Cryopreserved amniotic membrane and umbilical cord for a radiation-induced wound with exposed dura: a case report

Abstract: An 87-year old male received surgical excision of scalp melanoma and subsequent radiotherapy due to metastasis to the skull. A radiation-induced wound developed with osteoradionecrosis that required necrotic bone excision resulting in a 7.5x8.5cm wound over the exposed dura, which remained non-healing despite many attempts by local wound care management. Due to the refractory nature of the wound, strips of cryopreserved umbilical cord (cUC) allograft were applied over the exposed dura resulting in significant vascular granulation tissue formation in the central wound bed within four weeks. Re-epithelialisation around the wound perimeter was further promoted by injection of particulate amniotic membrane umbilical cord matrix (AMUC) at the 16th week, and completed by another application of cUC strips and injection of AMUC proximal to the necrotic bone at the 21st week. Vascularisation of the necrotic bone was further promoted by application of cUC and AMUC injection directly into the bony margins at 29 weeks and 34 weeks, respectively, followed by application with an AMUC-hydrogel paste, applied four times over an eight week interval. By 96 weeks, healthy re-epithelialised tissue had formed under the necrotic bony margins. This report highlights the unique regenerative capabilities of cUC and AMUC in promoting wound healing over exposed dura in a long-standing full-thickness, radiation-induced scalp and skull wound.
Declaration of interest: The author has no conflicts of interest to declare.

amniotic membrane • dura • osteoradionecrosis • radiation-induced skin injury • radiation therapy • reconstruction • regenerative therapy • scalp • skull • umbilical cord

It remains a challenging problem for surgeons to manage scalp and skull wounds that often arise from radiotherapy, osteoradionecrosis, trauma, chronic infection or oncological resections.[1–4] These range in complexity, from superficial skin and the outer cortical bone involvement, to full-thickness scalp and skull wounds with exposed dura.[2,4,5] Full-thickness wounds usually have impaired healing as a result of avascular and aseptic necrosis from the inflammation of damaged local vessels.[6] In addition, these wounds are often complicated by the presence of infection, soft tissue abscess, and prior/subsequent radiation.[4,7,8]

Successful reconstruction of these wounds requires consideration of the patient's age, the size and depth of the wound, and the surrounding tissue quality, especially the vascular supply. Primary closure can typically be achieved for small wounds (<10cm^2) but not larger ones due to the relative inelasticity of the galea and excessive tension that may lead to ischaemia, wound dehiscence and scarring.[9,10] Medium-sized (10–50cm^2) wounds are often reconstructed with local or regional flaps and those 50cm^2 are treated using free tissue transfer.[8,11,12] This requires the expertise of a multidisciplinary team (MDT) and brings risks, such as microanastomosis, long operative times, donor site morbidity, possibility of flap failure and the need for two operation fields.[11–13] Furthermore, the success of free grafts is limited by ischaemia of the surrounding irradiated tissue.[14]

Due to these limitations, other alternative solutions are needed to accelerate healing through modulation of inflammation and promotion of vascular granulation tissue. Cryopreserved umbilical cord (cUC) has previously been used as a treatment modality for similar cases, including chronic complex wounds with bone exposure, and demonstrated to promote complete re-epithelialisation through both anti-scarring and anti-inflammatory actions.[15,16] In addition, cUC has been used as a patch graft for the repair of full-thickness spina bifida wounds and has been shown to completely seal the lesion, prevent cerebral spinal fluid leakage and preserve the spinal cord tissue.[17,18] These advantageous properties and available clinical data makes cUC an attractive alternative for full-thickness scalp wounds.

This case report describes the use of cUC allograft together with injectable particulate amniotic membrane umbilical cord matrix (AMUC) to promote robust vascular granulation tissue, complete re-epithelialisation, and revascularisation of necrotic bone in a large, full-thickness, radiation-induced wound with dura exposure.

Ethics statement

Local Institutional Review Board (IRB) approval was obtained from Florida Hospital Orlando. The individual described in this manuscript has given written informed consent to publish these case details and pictures.

