lesions before adequate antibiotic treatment. (b) Overview picture of a hematoxylin–eosin stained skin biopsy, showing dermal granulation tissue with presence of suppurative, necrotising granulomas, composed of a central zone with numerous neutrophils (×25 magnification). (c) Detailed image of a hematoxylin–eosin stained skin biopsy showing a cluster of elongated rod-like structures (arrow) in the centre which may indicate the presence of mycobacteria (×400 magnification).

Case 3

The third case concerns a 69-year-old female who developed painful erythematous to purplish nodules on her left hand 1 month after initiation of methotrexate (7.5 mg/week) for an underlying bullous pemphigoid (Figure 3a). Initial biopsy was suggestive of Nocardia infection after which a treatment with co-trimoxazole was initiated. Due to the worsening of the lesions, a new biopsy was obtained (Figure 3b,c). Panfungal- and bacterial PCR remained negative, but this time culture showed mycobacterial growth, identified by PCR as *M. chelonae*. After susceptibility, testing ciprofloxacin (500 mg, 2×/day) in combination with azithromycine (500 mg 2×/day) was initiated. Improvement was evident after 2 weeks, with complete resolution in 8 weeks. Three-year follow-up showed no recurrence of lesions.

Case 4

A 67-year-old male presented with a 5-month history of painful grouped purple-red papules with pus evacuation on the left hand. He had started methotrexate (15 mg/week) and methylprednisolone (32 mg in tapering schedule) 3 months earlier because of a cryptogenic organizing pneumonia. Since erysipelas was initially suspected, treatment with amoxicillin clavulanic acid (dose unknown) and clindamycin (dose unknown) was initiated. Biopsies showed an aspecific deep fibrosing inflammation. There were no infectious agents visible in this specimen by Ziehl–Neelsen, Grocott and Periodic acid–Schiff stain. Subsequent mycobacterial culture was positive and further identification showed the presence of *M. chelonae*. Methotrexate was interrupted and methylprednisolone was further tapered to zero.

After susceptibility, testing combination therapy with clarithromycin (500 mg 2×/day) and doxycycline (100 mg 2×/day) was initiated but discontinued after 8 days due to side effects. Treatment was then adapted to azithromycin (500 mg/day). Four days later, doxycycline was associated. But again, because of side effects, both antibiotics were discontinued after 8 weeks of treatment. At 6-month follow-up, the lesions had completely healed.

Case 5

A 74-year-old female known with rheumatoid arthritis treated with methylprednisolone 32 mg/day and hydroxychloroquine 2 × 200 mg/day developed a painful wound on the left leg. Initial treatment with amoxicillin clavulanic acid failed and multiple new ulcerations developed (Figure 4a). Biopsy was compatible with polyarteritis nodosa and bacterial cultures remained negative. Methylprednisolone 64 mg/day and colchicine 0.5 mg/day were initiated, but lesions worsened. Acid-fast bacteria were found on the Ziehl–Neelsen stain and new biopsies showed positive mycobacterial cultures with the presence of *M. chelonae*, confirmed by PCR. Therapy with clarithromycin (2 × 375mg/day) and levofloxacin (500 mg 1×/day) led to improvement of the lesions after 10 days, complete healing in 4 months (Figure 4b) and treatment could be stopped after 5 months. Evaluation after 2 years showed no recurrence of the lesions.

