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Heterotopic Ossification

Heterotopic ossification (HO) is defined as aberrant bone formation in non-osseous tissue. It is a common complication of injuries sustained in military conflicts. Recent studies on combat related extremity trauma show nearly 70% of patients develop heterotopic ossification. The ectopic bone formation can result in significant morbidity including residual limb pain, soft tissue complications, difficulty with prosthetic wear and decreased joint ROM.

Heterotopic ossification following trauma commonly forms in muscle. However, multiple reports describe heterotopic ossification occurring in peripheral nerves known as neuritis ossificans. However in all case reports there was no clear history of trauma in the formation of neuritis ossificans. We present two cases where ectopic bone was encountered in nerve tissue at the time of reconstruction following traumatic laceration of peripheral nerves.

Case Report

Two patients with high energy penetrating injuries to their lower extremity and resultant sciatic nerve transection are presented.

Patient 1 is a 26 y/o male who sustained a gunshot wound to his left hip with resultant femoral neck fracture. Initial exam was notable for 0/5 knee flexion, 0/5 ankle dorsiflexion, 0/5 ankle plantar flexion, and absent sensation of dorsal and plantar aspects of the left foot. The femoral neck fracture was provisionally pinned on post injury day 1 and underwent definitive fixation at several days later Landstuhl Regional Medical Center. During ORIF a 3cm sciatic nerve gap was visualized. At Walter Reed National Military Medical Center the patient underwent sciatic nerve reconstruction 21 days from injury. During exposure of the sciatic nerve fibrotic tissue was encountered surrounding the nerve. The residual neuromas encountered were debrided and calcification was found within the nerve sheath. These calcified lesions were obtained for further study. The sciatic nerve defect was found to be 6 cm once debrided to healthy tissue. Multiple cadaveric allografts were used to reconstruct the nerve in end to end fashion. Intraoperative nerve stimulation confirmed adequate conduction. The patient was discharged to a rehabilitation facility 1 week post-operatively.

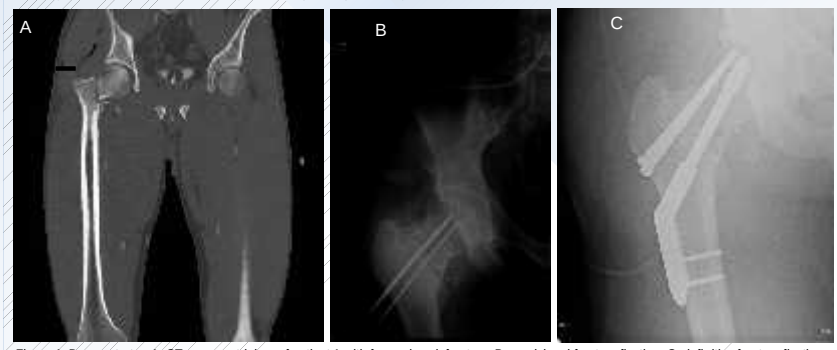

Figure 1: Demonstrates A: CT scan post-injury of patient 1 with femoral neck fracture, B: provisional fracture fixation, C: definitive fracture fixation.

Patient 2 is a 40 y/o male who sustained gunshot wounds to his left thigh and left eye in addition to multiple fragmentation injuries to the left buttock. Initial exam was notable for 0/5 knee flexion, 0/5 ankle dorsiflexion, 0/5 ankle plantar flexion, and absent sensation of dorsal and plantar aspects of the left foot. The patient underwent debridement of gunshot wounds following his injury and sciatic nerve transection was encountered. The patient underwent sciatic nerve reconstruction at Walter Reed National Military Medical Center on 29 days after injury. The tissue surrounding the nerve was fibrotic and the residual neuromas were found to have fibrotic tissue and calcification within the nerve sheath. Tissue samples of these calcified lesions were obtained for further study. The sciatic nerve defect was found to be 6 cm once debrided to healthy nerve tissue. Again multiple decellularized cadaveric allografts were used to reconstruct the nerve in end to end fashion. The patient was discharged to a rehabilitation facility following a short post-operative stay.

Figure 2: Intraoperative photos A: demonstrating proximal and distal neuromas encountered during dissection, B and C: incision of nerve sheath demonstrating HO in the nerve sheath and in surrounding tissue: D: resection of neuroma healthy nerve prior to grafting: E: end to end grafting wi... multiple cadaveric allografts

Tissue Analysis

Tissue samples from both patients were sectioned and stained with H+E and picosirus red and with immunomarkers for collagen 1, CD44, and other markers associated with heterotopic ossification formation (Substance P and BMP-2). The samples were then observed under brightfield and scanning electron microscopy.

