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ORIGINAL PAPER

One-stage treatment of chronic osteomyelitis with an antibiotic-loaded biocomposite and a local or free flap

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Abstract

Background Treatment of chronic osteomyelitis (OM) usually comprises surgical excision of infected bone and soft tissue, dead space management, and soft tissue closure. When soft tissue revision results in defects too large for direct closure, assistance from plastic surgeons is needed. This study reports outcomes for patients with OM treated by plastic and orthopedic surgeons in a one-stage operation with an antibiotic-loaded biocomposite (ALB) and a local or free flap.

Methods We report a series of 11 consecutive patients with OM treated from February 2017 to September 2019. The treatment protocol included surgical debridement, tissue sampling, dead space management using ALB, stabilization as needed, and soft tissue closure with a local or free flap.

Results Mean age at surgery was 62 years (39–79), mean BMI 28 kg/m^2 (23–39). Multiple comorbidities were present. Local flaps were used in six patients, one reverse lateral arm flap, one soleus flap, two gastrocnemius flaps, one latissimus dorsi flap, and one fascia plantaris flap. Free flaps were used in five patients, three gracilis muscle flaps and two antero-lateral thigh (ALT) flaps. Mean follow-up was 28 months (15–42). Nine patients (81.8%) healed uneventfully after the one-stage surgical intervention, while two patients (18.2%) experienced partial or complete flap necrosis and required additional surgery. No patients required amputation, and no mortalities were reported.

Conclusions One-stage treatment of OM using ALB, performed by a multidisciplinary team, led to zero amputations in a highly comorbid population, where amputation would otherwise have been unavoidable.

Level of evidence: Level IV, therapeutic study.

Keywords Osteomyelitis · Free flap · Local flap · Biocomposite

Introduction

Chronic osteomyelitis is a progressive inflammatory process characterized by recurrent or intermittent episodes of pain, erythema, impaired wound healing, and purulent fistulation [1]. The condition arises due to prolonged microbial infection leading to tissue necrosis, sequestrum formation, and bone destruction [2]. Patients are often subject to extended disease periods with high morbidity, requiring frequent hospitalization, repeat surgery, and numerous outpatient visits.

Standard treatment protocols for osteomyelitis usually include multiple surgical interventions, comprising repeat debridement of infected bone and overlying soft tissue, management of dead space, administration and removal of local antibiotic-loaded substrates, soft tissue closure [1], and long periods of systemic antibiotic therapy. Due to high treatment costs, multiple amputations, prolonged patient morbidity in the traditional treatment regime, and the advent of antibiotic-loaded biodegradable biocomposites, one-stage surgical protocols have recently been developed. The first study describing such a protocol, originating from the Oxford Bone Infection Unit, reported no signs of infection at 1-year follow-up in 96 of

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100 patients with chronic osteomyelitis treated with a one-stage procedure, while a total of four recurrences were successfully managed with one additional surgery [3]. The multidisciplinary treatment protocol comprised extensive surgical debridement, irrigation, internal/external fixation in case of instability, dead space management with an antibiotic-loaded biodegradable biocomposite (Cerament G, BoneSupport, Lund, Sweden), and primary skin closure, directly or by local or free microvascular muscle flaps [3]. This remarkably low recurrence rate (4% primary and 0% secondary) indicates a superiority of this regime, compared with the traditional staged surgery approach, where recurrence rates have been reported in the range of 22–32% [4, 5].

Cerament|G (BoneSupport, Lund, Sweden) is an antibiotic-loaded biocomposite (ALB) comprised of calcium sulfate and hydroxyapatite [6]. Injectable, biodegradable, and loaded with gentamicin, it functions as an osteoinductive and osteoconductive bone void filler, eluding bactericidal concentrations of gentamicin for up to 30 days, thus ensuring local control of the bacterial infection while simultaneously providing dead space management [7–9]. The ALB degrades gradually, and thus obliterates the need for a second surgical intervention for removal (as in traditional antibiotic-loaded substances such as gentamicin pellets). Allowing for soft tissue closure directly following administration, and not requiring subsequent removal, use of such an ALB allows for one-stage surgical management of osteomyelitis.

