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Case report

Restoration of skin defect using micro-autograft in an infant: the first experience

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Abstract

Background: The causes of many pathological conditions in neonates with very low gestational weight and fetal growth retardation remain unclear. One such condition is massive, rapid-onset skin necrosis in various parts of the body. In this article, we present the case of a small for gestational age neonate with extensive necrosis of the skin and subcutaneous tissues of the upper extremities and back.

Aim: To provide a detailed review of a clinical case of skin necrosis of the upper extremities and back in a small for gestational age infant.

Method: A report of a single case with a detailed description of an improved skin micro-autografting technique.

Result: Skin integrity was successfully restored after multiple debridements by using this micro-autograft technique in a small for gestational age infant.

Conclusion: Timely appropriate debridement followed by micro-autografts, as part of a comprehensive and interdisciplinary care approach, resulted in the successful treatment of a small for gestational age infant with extensive skin necrosis.

Keywords

Infant, skin micro-autografts, necrotomy, skin necrosis, xenografting.

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Introduction

Very low gestational weight and fetal growth retardation are major predictors of perinatal morbidity and mortality [1-3]. Searching for ways to reduce perinatal morbidity and mortality in high-risk neonates is a great challenge of modern medicine.

According to the available literature, up to 16% of all newborns are small for gestational age infants [4]. The high incidence of this pathology in elder children implies its great social and economic significance [5, 6].

Although there have been some great advances in understanding the risks of low birthweight, the causes of many associated pathological conditions and their rapid progression in affected infants remain unclear. One of these conditions is rapid and massive necrosis of the skin and adjacent tissues at various parts of the body. Affected newborns require complex intervention, including excision of the necrotic tissues and surgical restoration of the skin integrity. A lack of donor skin graft has been a major challenge in these cases, which has helped to drive innovation in the use of economical autodermoplasty principles [7]. However, despite numerous modifications of skin micro-autografting, no method has become widespread in clinical practice because of technical difficulties in performing the surgery and frequent negative consequences. Besides, they are predominantly used in treatment of wounds following full-thickness burns and traumatic injuries [8-10].

The lack of experience-based, practical information in the available medical literature concerning treatment of small for gestational age infants, by skin micro-autografting in particular, has prompted the authors to present this rare clinical case.

We report a case of necrosis of the skin and subcutaneous tissue of the upper extremities and back with no signs of thromboembolic complications in a small for gestational age infant with perinatal morbidity associated with generalized intrauterine infection of unspecified etiology. No similar reports have been found in the available medical literature.

Case description

A 4-day-old baby boy was transferred from the Department of Pregnancy Pathology of municipal non-profit enterprise (MNPE) "Vinnytsya Regional Clinical Hospital Vinnytsya Regional Council" to the Neonatal Intensive Care Unit at MNPE "Vinnytsya Regional Children's Clinical Hospital Vinnytsya Regional Council" in 2020, in grave condition.

According to medical history, the infant was born at 39 weeks of gestation to a gravida 2, para 2 mother. The pregnancy was associated with intrauterine growth retardation, oligohydramnios, and biochemical markers of intrauterine infection. At birth, the vital signs were normal, with Apgar scores of 7 and 8 at 1 and 5 minutes, respectively. Resuscitation was not performed. He weighed 2,050 g; his length was 48 cm, and head and chest circumference were 32.5 cm and 31 cm, respectively. His condition deteriorated rapidly over the next 2 days and he developed multiple organ dysfunction syndrome (MODS) and subcutaneous, intermuscular hematomas of the left upper arm and forearm. At age of 4 days, he was transferred to the Neonatal Intensive Care Unit in critical condition. Physical examination revealed pink skin, perioral cyanosis, thinning of the subcutaneous tissue layer, and subcutaneous intermuscular hematomas of the left upper arm and forearm with ecchymoses and edema. Spontaneous motor activity was decreased, neonatal reflexes were suppressed, and the range of motion of the upper extremities was notably diminished. He was breathing spontaneously at 52 to 54 breaths per minute, but the breathing was shallow with accessory use of the intercostal muscles and nasal flaring. Auscultation of the lungs revealed decreased breath sounds, and a box sound was noted over the lungs at percussion. The heart sounds were rhythmic, depressed; heart rate (HR), 150 beats per minute; systolic arterial pressure (SAP), 43 mmHg. He had been breastfed and the abdomen was soft with no guarding, no apparent tenderness. The bowel movements had been normal; the urinary output was decreased.