Scanning electron microscopy and H&E staining of the debrided nerve demonstrated calcification within the nerve sheath in close proximity to the nerve fascicle. Sections from the nerve were stained with picosirus red, a well-known collagen 1 specific stain that has become a marker in our lab for early fibrosis that precedes calcification. The stained sections were observed under bright field and polarized light and are represented in figure 3. There is significant positive staining surrounding the nerve fascicle representing early fibrosis, additionally there is positive staining within the nerve fascicle which may demonstrate a fibrotic process within the nerve fascicle.

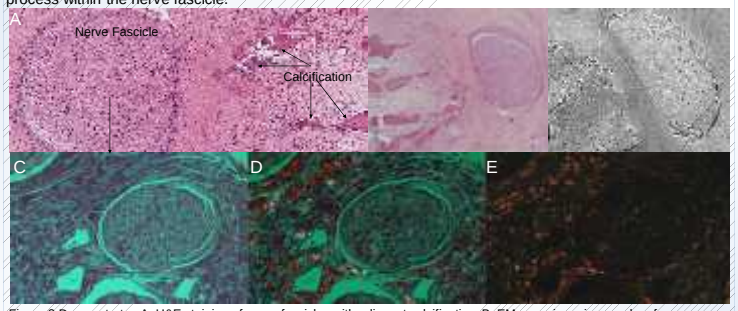

Figure 3 Demonstrates A: H&E staining of nerve fascicles with adjacent calcification, B: EM scanning micrographs of nerve fascicles with adjacent calcification, C-E: picosirus red staining demonstrating fibrosis within nerve fascicles.

Immunofluoresence of the nerve and surrounding tissue demonstrated positive staining for Substance P (SP), a known neuropeptide that may play a role in the development of heterotopic ossification. There was positive staining for BMP 2 within the nerve sheath and surrounding the individual axons. The tissue surrounding the nerve stained positively for CD44, a marker of mesenchymal progenitor cells (MPCs). Prior studies have shown MPCs are recruited to injury sites and have the capacity to undergo osteogenesis.

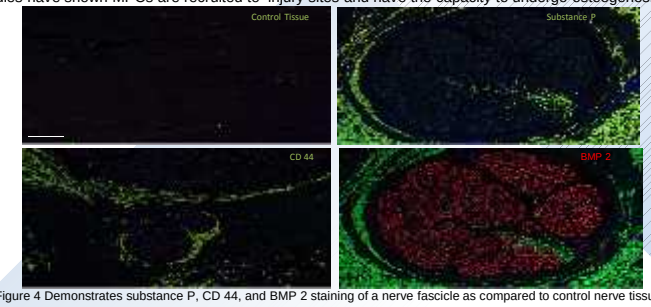

Figure 4 Demonstrates substance P, CD 44, and BMP 2 staining of a nerve fascicle as compared to control nerve tissue.

Discussion

At six month follow-up both patients demonstrated improved pain control with minimal narcotic use. Electromyography demonstrated early recovery of sciatic motor function although sensation of the foot was absent in both patients. Neither patient sustained complications related to the sciatic nerve reconstruction.

Analysis of the injured nerves showed positive staining for SP, BMP 2, and CD44 within the epineurium. Substance P is known to be increased at sites of ossification and has been shown to induce BMP-dependent HO. Bone morphogenic protein 2 is a known bone formation stimulation factor. Lastly, CD44 is a marker associated with mesenchymal progenitor cells that previous studies have shown it may be responsible for HO development. The presence of CD44 , SP, and BMP 2 staining cells within the epineurium highlights the early formation of heterotopic ossification in the nerve with presence of multiple cytokines associated with fibrosis and bone formation being found in the nerve.

Previous studies on neuritis ossificans have not shown a direct connection to trauma. This case report shows that trauma can be an inciting event for neuritis ossificans. It is interesting that neuritis ossificans is not encountered more often following combat related extremity trauma and in fact a more common occurance is to find neural structures encased in HO that are able to be disected from the ectopic bone. This was recently described by Polfer et al. This observation suggests that the nerve sheath may provide a protective function from the development of neuritis ossificans. It is possible that transection of the nerve or damage to the neural sheath is the inciting event that allows formation of HO in the peripheral nerve. Further knowledge of how HO effects peripheral nerves can aid surgeons in planning for complex HO resection and nerve reconstruction.

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