For optimal patient management, a multidisciplinary approach is essential. Lack of plastic surgical expertise may generate concern regarding soft tissue closure if the resultant defect is too large for direct closure, and thus lead to amputation or conservative debridement which in turn may result in residual microbes and recurrence of infection. Aggressive debridement of bone and soft tissue is key to complete eradication of pathogens [10]. In plastic surgery, soft tissue defects not suitable for direct closure or skin transplantation, which requires a vascularized recipient site, are managed instead using local flaps, pedicled flaps, or free microvascular flaps for closure. The choice of reconstruction depends on the localization and size of the soft tissue defect, the vascularization of the surrounding tissue, and on patient comorbidity as well as smoking status [11].

In this retrospective study, we report outcomes for patients with osteomyelitis treated at our institution by a multidisciplinary team consisting of orthopedic and plastic surgeons in a one-stage operation with an antibiotic-loaded biocomposite, where soft tissue closure was accomplished with a local or free muscle flap.

Material and methods

Inclusion criteria

All patients treated with a one-stage protocol for chronic osteomyelitis between February 2017 and September 2019 were included by retrospective review of patient records. The records were followed up in September 2020, allowing for a minimum of 1 year follow-up period.

Exclusion criteria

Patients in which soft tissue closure was performed with direct closure or negative pressure wound therapy (NPWT). Outcomes for these patient groups will be reported in a separate publication.

Diagnostic criteria

Osteomyelitis was diagnosed clinically as fistulating infection between skin, bone, joint, and/or osteosynthesis material, or abscess formation in relation to bone and osteosynthesis material, in combination with infectious biochemistry and destruction of bone, bone sequestre, or bone edema, as verified radiologically on MRI, PET-CT, or plain X-ray.

Data collection

Demographic data—including age, sex, BMI, smoking, alcohol and drug abuse—and clinical data—including comorbidities, diagnosis, localization of osteomyelitis, etiology, type of flap used for soft tissue closure, number of admissions, and complications—were collected retrospectively from electronic patient records.

Surgical management

All patients were treated with a one-stage surgical intervention by a multidisciplinary team consisting of orthopedic and plastic surgeons. Preoperative clinical and radiological assessments were performed to identify available donor flaps and vascularity of recipient soft tissue. A CT angiogram was routinely performed in all patients requiring a free flap, and in patients requiring a local flap but where surgery had been performed near the flap donor site possibly compromising the vascularity to the planned flap.

The surgical protocol involved extensive debridement with excision of affected soft tissue and bone till healthy tissue with punctuate bleeding (Paprika sign) was encountered. The bone was cleared using a bone reamer, bone curette, bone chisel, and Rongeur forceps. A minimum of five deep tissue samples were taken intraoperatively from the infected bone, using separate and sterile utensils for each sample. The resultant defect was irrigated with an isotonic saline solution. After drying the cavity with gauze and changing all instruments and gloves, the cavity was injected with Cerament G for dead space management and local treatment of bacterial infection. No patients required additional internal or external fixation due to instability.

A local or free microvascular flap was then raised and used to ensure soft tissue closure and covered by a split-skin graft when needed (see Fig. 1).

Antibiotic treatment

Antibiotic treatment was stopped minimum 2 weeks preoperatively. Postoperatively, patients were given 2 weeks of empirical IV antibiotics (penicillin and dicloxacillin), that was later adjusted based on culturing and continued by oral administration for a minimum of 4 additional weeks, in some cases longer depending on cultures.

Outcomes

The primary outcome was flap survival, defined as complete survival of the flap with no complete or partial flap necrosis and no revision surgery required within the follow-up period. Complications were defined as major when requiring surgical revision in the operating theater, and as minor when requiring bedside revision or medical therapy. Secondary outcomes were amputation, death, and recurrence of osteomyelitis (defined as recurrent symptoms with purulent fistulation or positive cultures from additional post-operative sampling).

Results

Patients

A total of 11 patients were included in the study, eight males and three females (see Table 1). Mean age was 62 years (39–79); mean BMI was 28 kg/m^2 (23–39).