Laboratory and diagnostic studies included complete blood count and blood biochemistry, urinalysis, blood glucose, blood group and Rh factor, microbiology, electrocardiogram, ultrasonography and X-ray of the chest, abdomen, and upper extremities, and neurosonography. Temperature, HR, respiratory rate (RR), mean arterial pressure (MAP), and oxygen saturation (SpO_2) were monitored. SARS-CoV-2 was excluded by enzyme-linked immunosorbent assay (ELISA) for virus-specific IgM and IgG antibodies [11, 12].

Within hours after admission, the left upper limb had turned purple, and areas of epidermolysis appeared with formation of multiple vesicles filled with clear fluid. Palpation of the area found it to be dense, tense, and tender (**Fig. 1A**). At the same time, dense, dark purple infiltrates appeared around the right cubital fossa (**Fig. 1B**) and on the back (**Fig. 1C**).

Laboratory parameters are shown in **Tab. 1**. The abdominal ultrasound showed 4 mm peritoneal fluid at the anterior wall and free fluid in the small pelvis to 6 mm. The ultrasound examination of upper left extremity showed no sign of impaired vascular patency; there was severe soft tissue edema with no fluid areas. Radiography showed signs of bilateral pneumonia and enlargement of the left upper extremity due to the soft tissue edema, with no sign of bony structures involvement. Neurosonography found no pathology. The patient was evaluated by a vascular surgeon. The diagnosis of subcutaneous and intermuscular hematoma of the left upper arm and forearm was made. Intravenous antibacterial and symptomatic therapy were initiated along with feeding with adapted milk formula.

On day 5 of life, the patient's condition had worsened to extremely critical due to MODS progression. The urine output dropped to 1.5 mL/kg/h dark amber urine. The physical examination showed distal spread of the skin necrosis with increasing perifocal edema on the left arm; eventually, there was generalized edema. There was cyanosis of the skin over the entire surface of the left forearm and the back of the hand, and flexion contracture of the left forearm with limited passive movements in the elbow and wrist joints; on palpation, tenderness and soft tissue tension were observed. The accessory intercostal muscles were recruited in respiratory movements and nasal flaring was noted. The box sound was found over the lungs on percussion with suppressed breath sounds on auscultation. Heart sounds were

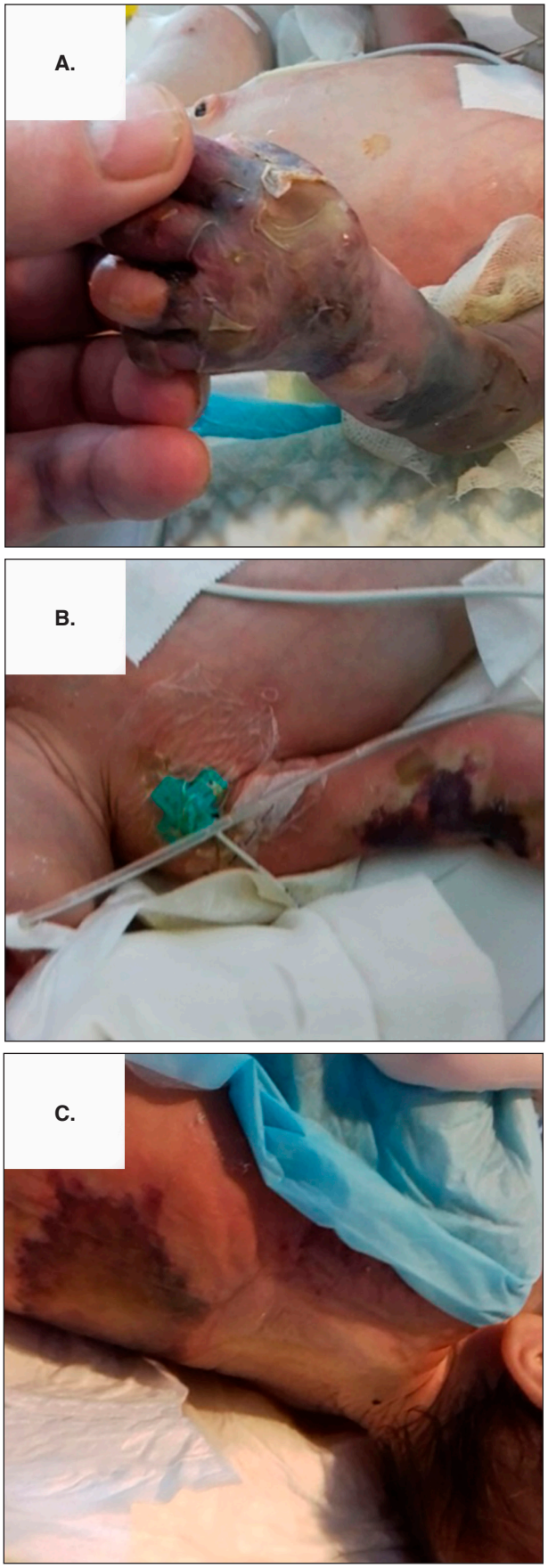

Figure 1. Formation of lesions of the left upper limb (**A**), around the right cubital fossa (**B**) and on the back (**C**) in a 4-day-old low birth weight infant boy shortly after admission to the Neonatal Intensive Care Unit.

