Aneurysmal Bone Cyst: its Pathogenesis Based on Angiographic, Immunohistochemical and Electron Microscopic Studies

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Based on angiographic, immunohistochemical as well as electron microscopic findings, authors outline a hypothesis for the etiopathogenesis of aneurysmal bone cysts. No changes were found at the arterial site in 16 studied aneurysmal bone cysts, with no signs of an arteriovenous shunt. In certain cases, however, dilated and tortuous efferent veins became visible in the late venous phase. Due to the impedance of venous flow, the intracystic pressure increases and the small veins become dilated causing formation of aneurysmal slits. This is supported by the immunohistochemical finding that S-actin shows concentric arrangement around the aneurysmal cavities. Endothelial lining and basal membrane remnants were detectable in places, though the aneurysmal slits were devoid of continuous endothelial lining and basal membrane. We suggested that the aneurysmal bone cyst corresponds to a hemodynamic disturbance and is due to primary or secondary venous malformation of the bones. (Pathology Oncology Research Vol 4, No 4, 277–281, 1998)

Key words: aneurysmal bone cyst, pathogenesis, angiography, histology

Introduction

The term aneurysmal bone cyst (ABC) was first used by Jaffe and Lichtenstein11 in their paper on solitary unicameral bone cysts, which appeared in 1942. ABCs are less common than osteosarcomas, with over 80 per cent of cases appearing in the first two decades of life. They mostly affect the metaepiphysyeal part of the long tubular bones and the flat bones, and may also rarely affect the short tubular bones of the hands and feet. ABCs are considered to be tumor-like lesions of bone, consisting of large blood-filled aneurysmal spaces without endothelial lining. They show rapid growth, aggressively blowing up the affected part of the bone and most often the first clinical symptom is a pathological fracture.25

A still growing number of scientific papers deal with the typical radiological and clinicopathological features as well as treatment results of the disease, there are, however, many controversial hypotheses regarding the etiology of aneurysmal bone cysts. The aim of the present work was to give a retrospective analysis of the angiographic, immunohistochemical and electron microscopic findings of our bone cyst cases in order to obtain more information about the etiopathogenesis of the process.

Materials and Methods

A total of 84 primary and 16 secondary aneurysmal bone cysts have been recorded in the files of the bone tumor registry of the Department of Orthopaedics of the Semmelweis University of Medicine between 1973 and 1998. Seventy seven per cent of the cases occurred in the first two decades of life (average age: 18.5 years). The most common localisations were the followings (in decreasing order): the proximal part of the humerus and
tibia, the pelvic bones, and the distal epimeta-physysis of the femur.

Angiography was performed in 16 primary and 4 secondary ABCs. The early arterial, parenchymal and venous phases were evaluated. Digital subtraction angiography was used in 6 cases.

Histology of the last 25 cases was re-evaluated: paraffin embedded, non-decalcified 4 μm thick sections were stained with hematoxylin-eosin, with the use of PAS (periodic acid-Schiff) and Gomori’s reticulin impregnation as well.

For immunohistochemical studies the peroxidase-antiperoxidase (PAP) method was applied. The following antibodies were used: anti-vimentin; CD31, CD68; anticolonagen-type IV and anti-smooth muscle cells (S-actin).

In 4 cases reembedding from the paraffin blocks was performed for ultrastructural examination. Typical areas were cut from the blocks, under light microscope control deparaffinised and embedded in Epon. The ultrathin sections were studied by Philips CM 10 electron microscope.

Results

Angiographic studies on 16 primary aneurysmal bone cysts

In the early arterial phase the aneurysmal bone cysts were supplied by the main artery in the majority of the cases. Thus for example, the aneurysmal bone cyst originating from the os pubis was supplied from the arteria obturatoria, in another case the cyst involving the acetabulum and the os ileum stub from the arteria iliaca interna, the cysts involving the femur-neck either from the arteria circumflexa anterior or posterior, those in the proximal metaphysis of the humerus from the arteria circumflexa humeri anterior or posterior. In rare cases there were two main arterial suppliers, from which occasionally one, usually with several side-branches ran to the cyst. These were normal in 10, and visibly dilated in 6 of the cases.

In the arterial phase the blood supply of the cysts and cyst walls was hypervascular in 8 cases, normovascular in 6 and hypovascular in 2 cases.

The arteries and arterioles ran in the connective tissue septum of the cysts, showing slight abnormalities (tortuous course, “corkscrew” veins, slight size differences).

None of the cases revealed simultaneous early arterial and venous impregnation referring to the presence of an arterio-venous shunt. Only two cases demonstrated a direct relationship between the arteries of the cysts and the large dilated aneurysmal spaces, causing the early saturation of the latter with contrast material.

In the late arterial phase, parenchymal phase the cysts were characteristic of having one, occasionally several central hypodense areas, surrounded by mostly hypervascular septa. By this time, the appearance of the aneurysmal spaces was obscure, filled with contrast material.

Figure 1. Angiograph (venous phase) demonstrates the dilated and torqued vein (black arrows) in the environs of an aneurysmal bone cyst (white arrows) in the iliac bone.

In the late arterial, venous phase the veins in and around the walls of the aneurysmal bone cysts numerically corresponded to the normal surroundings, though showing dilation in size and windy/tortuous course in a number of cases (Figure 1). The aneurysmal spaces were filled with contrast material in the venous phase as well.