***David Fernandez**,[1] MD
***Corresponding author email:** dffmdfacp@gmail.com
1 Florida Hospital Orlando, Orlando, US.

© 2019 MA Healthcare ltd

Fig 1. Wound healing after first cryopreserved umbilical cord (cUC) graft. Scalp and skull wound before treatment (**a**) and after application of strips of 4x3cm cUC graft (**b**). Progressive vascular granulation tissue emerged from the wound margin at two weeks (**c**) with more vascular granulation tissue in weeks 5–6 (**d**), at nine weeks (**e**), 11 weeks (**f**). White arrows indicate the same area where bone necrosis was located

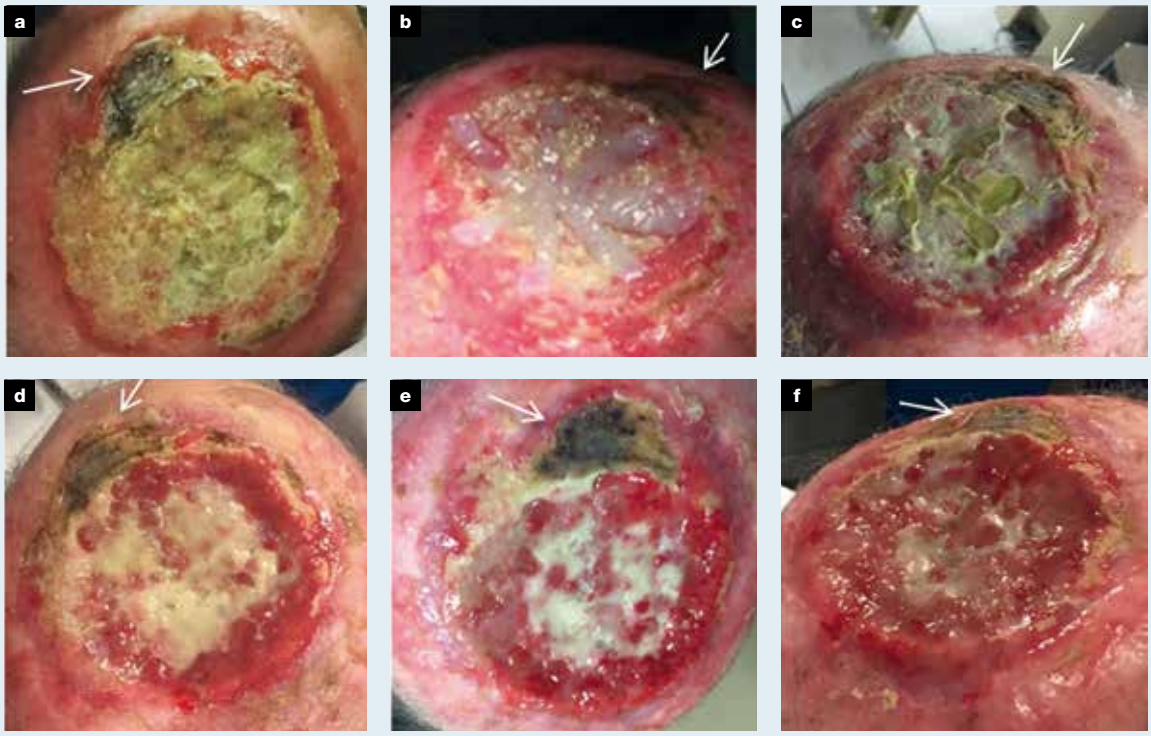
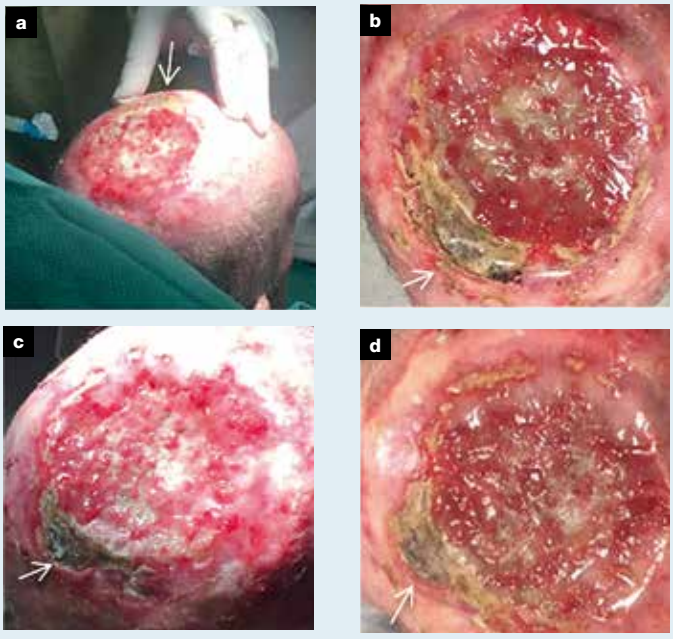