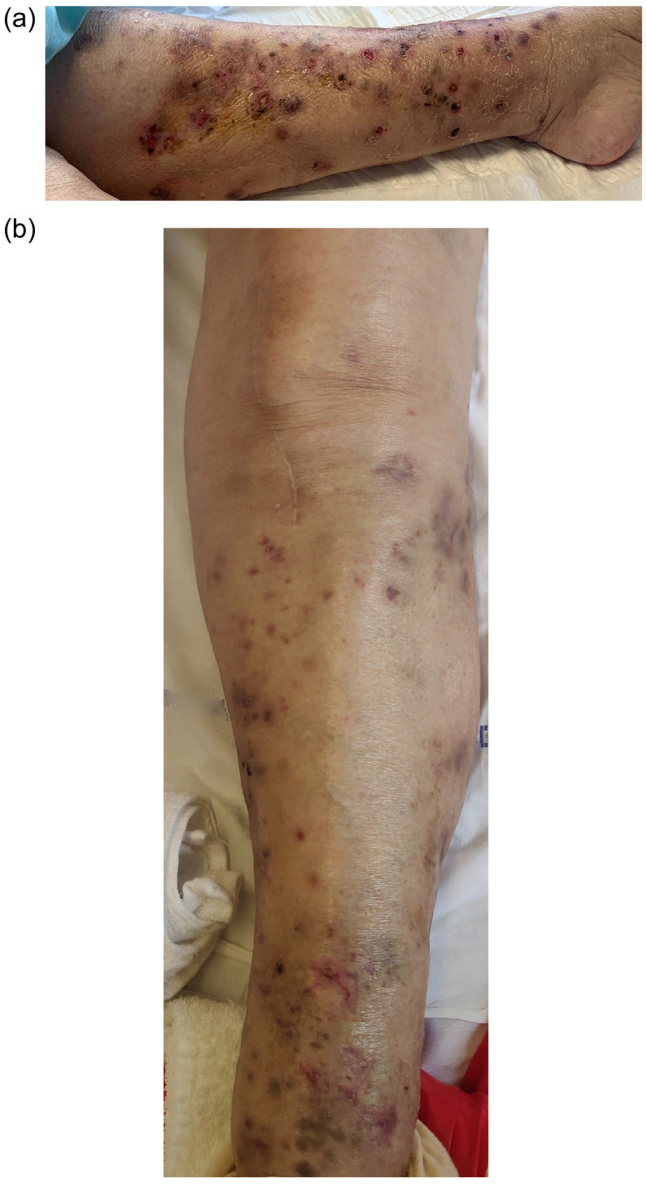

FIGURE 4 Clinical presentation of case 5. (a) Lesions before adequate antibiotic treatment. (b) Lesions 4 months after initiation of antibiotics.

TABLE 1 Clinical characteristics of patients.

		Case 1	Case 2	Case 3	Case 4	Case 5
Age		76 years	74 years	69 years	67 years	74 years
Underlying medical conditions		None known	Systemic lupus erythematosus IgA nephritis	Bullous pemphigoid	COP	Rheumatoid atritis
Immunosuppressive therapy		None	Oral prednisone Methotrexate	Methotrexate	Oral methylprednisolone Methotrexate	Oral methylprednisolone Methotrexate
Empiric antibiotic therapy		Minocycline Doxycycline Amoxicillin clavulanate	Amoxicillin clavulanate Doxycycline Flucloxacillin	Co-trimoxazole/ trimethoprim	Amoxicillin clavulanate Clindamycin	None
Diagnostic tests	Bacterial culture	Multiple classic bacterial cultures remained negative	Multiple classic bacterial cultures remained negative	Multiple classic bacterial cultures remained negative	– *Staphylococcus aureus* – *Streptococcus agalactiae*	Multiple classic bacterial cultures remained negative.
	Auramine Stain	Negative	Negative	Negative	Negative	Positive
	Mycobacterial culture NTM	Skin biopsy: Positive	Skin biopsy: Positive	Third skin biopsy: Positive	Negative on 4/4 biopsies	Positive
	Mycobacterial culture MGIT	Skin biopsy: Negative	Skin biopsy: Negative	Third skin biopsy: Positive	Positive in 2/4 biopsies	Positive
	PCR on sample	Not performed	*Mycobacterium chelonae*	Not performed	Negative on 1/1 biopsy	*M. chelonae*
	PCR on culture	*M. chelonae*	*M. chelonae*	*M. chelonae*	*M. chelonae* in 2/2 positive cultures	*M. chelonae*
Time to symptoms and diagnosis		3 months	3 months	3 months	5 months	5 months
Targeted treatment		Clarithromycin (500 mg 2×/day) and tigecycline IV (50 mg 2×/day)	Clarithromycin (500 mg 2×/day) and tobramycin IV (5 mg/kg/day)	Azithromycine (500 mg 2×/day) and ciprofloxacin (500 mg 2×/day)	Clarithromycin (500 mg 2×/day) and doxycycline (100 mg 2×/day)	Clarithromycin (2 × 375 mg/day) and levofloxacin (500 mg 1×/day)
Duration of treatment		12 months	6 months	8 months	2 months	5 months
Outcome		Cured	Cured	Cured	Cured	Cured

Abbreviations: COP, cryptogenic organizing pneumonia; IV, intravenous; MGIT, mycobacterial growth indicator tube; NTM, nontuberculous mycobacteria; PCR, polymerase chain reaction.