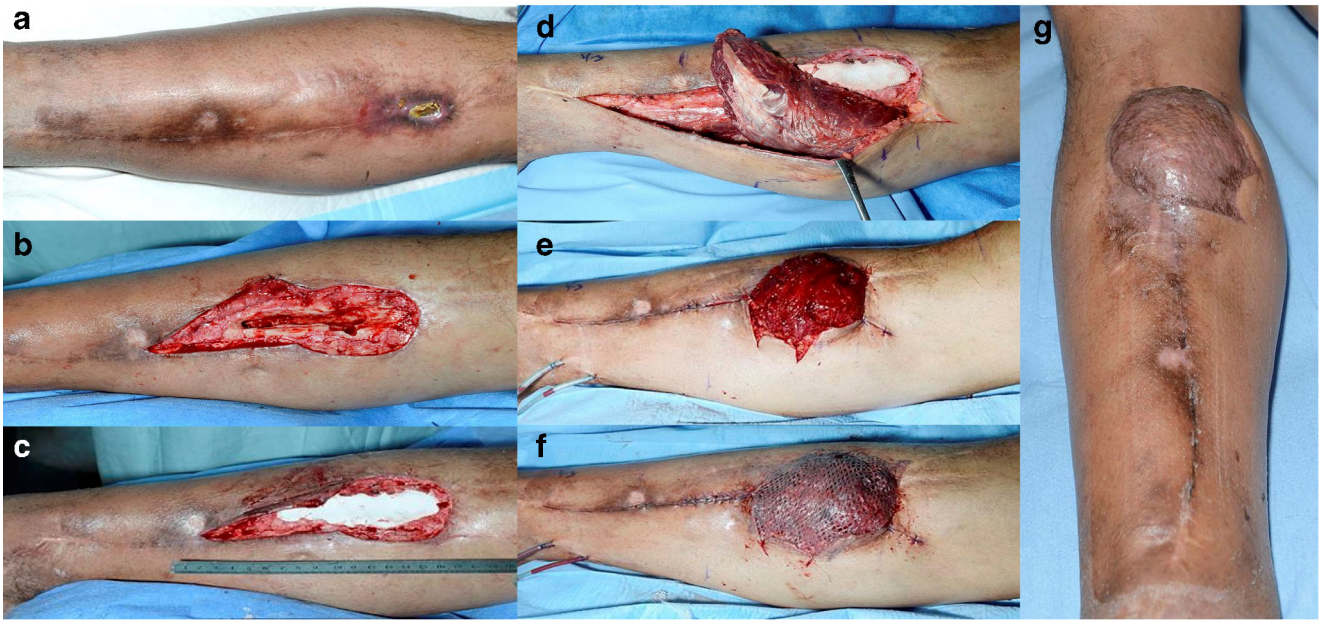

Fig. 1 A 63-year-old male suffering from gout, current smoker, had undergone multiple surgeries in his tibial bone during childhood due to an open fracture. After a 50-year disease-free period, osteomyelitis appeared in the proximal tibia (**a**). After multiple courses of antibiotics during a 3-year period, he was referred to our center for surgical management. After aggressive bone and soft tissue debridement (**b**), the cavity was filled with Cerament G (**c**). A local soleus flap was raised to cover the Cerament G (**d**), and the rest of the defect was closed directly (**e**). The soleus flap was covered with a split-thickness skin graft (**f**). No complications were seen, and at 2 months post-intervention (**g**), the patient had not experienced recurrence of osteomyelitis and ambulated freely

Table 1 Characteristics of included patients and flap outcomes. Age is given in years. *F/U*, follow-up in months; *IDDM*, insulin-dependent diabetes mellitus; *NIDDM*, non-insulin-dependent diabetes mellitus; *HT*, hypertension; *HC*, hypercholesterolemia; *IHD*, ischemic heart disease; *RA*, rheumatoid arthritis; *FVL*, factor V Leiden; *AML*, acute myeloid leukemia; *APO*, apoplexia (previous); *Depr*, depression; *ALT*, antero-lateral thigh flap; *RLA*, reverse lateral arm flap; *LD*, latissimus dorsi muscle flap; *ORIF*, open reduction internal fixation; *STI*, soft tissue infection; *Gastroc*, gastrocnemius flap