Fig 2. Wound healing after first injection of cryopreserved umbilical cord. At 16 weeks, 100mg of amniotic membrane umbilical cord particulate in 2cc of lidocaine was injected around the wound bed (**a**), resulting in more rpithelialisation from the wound periphery at 17 weeks (**b**), 18 weeks (**c**) and 21 weeks (**d**). White arrows indicate the same area where bone necrosis was located



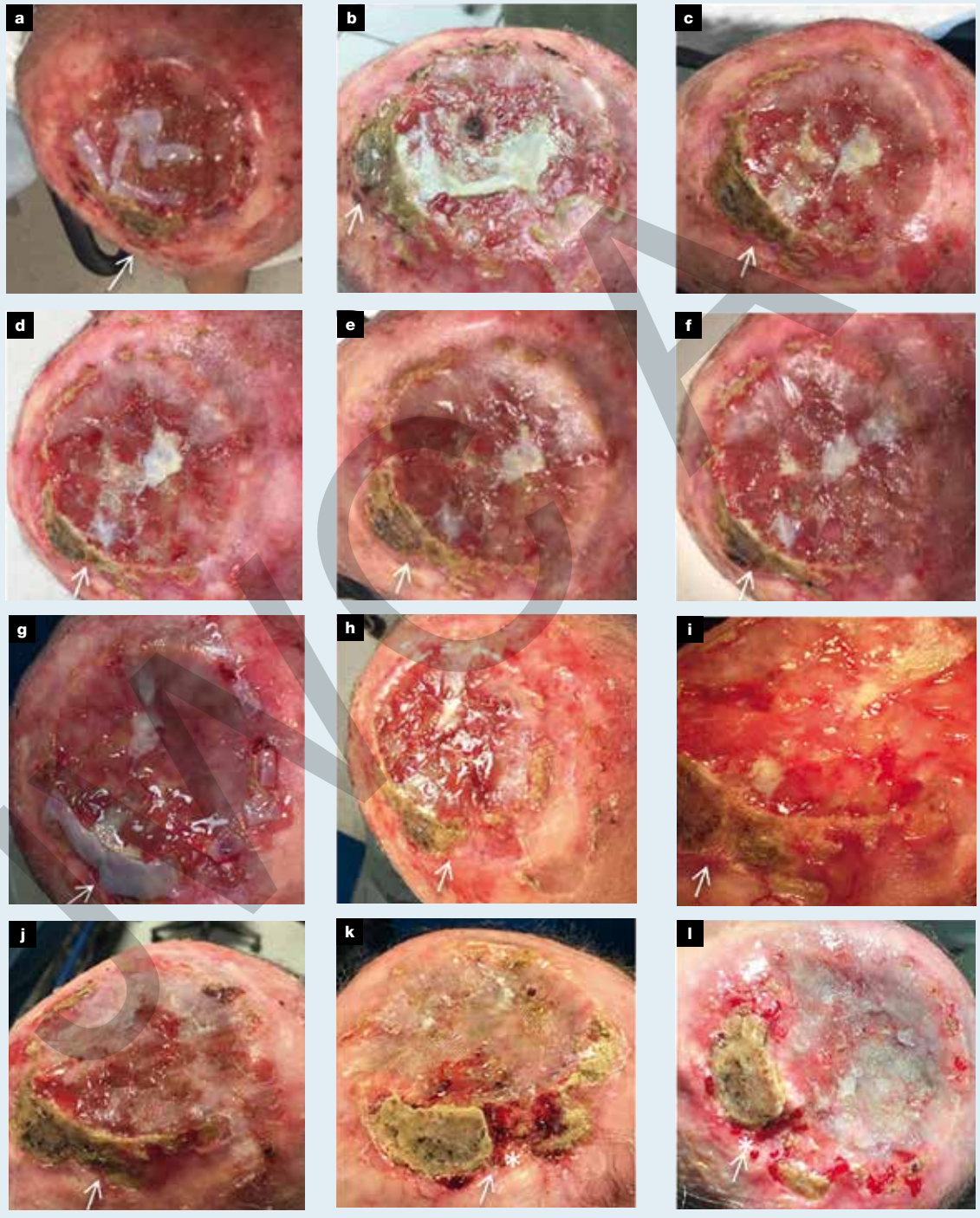
Case

An 87-year-old male with a history of renal transplantation due to polycystic kidney disease had developed skin melanoma on his scalp. The tumour was surgically excised followed by primary closure, however the melanoma recurred five years later and metastasised to the skull. Due to the vicinity to the underlying brain, the patient received radiation therapy with a total dosage of 60Gy in 30 fractions in 2011. In mid-2015, a dermal wound with underlying osteoradionecrosis had formed. The severely necrotic skull bone was excised resulting in a full-thickness wound (7.5x8.5cm) with exposed underlying dura and adjacent skull bone necrosis. The wound remained non-healing despite the use of many topical wound therapies. In addition, the patient received local carboplatin/poditaxel-based chemoradiation for recurrent squamous cell carcinoma in January 2016.