Table 1. Changes in laboratory parameters during treatment.

Parameters	1st day	4th day	5th day	6th day	29th day
RBC count	5.36 * 10^{12}/L	-	-	-	2.9 * 10^{12}/L
Hb	182 g/L	-	98 g/L	139 g/L	95 g/L
Hct	51.9%	-	30.0%	40.0%	30.0%
PLT	108 * 10^9/L	-	10 * 10^9/L	256.4 *10^9/L	174 * 10^9/L
WBC count	2.65 * 10^9/L with left shift	-	2.0 * 10^9/L	27.8 *10^9/L	15.2 * 10^9/L with left shift
CRP	-	111 mg/L	146 mg/L	57.2 mg/L	normal limits
Total bilirubin	202.4 µmol/L	-	-	92.4 µmol/L	normal limits
Direct bilirubin	55.2 µmol/L	-	-	44.4 µmol/L	normal limits
ALT	12 IU/L	-	-	56.9 IU/L	normal limits
AST	22 IU/L	-	-	67.2 IU/L	normal limits
Urea	7.2 mmol/L	-	13.4 mmol/L	23.5 mmol/L	normal limits
Creatinine	49 µmol/L	-	129 µmol/L	91 µmol/L	normal limits
Total protein	-	-	39.4 g/L	-	normal limits
K^+	-	-	2.8 mmol/L	2.28 mmol/L	normal limits
Fibrinogen	59.94 g/L	-	-	-	normal limits
Lactate	-	3.1 mmol/L	-	-	normal limits
APTT	47.1 seconds	40.3 seconds	> 100.0 seconds	-	normal limits
PT	45 seconds	30.4 seconds	47.2 seconds	-	normal limits
Ethanol	negative	-	-	-	-
SARS-CoV-2 IgM and IgG antibodies	negative	-	-	-	-
UA	normal limits	-	-	-	normal limits

RBC: red blood cell; Hb: hemoglobin; Hct: hematocrit; PLT: platelets; WBC: white blood cell; CRP: C-reactive protein; ALT: alanine transaminase; AST: aspartate transaminase; K^+: potassium; APTT: activated partial thromboplastin time; PT: prothrombin time; UA: urinalysis.

rhythmic and depressed; HR was 160 beats per minute; SAP, 45 mmHg. The patient was placed on mechanical ventilation, an orogastric tube was inserted, and parenteral nutrition was initiated. Repeat ultrasound of the left upper limb confirmed preserved patency of the brachial, radial, and ulnar arteries and veins; the SaO_2 was 95% on the left and 97%. on the right. After examination by burn specialists and the pediatric vascular surgeons, the decision was made to correct the infusion therapy and perform emergency debridement in the region of the left upper arm and forearm.

The following day (day 6 of life), the general state of the patient remained critical, with a tendency to further deterioration. There was drainage of 30 mL of coffee ground material containing blood from the orogastric tube, and the abdomen was bloated. The bowels were sluggish and the urine output was decreased to 30 mL/day. Examination of the left upper arm and forearm revealed decreased swelling and tension of the tissues, pink and pale-pink color of the distal fingers, and copious serous drainage from the surgical wounds. The abdominal ultrasound revealed dilation of the ureters up to 4 mm and free fluid in the abdominal cavity. The patient was evaluated by additional allied specialists including the neurologist, nephrologist, hematologist, orthopedic surgeon, and burn specialist, followed by correction of the intravenous therapy. Diagnosis: respiratory failure, necrotizing enterocolitis (NEC), acute renal dysfunction of the newborn at 39 weeks of gestation; MODS; disseminated intravascular coagulation (DIC); hemolytic anemia; necrosis of the skin and soft tissues of the upper extremities and back; hypoxic encephalopathy; suppression syndrome; flexion contracture of the elbow; and small for gestational age/low birth weight infant.