	Age	Sex	BMI	Comorbidities	Smoking	Bone	Etiology	Closure	Flap	Complication	F/U
#1	55	F	39	IDDM, HT, HC	Yes	Fibula	ORIF	Free	Gracilis	Major	34
#2	62	M	24	RA	No	Tibia	Arthrodesis	Free	ALT	No	24
#3	33	M	25	Asthma	No	Ulna	ORIF	Local	RLA	No	32
#4	75	M	25	-	No	Tibia + fibula	ORIF	Free	ALT	No	23
#5	63	M	31	Gout	Yes	Tibia	ORIF	Local	Soleus	No	26
#6	39	M	23	IHD, FVL, AML, APO	Past	Tibia	ORIF	Local	Gastroc	No	23
#7	64	M	29	NIDDM, HT, HC, APO, Depr	No	Humerus	ORIF	Local	LD	No	42
#8	67	M	26	-	No	Tibia	ORIF	Free	Gracilis	No	29
#9	79	F	29	HT	Past	Calcaneus	STI	Local	Plantaris	Major	42
#10	73	F	26	-	Past	Patella	ORIF	Local	Gastroc	No	15
#11	68	M	27	HT, HC, APO, gout	No	Tibia	ORIF	Free	Gracilis	No	15

Three did not suffer from any comorbidities. Two patients were current smokers, and two were previous smokers. None had a history of current or previous alcohol or substance abuse. In patients with a healed fracture, there were no cases of non-union. Osteomyelitis had followed traumatic or surgical skin defects in all cases but one, where OM had followed a soft tissue infection.

Soft tissue coverage

Depending on the size, location, and overall health status (comorbidities, smoking) of the patient, a local or free flap was used for soft tissue coverage. As complication rates are lower with local flaps, these were used when the size of the defect and availability of local tissue for reconstruction allowed for the use of a local flap. Otherwise, a free flap was used. Local flaps were used in six patients, one reverse lateral arm flap, one soleus flap, two gastrocnemius flaps, one latissimus dorsi flap, and one fascia plantaris flap. Free flaps were used in five patients, three gracilis muscle flaps and two antero-lateral thigh (ALT) flaps.

Outcomes

Patients were followed up by a chart review after a mean of 28 months (15–42). Nine patients had healed uneventfully after the one-stage surgical intervention and two patients had experienced major complications requiring re-operation, one partial flap necrosis and one complete flap necrosis.

Case #1

A 55-year-old female with a BMI of 39 kg/m^2, who suffered from insulin-dependent diabetes mellitus, hypertension, hypercholesterolemia, and was an active smoker, was treated for fibular osteomyelitis that followed a previous open fracture and received a free microvascular gracilis muscle flap covered with a split-thickness skin graft. Unfortunately, due to a venous thrombosis, severe stasis developed in the muscle flap necessitating revision surgery with a new venous anastomosis the following day. Further revision was needed 13 days later due to dubious vitality of the flap. The most superficial part of the muscle was found avital, but after resecting the outermost 5 mm of the flap, healthy bleeding tissue was encountered. NPWT was initiated, and after 3 weeks, the flap was covered with a secondary split-thickness skin graft. Six months later, the patient presented with throbbing pain in the area where osteomyelitis had been present, leukocytosis, and elevated C-reactive protein (CRP). However, there were no clinical signs of infection corresponding to the flap or surrounding soft tissue. An MRI strengthened the suspicion of osteomyelitis recurrence, and a fourth surgical intervention was performed. The

muscle flap was raised, and the underlying bone showed no clinical signs of osteomyelitis, but the area was revised, deep tissue samples were taken, the cavity refilled with Cerament G, and the flap re-inserted. Culturing of the deep samples showed no signs of bacterial growth. A chronic ulcer at the incision site developed postoperatively and proved refractory to conservative treatment. Three months later, the ulcer was resected, and the defect covered with a skin graft. The patient had not experienced further complications at 34 months follow-up from the one-stage intervention.

Case #9

A 79-year-old female with a BMI of 29 kg/m^2, past smoker, suffering from hypertension had initially been hospitalized for meningitis. She developed severe sepsis in relation to the meningitis and due to disseminated intravascular coagulation, developed multiple thrombi in digits on all 4 extremities, in addition to a large necrosis with exposed bone on her left heel. The digits were amputated, and after revision surgery, a split-thickness skin graft was transplanted on the left calcaneus. The graft failed, leaving exposed bone in which osteomyelitis was contracted. A one-stage protocol using a local fascia plantaris flap for soft tissue closure was performed, following an MR-angiogram that showed patency of both tibial arteries. The flap did not survive and was removed 2 weeks later. Revision of the calcaneus was performed 2 days later, and conservative wound treatment was initiated. Despite periodical improvement, the wound did not close, and a second one-stage operation was performed 10 months later, this time using a local propeller flap. Partial flap revision was needed after 5 days, and again after 14 days due to partial flap necrosis. The resultant soft tissue defect healed conservatively, and the patient had not experienced further complications at 42 months of follow-up from the first one-stage intervention (31 months after the last revision surgery).