The full-thickness wound did not heal for over one year (Fig 1a). The patient was referred to the Hyperbaric Medicine and Wound Management Center at Florida Hospital Orlando. A 4x3cm cUC graft (NEOX CORD 1K, TissueTech, Inc., US) was cut into strips, laid across the wound in an asterisk pattern (Fig 1b), and secured in place with a non-adhering dressing. Dressing changes were done every third day under home care. Subsequently, at four weeks, the graft had been absorbed and the wound bed began to show robust granulation tissue (Fig 1c–f). At 16 weeks, 100mg of AMUC particulate (NEOX FLO,

© 2019 MA Healthcare ltd

Fig 3. Wound healing after grafts and injections of cryopreserved umbilical cord (cUC). A second application of cUC graft was applied at 21 weeks to the central wound (a) with a second injection of 100mg of amniotic membrane umbilical cord particulate into the adjacent bony margin, resulting in complete re-epithelialisation and a round skull contour at 22 weeks (**b**), 24 weeks (**c**), 25 weeks (**d**), 26 weeks (**e**), and 29 weeks (**f**). At 29 weeks, strips of a third UC graft were applied as placed over the bone (**g**), resulting in more vascularisation from the bone margin at 30 weeks (**h**) and 32 weeks (**i**). At 34 weeks, a third injection of 100 mg of AMUC particulate was given at the bony margin, resulting in further maturation of the wound surface at 36 weeks (**j**). At 46 weeks, an AMUC hydrogel was applied four times over a period of 8 weeks to the surface of the necrotic bone, resulting in further vascularization and epithelization underneath and around the necrotic bone at 85 weeks (**k**, marked by *) and 94 weeks (**l**, marked by *). White arrows indicate where bone necrosis was located