On day 15 of life (postoperative day 10 following the first debridement), the patient was in critical but stable condition. He remained on mechanical ventilation with parenteral nutrition. His weight was unchanged at 2,050 g. HR was 136 beats per minute; SAP, 58 mmHg. Generalized edema persisted. The urine output had improved to 7.7 mL/kg/h and the gastrointestinal tract was functioning with bowel movements up to 4 times a day. The formation of a demarcation zone

around the left upper extremity with a decrease in tissue swelling was noted. By the decision of the multidisciplinary case management team including the burn specialists, suprafascial debridement was performed in the area of the left upper limb followed by coverage of the wound with lyophilized xenoderm porcine grafts.

On the first postoperative day after the second surgery (day 16 of life), the patient was in serious condition on mechanical ventilation. HR, 125 bpm; SAP, 52 mmHg. Urine output was to 400 mL/day. Enteral feeding with adapted milk formula was started using a 2 mL tube with no spitting up. There were 3 bowel movements. At ultrasound, there was a decrease in the amount of fluid in the abdominal cavity; the fluid was localized mainly at the flanks. Radiographic signs of resolving pulmonary infiltrate were registered. Microbiological analysis of wound contents identified the pathogen (*Klebsiella oxytoca*), which showed low sensitivity to cefotaxime. Postoperative wounds of the left upper extremity were covered with xenoskin (**Fig. 2A**); those on the back and right cubital fossa had thin necrotic eschar (**Fig. 2B**). Correction of transfusion therapy included the change of antimicrobial agents.

On day 20 of life, the patient underwent final debridement of the affected areas on the right cubital fossa and the back (**Fig. 3**).

On day 29 of life, the patient's condition remained serious but stable, with no negative dynamics and partial resolution of toxicity. Transition from ventilator to independent breathing with oxygen support through the mask was instituted. HR, 120 bpm; SAP, 42 mmHg. Urine output was about 370 mL/day. Microbial culture of the endotracheal tube contents found *Enterobacter cloacae*, 10^6 CFU/mL, which showed sensitivity to polymyxin, cefotaxime, and cefepime. Granulation tissue was forming at the surgical sites, with some small areas of necrosis and purulent drainage, and there was moderate edema and hyperemia of surrounding tissues (**Fig. 4A** and **Fig. 4B**). Changes in treatment regimen were made as needed.

On day 33 of life, the patient's condition was stable but still serious, with decreasing signs of toxicity. Physical exam findings showed no signs of deterioration. The baby was breathing on his own; RR was 45 breaths per minute; HR was 136 beats per minute; SAP, 51 mmHg. The urine output was approximately 350 mL/day and 3 normal bowel movements were recorded.

By the decision of multidisciplinary case management team, the child underwent additional debridement with resection of granulation tissue and xenograft with mesh xenoderm grafts with a

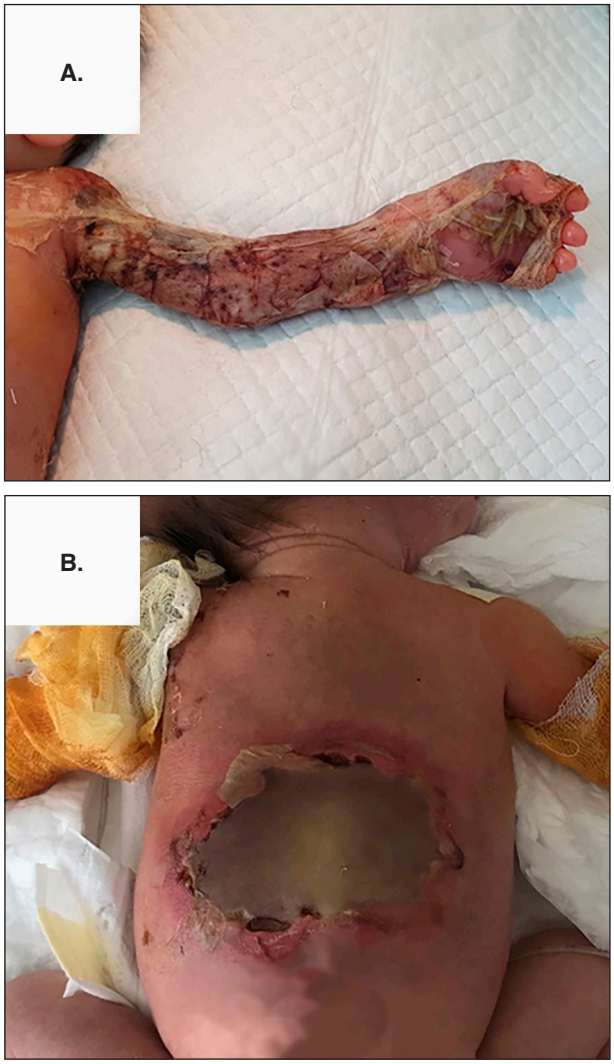

Figure 2. Skin defect of the left upper extremity covered with xenoskin (**A**) and skin defect of the back (**B**) on day 16 of life.

