Dehydrated human amnion/chorion membrane for the treatment of severe skin and tissue loss in an preterm infant: a case report

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Extreme prematurity complicated with severe congenital cutaneous candidiasis (CCC) is rare and clinically challenging. We present the case of a 615g dizygotic twin delivered at 24 weeks gestation with congenital candidiasis, who developed severe skin and tissue loss, successfully treated with dehydrated human amnion/chorion membrane (dHACM). The infant had a complicated medical course, including treatment for patent ductus arteriosus (PDA), necrotising enterocolitis (NEC), and neonatal abstinence syndrome (NAS). In the operating room after debridement, dHACM was placed over all abdominal and back areas of skin loss and covered with a non-occlusive, non-adherent silver dressing. This dressing regimen was chosen in an effort to provide not only topical antimicrobial coverage, but also to maintain a non-shear, moist wound healing environment, which was so important in the dry incubator environment of the neonatal intensive care centre. Over the next four weeks, the baby was medically managed, and the wounds healed on their own with only weekly bedside dressing changes. This case report provides the first example of successful complex management of extensive life-threatening wounds in a premature infant using dHACM.

advanced wound therapy; amnion; congenital cutaneous candidiasis; prematurity

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termin birth and low birth weight are among the most frequent causes of infant and neonatal death in the US. Complications of prematurity and complexity of medical management of these fragile newborns are often inversely related to gestational age at delivery and birth weight. Cutaneous congenital candidiasis (CCC) is a very rare disease, with less than 100 cases published in the medical literature. This life-threatening infection is thought to result from an ascending intrauterine Candida chorioamnionitis and manifests in the first hours to days post delivery. Tragically, the majority of neonates who present with systemic CCC succumb to the disease.

Amniotic membrane has been used as a skin-graft substitute and as a covering for various wound types for over a century, with the rationale that these allografts provide both a scaffold for cell migration and extracellular matrix deposition, as well as exogenous growth factors and cytokines that are important for wound healing. Key functions of the amniotic membrane are related to its immunologically privileged state, its reservoir of multiple growth factors involved with tissue growth and regeneration, and its anti-inflammatory properties. Such properties allow significant therapeutic opportunities to employ amniotic membrane for wound healing, tissue repair, and regenerative therapy. Native human amnion/chorion membrane contains growth factors, such as epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), keratinocyte growth factor (KGF), vascular endothelial growth factor (VEGF), transforming growth factors (TGFs), nerve growth factor (NGF), and many chemokines known to be important for the healing of both acute and chronic wounds. However, the use of natural amniotic membrane in clinical practice is precluded with issues relative to obtaining, preparing, and storing the material, as well as concern regarding the potential for infectious disease transmission. Recently a commercially available dehydrated human amnion/chorion membrane (dHACM) allograft (Epifix; MijMedx Group, Inc.; Marietta, GA) has become available which is sterilised, easily shipped and stored, and available in multiple sizes. This case report details the use of dHACM in the treatment of extensive life-threatening wounds related to CCC in a premature infant.

Case report
A male dizygotic twin was delivered at an estimated gestational age (EGA) of 24 weeks, with a birth weight of 615g, to an otherwise healthy 32-year-old gravida 2, para 0 women. Conceived via in vitro fer-
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Fig 1. Wound seven weeks post delivery. Deep partial thickness to full thickness with a granular appearance.

Fig 2. Frontal wounds upon admission to UCSD. Tight band-like strictures were noted at the regions just caudal to the large open wounds both ventrally and dorsally and extended onto the hips, thighs and perineum.

Fig 3. Close-up image of frontal wound.

Utilisation, the pregnancy was complicated by premature rupture of membranes (PROM) at 80 hours and maternal vaginal candidiasis. The infant, twin B, was born by cesarean section after vaginal delivery of twin A, with Apgars of two and nine, at one and five minutes post delivery, respectively. Emergency intubation was required in the delivery room and the infant was transported to the neonatal intensive care unit (NICU).

The baby was treated with surfactant and mechanical ventilation and diagnosed with respiratory distress syndrome (RDS). The clinical course was further complicated by CCC sepsis, with both cutaneous and renal involvement. Initial treatment of CCC consisted of broad-spectrum antibiotics and antifungals, despite which the infant developed progressively enlarging cutaneous wounds on both the lower abdomen and back. Evaluation for continued and worsening hypotension identified a patent ductus arteriosus (PDA). After consultation with the surgical team, at seven weeks of age the infant was transferred to our facility (University of California at San Diego Medical Center, UCSD), which maintains a NICU as well as a regional burn centre.

Initial wound assessment

On presentation to our institution, the infant's wounds were calculated to manifest approximately 10.5% total body surface area (TBSA) to the back and 1.5% TBSA to the lower abdomen. They appeared to be deep partial thickness to full thickness in depth with a granular appearance (Fig 1). Distinct tight band-like strictures were noted at the regions just caudal to the large open wounds both ventrally and dorsally and extended onto the hips, thighs and perineum (Fig 2 and 3).

Additional medical issues

In addition to his wounds, the infant was noted to have significant osteopenia. Cardiac ultrasound confirmed PDA, with an enlarged left ventricle, and PDA ligation was performed. This was noted to be a particularly challenging case due to internal anatomy and severe tissue oedema. Neonatal cranial ultrasound demonstrated extra axial oedema, but was an otherwise normal examination.