© 2019 MA Healthcare ltd

TissueTech, Inc., US) in 2cc of lidocaine was injected around the wound bed to induce re-epithelialisation from the wound perimeter (Fig 2a–d). At 21 weeks, strips of a second cUC graft (1x3cm) was applied together with a second injection of 100mg of AMUC particulate into the adjacent bony margin, resulting in more soft tissue formation, complete epithelialisation and a rounded contour of the skull (Fig 3a–f). At 29 weeks, strips of a third cUC graft (3x3cm) was placed over the bone and at 34 weeks a third injection of 100mg of AMUC particulate was applied to the bone margin, resulting in more vascularisation from the bony margin (Fig 3g–l). Then at 46 weeks, a paste made of 100mg of AMUC particulate and hydrogel (SAF-Gel, Convatec, US) was applied four times over a period of eight weeks to the surface of the necrotic bone. The necrotic bone was then routinely non-surgically debrided during wound care visits. Approximately one year post-application, the necrotic bony fragment was removed by the physician revealing vascularised and re-epithelialised tissue that had formed underneath and around the necrotic bone (Fig 3k, l).

Discussion

Due to the inherent complexity of scalp and skull wounds, several risk factors and comorbidities need to be taken into consideration to achieve successful reconstruction. In the present case, a chronic radiation-induced wound presented over the exposed dura despite many attempts by local wound care management. Surgical intervention was avoided due to the patient's age, compromised renal function, and exposure to radiation and chemotherapy that would inhibit the wound healing capabilities and contraindicate the surgical transfer of a free graft. Nonetheless, sequential uses of strips of cUC allograft and injection of particulate AMUC aided the healing process by promoting robust granulation and complete healing of the wound. Furthermore, we also observed healing by revasularisation in and around the irradiated necrotic bone. Hence, this single case report suggests that combination of cUC graft and injection of particulate AMUC may be an alternative way of managing full-thickness wounds with multiple comorbidities, similar to what has been reported in complex diabetic foot ulcers with osteomyelitits and other comorbidities, such as peripheral vascular disease, renal failure, ischaemia and gangrene.[19] The potential mode of action might include the reported anti-inflammatory, anti-scarring, and regenerative properties of AMUC, which collectively promotes vascularisation and new granulation tissue.[20] In particular, cUC and AMUC particulate matrix (as used in this case) retains the structural and biological characteristics of fresh UC and is commercially available. These tissues are donated from full-term human placentas recovered after caesarean-section delivery and are processed/cleaned under aseptic conditions and then stored at –80°C.[21]

Conclusion

In this case report, sequential uses of strips of cUC and injection of particulate AMUC achieved complete healing of a large, chronic, full-thickness defect with dura exposure and progressive vascularisation of necrotic bone. Further investigation to determine how this treatment modality might promote healing of chronic, ischaemic and necrotic wounds in patients with multiple comorbidities or undergoing irradiation and oncological treatments.[22] JWC