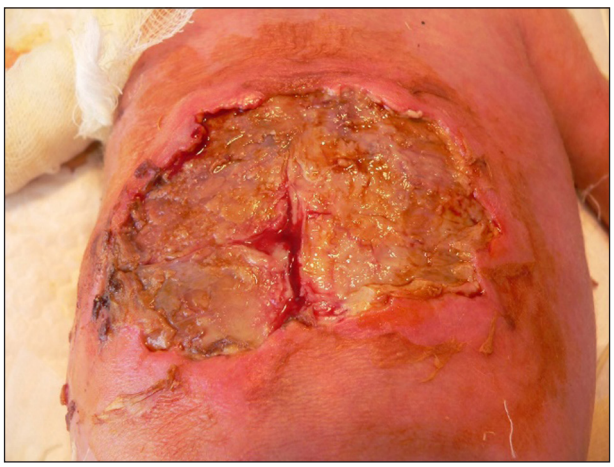

Figure 3. Wound defect of the back after necrectomy.

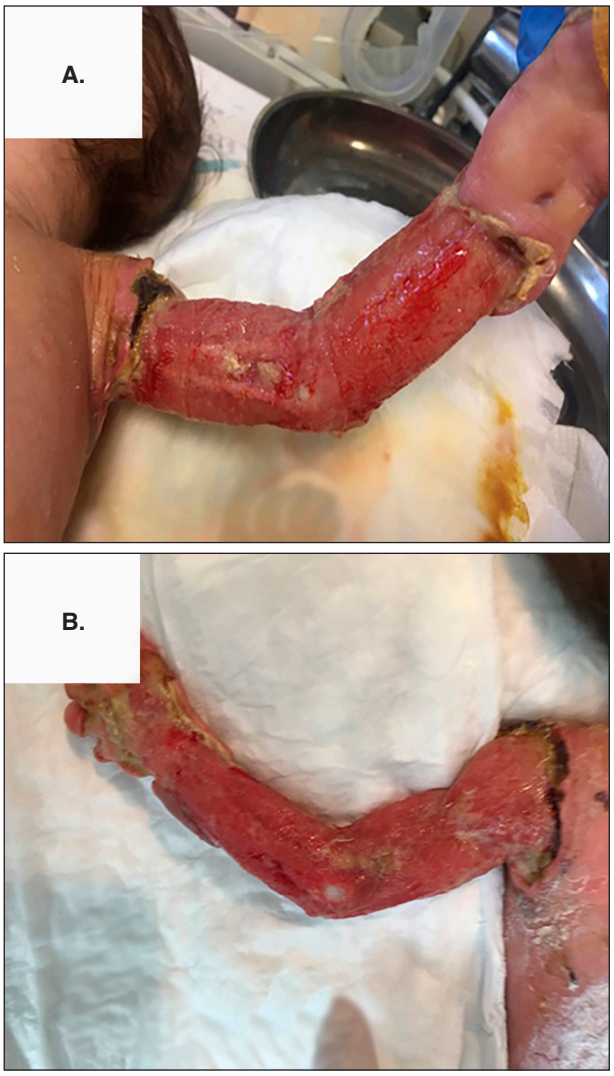

Figure 4. Granulating wounds of the left upper extremity on day 29 of life (**A**, **B**).

perforation ratio of 1:4 and skin micro-autograft of the left upper extremity (**Fig. 5**).

Following this penultimate operation, the patient's condition steadily improved; he continued breathing on his own and signs of toxicity continued decreasing. Enteral nutrition intake improved, and bowel function and urine output were normalized. The laboratory tests also showed a distinct tendency to normalization. Examination of the wound surface revealed clearly marked engraftment of micrografts with rapid marginal epithelialization (**Fig. 6A** and **Fig. 6B**).

On day 47 of life, the patient's condition remained stable but still serious due to underlying disease. Independent breathing at 50 breaths per minute; HR, 144; SAP, 56 mmHg. Physical exam showed no negative change. For residual wound closure, final skin autografting was performed on day 47 of life (**Fig. 7**).

