Clinical And Histological Predictors Of Heterotopic Ossification In Warfighters From OIF And OEF

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Introduction: Over 2200 major limb amputations have occurred as a result of Operations Iraqi Freedom (OIF) and Operation Enduring Freedom (OIF). Approximately 63-65% of these service members developed HO in the musculature and peri-articular regions, with 20-40% requiring surgical excision of their ectopic bone. Although surgical resection of HO has been well described in the orthopaedic literature, these reports often lack sound medical evidence and histological corroboration. While results from early resection have been promising, premature removal may result in ectopic bone regrowth, which may require additional surgery and lead to a delay in successful rehabilitation. This study sought to determine if histological measures could predict HO growth/development in order to best determine the optimal timing of surgery in order to reduce the likeliness of recurrence.

Methods: Service members at WRNMCC requiring surgery for removal of symptomatic HO were enrolled in this study. Prior to HO removal, patients were treated per the standard of care and HO maturation was determined based on alkaline phosphatase (AP) levels, nuclear scintigraphy, orthogonal radiographs and consideration for traumatic brain injury (TBI). Participants were given oxytetracycline (250mg /tid) on 4 separate dates before their scheduled surgery for fluorochrome double labeling. Following resection, HO samples were analyzed using scanning electron microscopy (SEM) and light microscopy/bone stains to calculate the mineral apposition rate (MAR) (Figure 1). The percent of osteoblastic (%OBA), osteoclastic (%OCA) and resting bone (%RB) were evaluated. Quantitative data was analyzed using Pearson’s correlation coefficients using Minitab 15 statistical software.

Results: Twenty-eight service members who required removal of symptomatic HO following combat related trauma are reported. Twenty-seven of the subjects were male and improvised explosive devices (IEDs) were the primary injury mechanism (21/28 incidences). Subjects were 26.3 +/- 5.6 years of age at the time of injury and ectopic bone resection occurred on average 12.2 +/- 8.0 months from the date of their injury. Pre-operative X-rays were scored as 13 cases of mild HO, 7 moderate and 8 severe (examined by an orthopaedic surgeon blinded to patient information). Pre-operative alkaline phosphatase levels (AP) levels were 112.6 +/- 49.1 ui/L. TBI occurred in 64% of the subjects (16 mild, 1 moderate, and 1 severe per DoD ratings).

Histological data indicated that MAR levels were approximately 1.6 times higher than non-pathological human bone (1.62 +/- 0.23 μm/day, range: 1.11-2.51 μm/day). SEM images showed HO bone as a highly vascular network in varying stages of remodeling and the %OBA, %OCA and %RB were 28.9 +/- 13.7%,
8.8+/- 5.8% and 62.4 +/- 18.5% respectively; therefore demonstrating that the resected HO masses were actively modeling and remodeling at the time of surgical intervention (Figure 2).

Bivariate correlations indicated that the %OBA and pre-surgical AP levels were significant and directly related (p=0.018, Pearson coefficient=0.469), thereby demonstrating a link between a clinical predictor and the amount of bone growing in situ. MAR and HO anatomical location were significant (p=0.050) with bone growth rates being highest for upper extremity injuries (2.01 um/day) followed by above knee (1.64 um/day), pelvis (1.64 um/day) and below knee (1.36 um/day). MAR and post-operative AP levels were nearly significant and directly related (p=0.051, Pearson coefficient=0.467), indicating that as AP levels increased there was a higher potential for the ectopic bone to be more metabolically active.

Partial correlations controlling for non-steroidal anti-inflammatory drug (NSAID) usage, TBI and anatomical location indicated a significant relationship between MAR and recurrence (p=0.024). In this study there were 7 reported cases of HO recurrence (4 minimal, 3 mild) of which none required secondary surgery. Linear regressions indicated that our team can predict within an 8% error the expected MAR rate of a warfighter with post-combat HO based on the following equation: MAR = 0.006 (AP post-op) - 0.009 (weight lb) +0.187 (TBI severity) + 2.745. This equation may be useful for determining an appropriate time for HO resection when neurological injuries are present and the bone is still metabolically active.

Discussion: As demonstrated through Pearson's correlation coefficients, MAR relates to HO location and AP levels at the time of surgical resection. Based on %OBA and SEM/light microscopy images it was evident that HO masses were still actively modeling/remodeling even at the time of surgical intervention. Bone growth rates were highest for upper extremity injuries followed by above knee, pelvis and below knee ectopic bone sites. All of these sites exceeded values observed in non-pathological human bone. When NSAID, TBI and HO locations were treated as covariates in this analysis, HO recurrence and MAR were significantly related, thus providing a unique tie between clinical predictors and histological analysis not yet seen before. In the future, surgeons may be able to use the MAR equation above as a tool for planning resection time periods to mitigate recurrence.

Significance: The etiology of heterotopic ossification (HO) remains unknown and nothing curative exists for symptomatic and established HO except operative excision. This poses additional risk of recurrence and surgical complications. Correlative factors such as gender, genetics, infection, and age have been associated with ectopic bone growth, but these studies have lacked detailed histological analysis. Most concerning, is that if HO is resected prematurely, the bony mass may recur and require additional surgical procedures. A screening mechanism linking clinical predictors and histological analysis may be useful for optimizing the timing of surgical resection to reduce the risk of HO recurrence.
Figure 1: Double labels used to calculate MAR.
Figure 2: SEM showing regions of bone chips, osteon formation, hypermineralization and new HO growth/development.