References

1 Greenwood JE, Wagstaff MJ, Rooke M, Caplash Y. Reconstruction of extensive calvarial exposure after major burn injury in 2 stages using a biodegradable polyurethane matrix. Eplasty 2016; 16:e17
2 Larrañaga J, Rios A, Franciosi E et al. Free flap reconstruction for complex scalp and forehead defects with associated full-thickness calvarial bone resections. Craniomaxillofac Trauma Reconstr 2012; 05(04):205–212. https://doi.org/10.1055/s-0032-1322534
3 Lin S, Hanasono M, Skoracki R. Scalp and calvarial reconstruction. Semin Plast Surg 2008; 22(04):281–293. https://doi.org/10.1055/s-0028-1095887
4 Beasley NJ, Gilbert RW, Gullane PJ et al. Scalp and forehead reconstruction using free revascularized tissue transfer. Arch Facial Plast Surg 2004; 6(1):16–20. https://doi.org/10.1001/archfaci.6.1.16
5 Paul K, Sharma S, Paul D. Bipedicle flap for reconstruction of post-electric scalp burn defect. Int Surg J 2017; 4(5):1783–1785. https://doi.org/10.18203/2349-2902.isj20171588
6 Ahmed S, Gupta N, Hamilton JD et al. CT findings in temporal bone osteoradionecrosis. J Comput Assist Tomogr 2014; 38(5):662–666. https://doi.org/10.1097/RCT.0000000000000096
7 Kaigler D, Wang Z, Horger K et al. VEGF scaffolds enhance angiogenesis and bone regeneration in irradiated osseous defects. J Bone Miner Res 2006; 21(5):735–744. https://doi.org/10.1359/jbmr.060120
8 O'Connell D, Teng M, Mendez E, Futran N. Microvascular free tissue transfer in the reconstruction of scalp and lateral temporal bone defects. Craniomaxillofac Trauma Reconstr 2011; 4(04):179–188. https://doi.org/10.1055/s-0031-1286119
9 Temple CL, Ross DC. Scalp and forehead reconstruction. Clin Plast Surg 2005; 32(3):377–390. https://doi.org/10.1016/j.cps.2005.02.002
10 Raposio E, Santi P, Nordström RE. Effects of galeotomies on scalp flaps. Ann Plast Surg 1998; 41(1):17–21. https://doi.org/10.1097/00000637-199807000-00004
11 Laedrach K, Lukes A, Raveh J. Reconstruction of skull base and fronto-orbital defects following tumor resection. Skull Base 2007; 17(1):059–072. https://doi.org/10.1055/s-2006-959336
12 Kwon SG, Kim YO, Rah DK. Anterior cranial base reconstruction with a reverse temporalis muscle flap and calvarial bone graft. Arch Plast Surg 2012; 39(4):345–351. https://doi.org/10.5999/aps.2012.39.4.345
13 Frederick JW, Sweeny L, Carroll WR et al. Outcomes in head and neck reconstruction by surgical site and donor site. Laryngoscope 2013; 123(7):1612–1617. https://doi.org/10.1002/lary.23775
14 Shonka DC Jr, Potash AE, Jameson MJ, Funk GF. Successful reconstruction of scalp and skull defects: Lessons learned from a large series. Laryngoscope 2011; 121(11):2305–2312. https://doi.org/10.1002/lary.22191
15 Tseng SC, He H, Zhang S, Chen SY. Niche regulation of limbal epithelial stem cells: relationship between inflammation and regeneration. Ocul Surf 2016; 14(2):100–112. https://doi.org/10.1016/j.jtos.2015.12.002
16 Couture M. A single-center, retrospective study of cryopreserved umbilical cord for wound healing in patients suffering from chronic wounds of the foot and ankle. Wounds 2016; 28(7):217–225
17 Papanna R, Moise KJ Jr, Mann LK et al. Cryopreserved human umbilical cord patch for in-utero spina bifida repair. Ultrasound Obstet Gynecol 2016; 47(2):168–176. https://doi.org/10.1002/uog.15790
18 Papanna R, Mann L, Snowise S et al. Neurological outcomes after human umbilical cord patch for in utero spina bifida repair in a sheep model. AJP Rep 2016; 06(03):e309–e317. https://doi.org/10.1055/s-0036-1592316
19 Caputo WJ, Vaquero C, Monterosa A et al. A retrospective study of cryopreserved umbilical cord as an adjunctive therapy to promote the healing of chronic, complex foot ulcers with underlying osteomyelitis. Wound Repair Regen 2016; 24(5):885–893. https://doi.org/10.1111/wrr.12456
20 Tseng SC. HC-HA/PTX3 purified from amniotic membrane as novel regenerative matrix: insight into relationship between inflammation and regeneration. Invest Ophthalmol Vis Sci 2016; 57(5):ORSFh1. https://doi.org/10.1167/iovs.15-17637
21 Cooke M, Tan EK, Mandrycky C et al. Comparison of cryopreserved amniotic membrane and umbilical cord tissue with dehydrated amniotic membrane/chorion tissue. J Wound Care 2014; 23(10):465–476. https://doi.org/10.12968/jowc.2014.23.10.465
22 Costa D, Walen S, Varvares M, Walker R. Scalp rotation flap for reconstruction of complex soft tissue defects. J Neurol Surg B Skull Base 2015; 77(01):032–037. https://doi.org/10.1055/s-0035-1556874

© 2019 MA Healthcare ltd