Initial wound management

The neonatal intensivists and cardiac surgery team asked that any formal wound debridement be delayed to allow prompt PDA closure, minimise any bacterial shower and allow the baby to recover and become haemodynamic stability. Local topical antimicrobial dressings were maintained and, two days after cardiac surgery, superficial debridement was performed at the bedside, with biopsy and culture. The wounds were then provisionally covered with allograft, sutured in place with fine sutures and covered by a non-con-
Fig 4. Temporary allograft, sutured in place with fine sutures and covered by a non-constricting, non-adherent silver dressing.

stricting, non-adherent silver dressing (Restore; Hollister Wound Care; Libertyville, IL; Fig 4).

Consideration of possible abdominal compartment syndrome, loss of domain, respiratory compromise and requisite decompression were strongly considered; however rapid pulmonary, renal and haemodynamic parameters made such intervention thankfully unnecessary. Histologic review revealed a granulation tissue pattern with dystrophic calcifications to the wound bed without evidence of malignancy. Periodic Acid-Schiff (PAS) and Gram and Grocott's Methenamine Silver (GMS) stains were normal.

Treatment with dHACM

Ten days after the initial debridement and allograft placement, the infant underwent a second procedure to replace the initial allograft with dHACM. After removal of the allograft, the wounds were gently cleansed with a soft surgical scrub brush (Fig 5) and dHACM was placed directly on the wound surface (Fig 6).

The dHACM was covered by Restore and gently wrapped in a light non-constricting gauze dressing, all secured in position with Steri-Strips (3M) in an effort to minimise peripheral tissue injury and pain, while facilitating subsequent dressing changes. Approximately every five days, the outer dressings were changed and the wound site carefully cleansed with a dilute and soft Hibiclens (Molnlycke) scrub brush. Of particular note was the rapid decrease in cutaneous oedema surrounding the wounds. The tight constriction bands attenuated and softened in the days to weeks following dHACM placement.

Over the next four weeks, the baby was medically managed, and the wounds healed on their own with only weekly dressing changes. Ten days after the first dHACM application the wounds were estima-
presented with tight band formations. Vigilant occupational and physical therapy appeared to help significantly as there were little to no residual functional joint contractures.

**Ongoing medical management**

The baby’s hospitalisation course was notable for medical treatment of necrotising enterocolitis (NEC), which resolved without significant complication. Stage three plus retinopathy of prematurity required retinal laser surgery to be performed. The significant osteopenia resulted in an incomplete distal radius fracture, which healed with conservative management.

Initial concerns of immunosuppression, possible severe combined immunodeficiency (SCID), identified as low B and T-cell counts with high natural killer (NK) cell counts. As his condition improved, CD8 T-cell count continued to lag while CD4 and NK cell counts normalised. Fig 2 and 3 show back and front wounds 11 months after initial treatment with dHACM.

Now at more than one year of age, he continues to thrive, grow, be active and playful. He has since undergone uneventful bilateral inguinal hernia repairs. We anticipate that in the near future the child will require a release at the lower abdominal/pubic site region which is a much simpler problem to address now.

**Discussion**

The successful management of this incredibly ill premature neonate required the comprehensive and generally well-coordinated efforts of a very large team of specialists, staff, therapists and a very involved and understanding family. To our knowledge, this is the first report of treating extensive life-threatening wounds related to CCC in a premature infant using dHACM.

Of particular challenge in this case was optimising and protecting the wound bed, promoting satisfactory and timely closure while minimising risk to the child. In the past, we would likely have treated the wound with TransCyte (Advanced Tissue Sciences, La Jolla), neonatal fibroblasts and biobrane, but unfortunately this is no longer commercially available. Allograft proved a very reasonable choice for initial wound coverage option, minimising heat and fluid losses and protecting the wound site; however we had concerns with promotion of granulation tissue which might have impeded re-epithelialisation. Cultured epithelial autograft (CEA) was similarly considered, however this would have required an excisional biopsy and approximately four weeks to engineer, incurring incredible expense and delay. The application and care of CEA is well established in major burn centers and, while potentially life-saving, requires significant care and handling. Severe scar formation and contracture further compromise its application in cases such as these. Autologous and cultured cell sprays share similar concerns. Given the morbidity, mortality and complexity associated with significant autografting in premature infants, this therapeutic option cannot be entertained lightly. In this case, the use of a commercially available off-the-shelf product proved...
a valuable adjunct in the management of a very complex problem.

Human placental tissue contains a multitude of growth factors and cytokines that are essential for wound healing. Widespread use of placental tissue for allografts has been limited by many factors, including the ability to preserve biological activity during processing. Recently, a method called the PURION Process (MiMedx, Marietta, GA) was developed that gently cleans, sterilises and dehydrates placental tissue obtained from screened and tested donors. Biochemical analysis of dHACM via enzyme-linked immunosorbent assay (ELISA) has isolated key growth factors and cytokines, tissue-bound and soluble (Table 1). Clinical trials have supported these biochemical findings by demonstrating that dHACM is efficacious for the healing of chronic diabetic foot ulcers. The case presented above has illustrated that dHACM can achieve timely healing in other wound types and in complex situations. Further experience will likely show promise in treating a wide variety of challenging wound healing presentations.

**Conclusions**

The case presented here highlights a successful outcome where a thorough and comprehensive multidisciplinary approach optimised the care of this critically ill child.

**References**