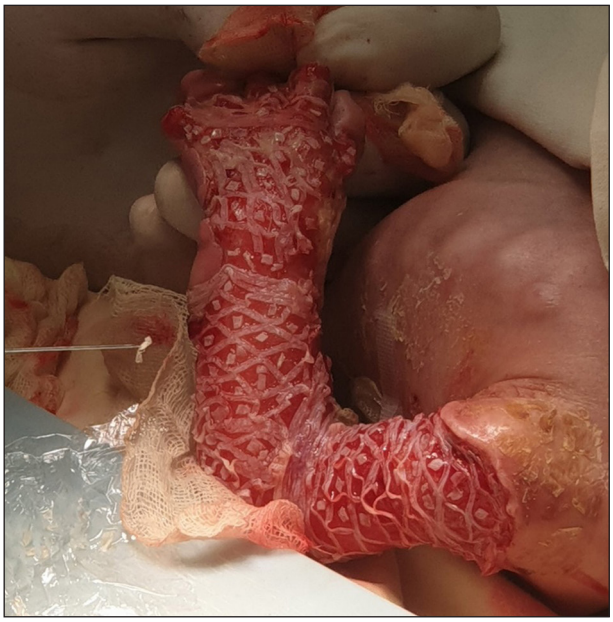

Figure 5. Day 33 of life (hospital day 33): intraoperative view of the wound at the stage of introduction of skin micro-autografts into the mesh cells of lyophilized xenografts.

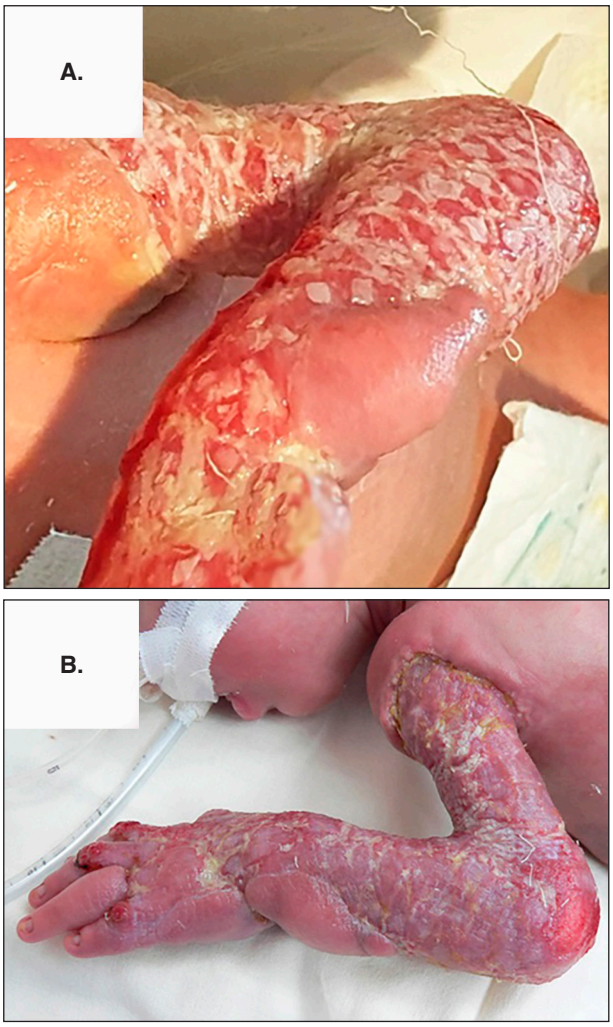

Figure 6. Wound healing on postoperative days 7 (**A**) and 14 (**B**) after skin micro-autografting.

