Bone Formation in Elastase-Induced Rabbit Aneurysms Embolized with Platinum Coils: Report of 2 Cases

SUMMARY: Histologic findings in 71 elastase-induced rabbit aneurysms embolized with platinum coils were retrospectively reviewed. Mature bone formation was found in 2 aneurysms, one with coils implanted for 3 months and the other with coils implanted for 1 year. We present the histologic findings and offer potential explanations for these observations. These findings may be relevant in understanding mechanisms of aneurysm healing after coil embolization.

Case Reports

Subject 1
Light microscopic examination revealed that the aneurysm dome was primarily filled with hypocellular, loose connective tissue. Localized, irregular attenuated connective tissue in the center of the dome, as well as along the neck, was noted, which contained densely packed collagen fibers.

Near the neck area, several bony trabeculae were observed (Fig 1A, -B). A thin layer of flattened cells lined the bone trabeculae. Ovoid osteocytes in the cavelike lacunae were trapped within the formed bone matrix. A marrow cavity was also present, containing loose reticular connective tissue with various types of blood elements; single layers of cells lining thin-walled vessels; spindle-shaped stromal cells; and conspicuous, large adipose cells (Fig 1B). Dense connective tissue peripherally surrounding the bone trabeculae was in continuity with the periosteum and the marrow cavity.

Subject 2
Light microscopy showed that approximately two thirds of the aneurysm dome was filled with vascular, loose connective tissue. Dense, irregular connective tissue, which contained diffuse collagen deposition, occupied approximately another third of the dome.

Localized bony trabeculae were noted within the aneurysm dome (Fig 2A, -B). The bony trabeculae were lined and covered with a thin layer of cells, probably representing osteoprogenitor cells (Fig 2B). Ovoid osteocytes in the cavelike lacunae were surrounded by bony matrix. One central canal with connective tissue was present within the bony matrix. A marrow cavity between trabeculae, containing various types of blood elements and blood sinusoids (Fig 2B), was also present. Dense connective tissue with abundant collagen fibers surrounded the bony trabecula. The connective tissue was in continuity with the marrow cavity and the periosteum.

Discussion
Platinum coils represent the first-generation materials for embolization of intracerebral aneurysms. Limited histopathologic data in coil-embolized aneurysms in humans and animal studies have suggested that platinum coils are biologically inert and fail to elicit a fibrotic response. This muted response has prompted numerous investigators to explore coil modifications. Histologic response to the coils has been the impor-
tant parameter for evaluating the efficacy of new, modified endovascular devices. To date, thrombosis and loose or attenuated connective was the primary tissue type in all of the reports after coil embolization. Recently, Killer et al reported cartilage neoformation in aneurysms embolized with Hydro-Coils 1 year after coiling. To our knowledge, there are no reports demonstrating bone formation within aneurysm after coil embolization.

The current study found bone formation in 2 of 71 elastase-induced rabbit aneurysms after platinum coil embolization. Although a quantitative analysis comparing aneurysms with and without bone formation was not performed, it appears that the 2 cases with bony metaplasia also had markedly attenuated connective tissue within the aneurysm dome. This connective tissue was in continuity with the periosteum and the marrow cavity, indicating that the bone developed not from an endochondral ossification but rather from the connective tissue mesenchyme (intramembranous ossification). We hypothesize that the mesenchymal stem cells (MSCs) in the connective tissue differentiated into osteoprogenitor cells. These cells then differentiated into osteoblasts, which then secreted collagen and bony matrix.

The origin of these osteoprogenitor cells remains unclear. Improved understanding of the origin of these cells may be of fundamental importance in understanding the mechanism underlying the healing of aneurysms after coiling. Cells residing in aneurysm cavities after coiling may be derived from circulating progenitor cells trapped in the thrombus after embolization or they may be locally derived from the adjacent arterial wall. Recent studies suggest that MSCs may be found in numerous tissues beyond the bone marrow. These extramarrow MSCs are similar to bone marrow-derived stem cells, which can differentiate into different various cell lineages. MSCs may also be found in the arterial wall and may contribute to the bone formation in ectopic tissue. These MSCs also may enter the circulation, contributing to the population of circulating progenitor cells and engrafting other tissue.

The bone formation in one of our 2 cases was close to the aneurysm wall, whereas in the other case it was located at the neck area, close to the parent artery blood flow. It is difficult to

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**Fig 1.** A, Lower-power view of H&E staining section of 3-month platinum coil embolized aneurysm, showing the mature bone formation near the neck area (arrow). (H&E, original magnification ×30).

B, Higher-power view of formed bone in A, showing the bony trabeculae (short arrow) and bone marrow (long arrow), which contains loose reticular tissue with blood elements, thin-walled vessels, stromal cells, and adipose cells (H&E, original magnification ×100).

**Fig 2.** A, Lower-power view of H&E staining section of 1-year platinum coil embolized aneurysm, showing the localized formed bone and marrow within the aneurysm dome (arrow). (H&E, original magnification ×15).

B, Higher-power view of formed bone in A, showing the bony trabeculae (short arrow) and bone marrow (long arrow), which contains various types of blood elements and blood sinusoids (H&E, original magnification ×100).
determine the origin of these bone-forming cells (from the artery wall or from circulating cells) in the current study. Further study of the role of the progenitor cell in the aneurysm healing after coiling is ongoing our group.

Beyond understanding of cell lineage, these 2 cases of bone formation within aneurysms also raise the question about the role of cytokines in aneurysm healing. Numerous cytokines have been found to be the regulators of development and activation of bone cells during bone remodeling. An increase in the gene expression of tumor necrosis factor-α and osteopontin has been shown in the coiled aneurysm of our rabbit model (unpublished data). These data support the idea that these proteins may induce bone cell formation.

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