No patients required amputation, and no mortalities were reported.

Burden of morbidity

From the onset of osteomyelitis to end of in/outpatient hospitalization, between 1 and 3 years passed (see Table 2). Prior to the one-stage surgical protocol, patients had undergone zero to 12 surgical interventions, and had been admitted zero to 12 times comprising 10 to 228 days of admission.

Discussion

Chronic osteomyelitis causes a high burden of morbidity, including frequent hospitalizations, long periods of medication, and often requires several surgical interventions. The one-stage protocol has proven effective in eliminating osteomyelitis [3]. Inspired by the protocol from the Oxford Bone Infection Unit, we established a multidisciplinary team for the treatment of osteomyelitis at our institution to optimize the outcome and survival of these challenging patients.

Table 2 Burden of morbidity. Disease length: time from onset of OM to the end of in-/outpatient hospitalization. *No.*, number of; *adm*, admissions; *ortho*, orthopedic; *plast*, plastic surgery; *OP*, operations; *y*, years; *m*, months

	Disease length	No. adm	No. ortho adm	Length ortho adm (days)	No. plast adm	Length plast adm (days)	No. OP before one-stage OP	No. OP ortho after one-stage OP	No. OP plast after one-stage OP
#1	1 y 7 m	2	1	8	2	61	1	1	4
#2	1 y	4	4	49	1	15	3	0	0
#3	1 y 1 m	2	1	3	1	7	1	0	0
#4	9 m	1	0		1	12	0	0	0
#5	11 m	1	0		1	16	0	0	0
#6	6 m	2	1	16	1	20	3	0	0
#7	3 y 3 m	12	11	214	1	14	12	0	0
#8	1 y 8 m	2	1	2	1	16	1	0	0
#9	2 y 3 m	5	3	46	2	16	2	1	3
#10	1 y 2 m	4	3	26	1	15	2	0	0
#11	11 m	1	0		1	13	0	0	0

Outcomes

Two of the 11 included patients experienced partial or complete flap necrosis. Both, however, recovered following revision surgery and avoided amputation. Both patients suffered from significant comorbidities, one was an active smoker and one a past smoker.

Flap survival relies on sufficient recipient site vascularization, and smoking is a known risk factor for developing complications after any surgical procedure [12]. Tobacco use decreases the oxygen supply to peripheral tissues, thus impairing healing processes and increasing the risk of infection. A past history of smoking may alter the vascularization of the peripheral tissue, and thus contribute to an increased risk of complications.

Often multiple surgeries are performed on areas affected by osteomyelitis, resulting in poorly perfused overlying scar tissue. Aggressive soft tissue debridement, including removal of all poorly perfused scar tissue, is therefore essential for revascularization of the area and to ensure eradication of all soft tissue infection [1], and such debridement is dependent on the possibility of wound coverage, that can be provided by plastic surgeons. Comorbidities such as peripheral vascular disease and diabetes mellitus can significantly reduce chances of flap survival. Two of the included patients suffered from diabetes. One suffered from insulin-dependent diabetes mellitus (IDDM) and experienced a venous thrombosis resulting in partial flap loss. The second patient suffered from non-insulin-dependent diabetes mellitus (NIDDM) and did not experience any complications. A known complication of diabetes is microvascular disease and reduced peripheral perfusion due to inflammation, metabolic disruption, and collagen derangement [13]. Atherosclerosis is promoted by hyperglycemia and leads to decreased perfusion and risk of vascular infarction [14]. Strict glycemic optimization is thus essential in the preoperative phase to increase chances of flap survival. As several patients were elderly and suffered from hypertension, hypercholesterolemia, diabetes, and previous cardiovascular insult, some degree of arteriosclerosis was likely present in these patients. However, none of the included patients had been diagnosed with peripheral vascular disease.

One of the patients that experienced a complication was operated shortly after suffering from meningitis and severe sepsis, which may have adversely influenced the outcome, due to an increased level of inflammation. This underlines the importance of preoperative patient optimization.