DISCUSSION

In this case series, we report five patients diagnosed with *M. chelonae* skin infection at our centre from 2018 to 2021 (Table 1). Despite a reported increase in incidence, these infections are often misdiagnosed due to the variety in clinical presentation.[4] The classic cutaneous presentation includes painful ulcerations, purpuric nodules, abscesses and draining sinus tracts, predominantly on the extremities, as observed in all our cases.[1,11] Disseminated cutaneous disease is common in immunocompromised patients.[4,6] Notably, four out of five patients were taking immunosuppressive medication (Table 1). Corticosteroid usage has been reported as an important risk factor in *M. chelonae* infection and in this case, series three out of five patients were taking oral corticosteroids (Table 1). Despite taking immunosuppressive drugs, the patients in our case series developed local skin infections without dissemination to other organs. Compared to other NTM, such as *Mycobacterium avium* complex *and M. abscessus, M. chelonae* causes lymphadenitis and pulmonary infections less frequently.

In our case series, the diagnosis was complicated and delayed, with a mean time to diagnosis of 4 months (Table 1). This is consistent with results from the literature, which describes a median time between the onset of symptoms and diagnosis of 7.9 months.[12] In addition to a detailed history (prior contaminated water or environmental exposures, preceding cutaneous trauma or surgery, intake of immunosuppressive drugs), diagnosis requires biopsy of the skin lesions for both histological evaluation as well as mycobacterial culture and/or PCR.[4,9] Histopathology can show neutrophilic abscesses in the presence of granulomatous inflammation and/or reactive vasculopathy.[4,11] Histopathological characteristics are unfortunately not pathognomonic and aspecific.

The gold standard for the diagnosis is the identification of *M. chelonae* often requiring multiple tissue samples Table 1). The identification can be done by culture and/or by PCR since basic bacterial cultures cannot detect mycobacterium.

To date, there are no clear evidence-based guidelines regarding treatment for infections caused by *M. chelonae*.[6,11] Because of the unpredictable antibiotic resistance of *M. chelonae*, most authors recommend susceptibility testing before initiation of an antibiotic regimen.[9,12] However, culture and susceptibility testing of *M. chelonae* can be difficult and time-consuming. Therefore, some authors suggest initiating antibiotic therapy before results of antibiogram, since this may take 4–6 weeks.[6]

Of the NTM group, *M. chelonae* along with *M. abscessus* are considered the most difficult to treat.[13] To avoid selecting resistant strains, use of combinations of antibiotics is preferred.[14] According to literature, it is recommended to use a macrolide (e.g. clarithromycin), in association with a quinolone (e.g., levofloxacin or ciprofloxacin). Besides initiation of antibiotics, interruption or lowering the dose of immunosuppressive drugs is advised where possible to obtain an adequate immune response.[14]

Duration of treatment depends on clinical response and varies between 4 and 12 months.[14,15] Except for the fourth case, all patients in our series were treated for at least 6 months. In all patients, there was an adequate healing of the lesions after 4–12 months (Table 1).

AUTHOR CONTRIBUTIONS

Celine De Krock, Otto Van de gaer and Petra De Haes made substantial contributions to all the following: the conception and design of the study, acquisition of data, or analysis and interpretation, drafting the article or revising it critically for important intellectual content and final approval of the version to be submitted. Emmanuel André, Jan Leo Lenaerts, Patrick Verschueren and Paul De Munter made substantial contributions to all the following: drafting the article or revising it critically for important intellectual content and final approval of the version to be submitted. Celine De Krock and Petra De Haes take responsibility for the integrity of the work, from inception to finished article.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The ethics committee of KU Leuven approved this study under the registration number of MP019134. All patients in this manuscript have given written informed consent for participation in the study and the use of their deidentified, anonymized, aggregated data and their case details (including photographs) for publication.

ORCID

Celine De Krock http://orcid.org/0009-0008-1142-2352

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