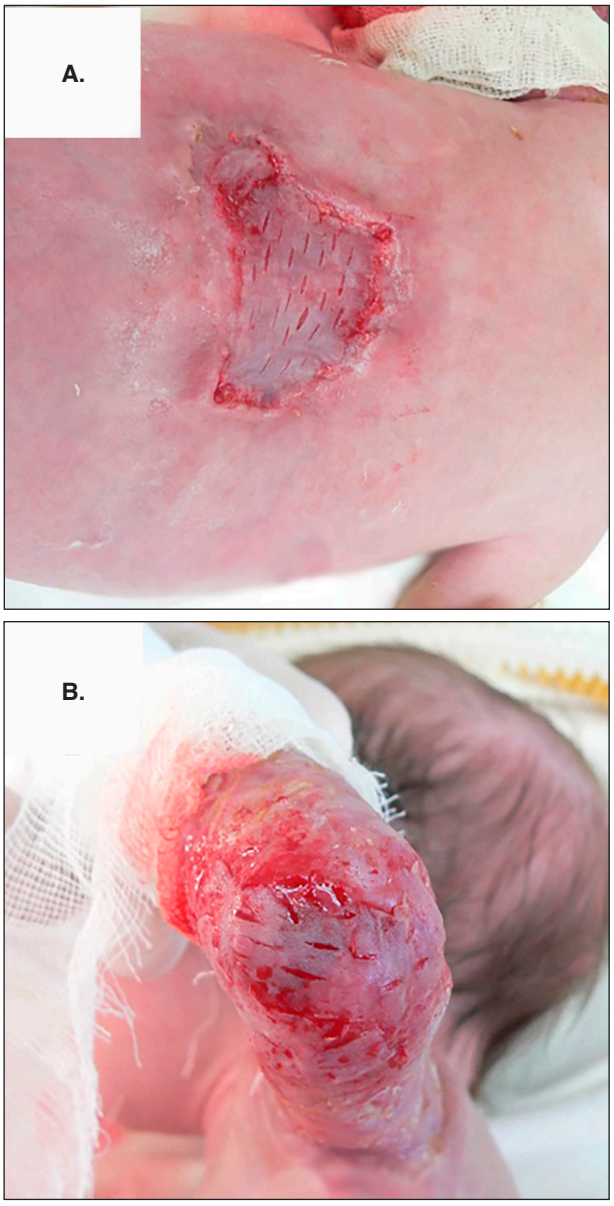

Figure 7. Intraoperative view of the wounds on the back (**A**) and the left elbow (**B**) during the final skin autografting.

The patient showed continued improvement after the final surgery and he began gaining weight; on day 53 of life, the weight was 2,540 g. There was improvement in hemodynamic, clinical, and laboratory parameters (RR, 40 breaths per minute; HR, 144 beats per minute; SAP, 62 mmHg). Granulating wounds of the back and elbow joints were healing under the skin autografts, while donor wounds were healing by islet epithelialization. On day 57 of life, the patient was advanced to mixed feeding.

On day 66 of life, the wounds were considered healed. The patient was discharged with satisfactory performance status for further observation by his family physician (**Fig. 8**).

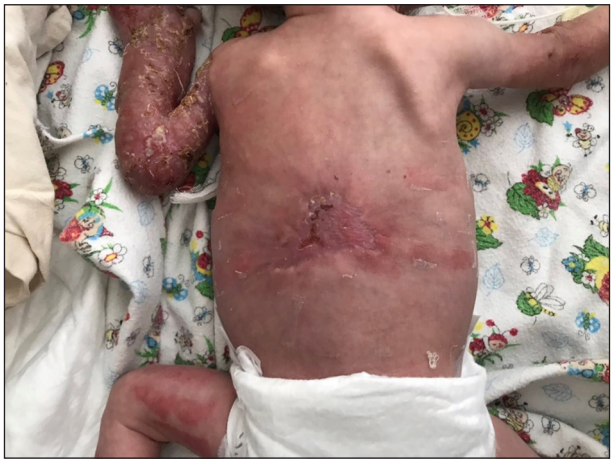

Figure 8. The patient prior to hospital discharge.

Discussion

Great effort has been devoted to the study of problems related to the management of small for gestational age infants all over the world [13, 14]. The research is focused on the causes and risk factors of intrauterine growth retardation leading to delivery of children with extremely low birth weight. Intrauterine infection and fetal distress are found to be the major risk factors [15]. In the case presented here, we determined that intrauterine infection contributed to the development of DIC in the infant and was responsible for inadequate blood supply, followed by aggravation of MODS and deterioration of the patient's general condition. Such a sequence of events corresponds to current principles of understanding this pathogenetic chain [16]. DIC is a serious acquired clinical condition that can arise as a complication of a variety of underlying pathologies, most commonly infection and sepsis, when activation of hemostasis leads to excessive thrombin consumption and development of microvascular obstruction [17]. Early diagnosis of neonatal DIC and immediate proper intervention are of great importance [18]. A multicenter study in Japan has reported that there is a 12-times greater hospital mortality rate among infants with DIC (14.1% versus 1.2%, $p < 0.001$) and that the hospital stay of infants surviving DIC is twice as long as that of those with no such pathology (69.5 days versus 32.6 days, $p < 0.001$) [19].