Highly comorbid patients with osteomyelitis and poor vascularization are at high risk of amputation, and high amputation rates have been reported in patients with osteomyelitis [15]. In our patient cohort, no amputations were necessary, and no mortality was observed. Limb salvage using the one-stage protocol is thus feasible, even in a patient population with multiple comorbidities.

Closure of soft tissue defects

In our study population, six local flaps and five free flaps were used. Depending on the defect in question, soft tissue closure can be achieved with several solutions, including local flaps, pedicled flaps, or free microvascular flaps. In addition to size and localization of the defect, availability, and vascularization of tissue surrounding the defect, the choice of closure also depends on the health status of the patient, including diabetes, vascular disease, obesity, and smoking status [11]. As part of the preoperative assessment at our institution, a CT-angiography is usually performed in order to evaluate the vascular status of both donor and recipient sites. Larger defects, or defects with exposed vital structures such as nerves, blood vessels, tendons, or bone, should be closed with a vascularized local or free flap in early stages [11]. The distal third of the lower leg is a particularly challenging site due to limited availability of local tissue. Therefore, free microvascular flaps are often used in this area [11, 15]. The gracilis muscle flap is particularly well suited for smaller defects, due to minimal donor site morbidity and good vascularization.

The necessity of a multidisciplinary approach

The establishment of multidisciplinary teams and highly specialized centers is essential in creating one-stage protocols for the treatment of chronic osteomyelitis. As eradication of infection includes not only debridement of infected bone but also thorough excision of all affected soft tissue, resultant soft tissue defects may be large. Involving plastic surgeons at an early stage in the planning of surgical management allows for effective debridement and immediate closure of even large resultant soft tissue defects. Often, patients with chronic osteomyelitis have undergone multiple surgeries and admissions. In our cohort, one patient had undergone 12 surgical interventions prior to the one-stage protocol and had not required further surgery at 29 months follow-up after the one-stage intervention. The remaining patients had undergone 0–3 interventions prior to the one-stage operation. A multidisciplinary approach allows for one-stage surgical management of chronic OM, thus reducing amputation rates and

morbidity for the patients, and decreases treatment costs and disease length [3].

Limitations

This is a small study sample with few patients, demonstrating that one-stage surgical treatment of osteomyelitis is feasible, but not always without complications. In our study, the mean follow-up time was 28 months, and the shortest follow-up time was 15 months. As recurrence of OM can present several years after surgical treatment, this is still a relatively short follow-up time. For flap evaluation, complications such as flap necrosis and thrombosis are generally evident within the first days, whereas wound healing problems, infection, and other complications may appear and require additional treatment within the first months following surgery. Therefore, the follow-up time is sufficient for evaluation of flap survival. However, the small number of patients does not allow for strong conclusions to be made, and studies on larger patient populations must be performed to validate this approach.

Other limitations of this study include the heterogenous patient material. Of the 11 included patients, two suffered from OM in the upper extremity (humerus and ulna, respectively), the rest in the lower extremity (six tibia, two fibula, one patella, and one calcaneus, respectively). Though specific aspects may not be directly comparable between patients, conclusions may still be drawn from the overall outcomes including flap survival.

When evaluating new products such as the ALB used in this study, both price and effectiveness should ideally be compared with similar products, which is beyond the scope of this paper. The value of the one-stage OM surgery described in this manuscript, including the price of any ALB used as a bone void filler, lies in the potential avoidance of lost workdays, outpatient visits, antibiotic days, admittance days, and revision surgeries that osteomyelitis patients often undergo.

Conclusion

One-stage treatment of osteomyelitis using an antibiotic-loaded biocomposite, performed by a multidisciplinary team with plastic- and orthopedic surgeons, led to zero amputations in a highly comorbid population, where amputation might otherwise have been unavoidable.

Code availability Not applicable.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Anne Kathrine Lorentzen and Magnús Pétur Bjarnason Obinah. The first draft of the manuscript was written by Anne Kathrine Lorentzen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability All data and materials comply with field standards.

Compliance with ethical standards

Conflict of interest Anne Kathrine Lorentzen, Lilan Engel, Hans Gottlieb, and Magnús Pétur Bjarnason Obinah declare that they have no conflicts of interest.

Ethical approval The local research ethics committee has confirmed that no ethical approval is needed for this retrospective study.

Informed consent All required informed consent was obtained from patients, including signed informed consent regarding publishing photographs.

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