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Session: One Pathology: Comparative Considerations in Disease Research

Seminar Title: Preventing steroid-induced osteonecrosis: from animal model to clinical trial

Steroid-induced osteonecrosis (ON) is a debilitating complication in children treated for acute lymphoblastic leukemia. Symptomatic ON occurs in approximately 15% of children treated with glucocorticoids, and results in severe pain, compromised movement, and eventual joint replacement. The laboratory of Dr. Mary Relling at St. Jude Children's Research Hospital developed a mouse model of steroid-induced ON to study the effect of different treatment regimens, drug interactions, and age, sex and gene variants. The base model involves the treatment of Balb/cJ mice with 4 mg/L of dexamethasone administered in the drinking water continuously for 6 weeks, beginning at 4 weeks of age. In this model ON occurred most frequently in the distal femoral epiphysis of mice, so the knee joint was examined histologically; this is the only method sensitive enough to determine the presence of osteonecrosis.

The use of a mouse model vs. other larger animal models of steroid-induced osteonecrosis afforded the ability to examine the whole joint and surrounding tissues in one section. In larger animals (including humans), sections of bone are taken for examination and the surrounding soft tissue and vasculature is not included. Because of this, I was able to examine the blood supply to the distal femoral epiphyses and discovered the presence of vascular pathology, demonstrating that vascular dysfunction was the underlying cause of osteonecrosis.[1] Lesions were present in the extraosseous arteriole coursing along the cranial surface of the medial epicondyle, which entered through foramina into the epiphysis. Grading criteria were later generated for these lesions:[2]

Grade	Histological description
0	Within normal limits; smooth muscle and endothelial cells intact
1	Loss of smooth muscle cell nuclei, endothelium intact
2	Loss of smooth muscle cell and endothelial cell nuclei, with or without mild thickening of the vessel wall but no luminal occlusion
3	Loss of smooth muscle cell and endothelial cell nuclei with thickening of the vessel wall to the point of causing luminal occlusion
4	Loss of smooth muscle cell and endothelial cell nuclei with thickening of the vessel wall, luminal occlusion, and thrombosis of the vessel proximal to/above the physis

After studying the research involving the effect of steroids on blood vasculature, I hypothesized that the link between steroids and the vascular lesions was hypertension. This prompted the lab to perform a preclinical trial testing the concurrent use of an antihypertensive with steroid therapy. The use of an antihypertensive reduced the incidence of osteonecrosis from 65% down to 20%.[3] Retrospective reviews demonstrated that both children with ALL and adults with various conditions, when treated with steroids were more likely to develop osteonecrosis if they had concurrent hypertension, suggesting the pathogenesis is similar in humans. This work provided the basis of the current St. Jude clinical trial named HYPERION supported by NIH grant 1K08CA250418. This trial is evaluating the effect of antihypertensive control on the incidence of osteonecrosis in children receiving treatment for ALL.

1. Janke LJ, Liu C, Vogel P, Kawedia J, Boyd KL, Funk AJ, Relling MV. Primary epiphyseal arteriopathy in a mouse model of steroid-induced osteonecrosis. *American Journal of Pathology* 2013 July;183(1):19-25.
2. Finch E, Janke LJ, Smith C, Karol S, Pei D, Cheng C, Kaste S, Inaba H, Pui CH, Wolf J, Relling MV. Bloodstream infections exacerbate incidence and severity of glucocorticoid-induced osteonecrosis. *Pediatric Blood & Cancer*, 2019 Jun;66(6):e27669.
3. Janke LJ, Van Driest SL, Portera MV, Atreya RV, Denny JC, Pei D, Cheng C, Kaste SC, Inaba H, Jeha S, Pui CH, Relling MV, Karol SE. Hypertension is a modifiable risk-factor for osteonecrosis in acute lymphoblastic leukemia. *Blood.* 2019 Sep 19;134(12):983-986.