Neonatal MODS is another serious and life-threatening condition that is thought to arise from inappropriate generalized inflammatory reactions of the newborn to various acute conditions. Histological examination of vascular endothelial changes associated with multiorgan failure has

shown the most severe abnormalities develop in the lower respiratory tract (in particular in pneumonia) and in the gastrointestinal tract (i.e., pancreatic necrosis and necrotizing enterocolitis followed by endotoxemia and release of inflammatory cytokines) [20-22].

Our patient exhibited rapid development of an extended subcutaneous and intermuscular hematoma of the left upper arm and forearm and a hematoma of the right cubital fossa and back, which subsequently led to progressive development of necrosis of the skin and adjacent soft tissues. No direct etiopathogenetic causes for the development of such changes have been established, and no relevant reports have been found in the available medical literature. Generally, skin necrosis with deep soft tissue damage is known to be quite rare in newborns. In previously reported cases, disseminated deep necrosis of the skin with involvement of adjacent tissues was accompanied by thrombosis of the brachial artery, brain damage due to occlusion of cerebral arteries, and embolism of the inferior vena cava, umbilical, and portal veins, or others [23]. Our patient had no sign of any thromboembolic event. Other factors in necrosis development, having more complicated pathogenetic mechanisms, have also been mentioned in the literature, including homozygous protein C deficiency, consequences of neonatal purpura fulminans, etc. [24]. However, in our case, these entities did not appear contributory as causes or mechanisms of extended deep tissue damage in the small for gestational age infant.

Despite the incomplete understanding of all components of the pathological process that occurred in our patient, the range of chosen diagnostic and therapeutic measures corresponded to the principles of a pathogenetic approach to treatment. This implied not only the choice of drugs for complex intravenous therapy, but also the surgical methods, including the removal of devitalized tissues that are a powerful source of toxic breakdown products and pathogenic microorganisms capable of activating inflammatory mediators that disrupt the functioning of all components of the immune system, with resultant MODS, followed by rapid restoration of skin integrity [25]. Another problem turned out to be limited possibilities in obtaining skin autografts due to the critical condition of the patient and the apparent deficiency of potential donor surfaces. It is in such cases that biotechnological human skin equivalents would be a proper option. Their active development began in the twentieth century and is underway now [26, 27]. In this respect, the use of mesenchymal stem cells as pluripotent cells with unique biological properties should be considered [28]. However, because of demanding technical requirements, high price, time needed for preparation, multi-stage interventions, high risk of complications, debatable outcomes, and a number of legal and ethical challenges, their use in clinical practice is limited [29].

The use of currently available wound coverage materials, of biological origin in particular, has not become a complete solution to this problem as they frequently have only a temporary protective effect, especially in deep injuries [30-33].

Therefore, future research should be focused on the development of clinically and economically efficient methods of skin autografting which would meet the basic requirements of transplantation: availability, immune compatibility, relative stability, and obvious effectiveness [34].

This is precisely why we have developed a specific technique for restoration of skin integrity in extensive deep defects and implemented the following personalized therapy design. First, wound closure with lyophilized xenoderm grafts after debridement is a key element in preparation for skin micro-autografting, which in its turn involves covering the granulating wound surface with perforated lyophilized xenoderm grafts. Next, the introduction of skin micro-autografts into the meshes of lyophilized xenoderm grafts is followed by coverage with a gauze bandage and polyvinyl chloride film to ensure a wet chamber effect. Low-intensity biogalvanic currents without external power sources are applied to stimulate microcirculation, and the wound surface is irrigated with antiseptic solutions and epidermal growth factor (EGF). The use of EGF as a drug with a specific wound-healing effect activates reparative processes by stimulating relevant cellular elements [35].

Conclusion

The case presented here describes a rare event, and the true causes of such a condition, as well as its course, are still not well understood. Although this patient is expected to have a long period of rehabilitation with a high probability of repeated reconstructive surgeries in the future, the authors are pleased by the results so far. Despite the life-threatening illnesses and prolonged

critical condition of the infant, and the numerous surgeries and procedures he underwent, he was discharged home in satisfactory condition. Such treatment success becomes possible because of comprehensive care strategies developed by multidisciplinary case management teams, timely appropriate interventions, and the choice of improved skin micro-autografting techniques.

It is realized that the proposed principles of surgical treatment are far from perfect, requiring further improvement and much more experience-based knowledge, but in this clinical case such timely intervention proved to be rather effective and life-saving. We hope the information presented and the experience of the authors will be of practical help to other surgeons who are treating neonates with similar pathology.

Informed consent

Written informed consent has been obtained from the patient's mother for the publication of this case report.

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Declaration of interest

No potential conflict of interest relevant to this article was reported.

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