Histological studies

By light microscopy the large aneurysmal spaces were divided by connective tissue septa. In other places larger solid areas appeared. The aneurysmal spaces were lined with flattened cells, the lumen was filled with erythrocytes. In the connective tissue septa unorganised, freshly formed bone trabeculae were observed among the connective tissue cells. The osteoclast-type giant cells were partly located in a single row parallel with the cyst surface, and partly in larger groups at the solid areas, occasionally mimicking bone tumors of giant cell type. Hemosiderin, extravasated erythrocytes, groups of histiocytic cells with foamy cytoplasms were all detectable in the septum walls
at solid areas. At the site of the connective tissue septa, the extracellular matrix had a rich collagen fibre network, while a loose fibroblastic structure of the myxoid matrix was manifested in the solid areas. These areas were poor in arteries, while at other places an increased number of partly closed, partly open capillaries were observed. Proliferative growth characteristics of angiogenic tumors were detected in neither case. No thick walled muscular arteries indicative of angio-venous shunt, or any nearby veins were present. Cystically dilated vein structures with thin walls and rather wide lumens were noted, however, forming a transition between the aneurysmal spaces and the smaller veins/capillaries (Figure 2).

**Immunohistochemistry**

Immunohistochecmical studies revealed the aneurysmal bone cysts to have connective tissue cells showing strong vimentin positivity as well as dispersely located mononuclear cells and osteoclast giant cells showing CD68 positivity (Figure 3). The antibody CD31, labelling endothelial cells, showed strong reaction with the endothelial cells of the stromal vessels and dilated cystic formations, while only occasional reaction was found among the flattened cells on the surface of the large aneurysmal spaces (Figure 4). The basal membranes surrounding the stromal small veins and cystically dilated vein structures reacted with type IV collagen antibodies, but this was not the case in the lumen of the aneurysmal spaces, in the environments of the flattened cells.

Large amount of smooth muscle actin positive cells appeared both around the aneurysmal spaces and in the solid areas. Multilayers of smooth muscle cells, myofibroblasts were located in concentric manner around the cystically dilated venous structures and aneurysmal spaces (Figure 5).

**Electron microscopy**

Transmission electron microscopy provided good demonstration of the endothelial cells and basal membranes of the stromal capillaries. Neither the capillaries, nor the cystically degenerated venous structures showed multilayered basal membrane formation or endothelial cell proliferation which are characteristic otherwise of neoplastic proliferation. The surface of the aneurysmal spaces was covered by flattened fibroblast-like cells and randomly by osteoclasts. At other areas, cell organelle remnants were found to be adhered to detached basal membrane.

**Discussion**

Nowadays, all authors agree upon the fact that aneurysmal bone cysts develop as a consequence of a hemodynamic disturbance, in the form of a primary lesion in about two thirds of cases, and on the grounds of other benign or malignant bone tumors, tumor-like bone deformations in about one third of cases. Accordingly, aneurysmal bone cysts have been reported in giant cell bone tumors, solitary bone cysts, non-ossifying bone fibromas, osteoblastomas,
chondroblastomas, and even in association with osteosarcomas.\(^6\),\(^13\),\(^20\) These findings would prove that the local hemodynamic disturbance would have several causes, or rather different origin.

Beyond the description of hemodynamic disturbance, however, little is known about the etiology of the aneurysmal bone cyst, even though numerous hypotheses have seen light throughout the past decades.

Tillman\(^29\) called attention to a tight connection, transitional form between the aneurysmal bone cyst and the unicameral, or juvenile bone cyst, with many authors raising the vascular origin of the latter.\(^9\)

Certain authors believe the aneurysmal bone cyst to be of secondary, reactive nature, developing from existing lesions, possibly cysts or angiommas,\(^4\),\(^12\),\(^18\) and induced by the already present bone tumor.\(^14\) Others consider it to be a cystic degeneration of a certain type of hemangioma.\(^10\),\(^23\) Lichtenstein,\(^15\) then later others,\(^4\),\(^25\) also raised the possibility that trauma plays a great role in its development, the process taking place as a juxtacortical post-traumatic transformation. Lichtenstein\(^16\),\(^17\) further raised the issue that locally, there could be a thrombosis of a larger vein or an intraosseal arteriovenous shunt, which notion was later supported by many others\(^4\),\(^7\),\(^10\),\(^21\),\(^26\) and could be evidenced also by the increase in intracystic pressure.

Considering our material, none of the 16 angiographic cases showed venous saturation in the early arterial phase, unambiguously being against the role of an arteriovenous shunt.

In harmony with the studies of Schobinger\(^29\) and Lindblom,\(^19\) the normal appearance and course of the arteries supplying aneurysmal bone cysts indicate that the cause of the lesion should be sought after elsewhere than on the arterial side.

Our cases were studied by histological, immunohistochemical methods and by electron microscopy, but nevertheless, the vascular tumor nature of the process could not be proved. Certain areas were poor in arteries, while in other places not even the increased amounts of capillaries demonstrated proliferative, neoplastic character. The latter is typical of the presence of endothelial cell proliferation and multilayered basal membrane.\(^22\)

Studying the venous structures, a total absence of thick-walled muscular arteries was manifested in the stroma, contrary to the wide transition observed between the capillaries, smaller venules and the wide-lumened, dilated, thin-walled venous structures. As opposed to certain observations,\(^23\),\(^21\) the endothelial lining of these showed intact underlying basal membranes both by electron microscopy and immunohistochemistry.

Our opinion is that the large aneurysmal spaces could also be the degenerative remnants of previous venous structures, despite the fact that endothelial cell lining and basal membrane are missing. Indicative of this are cytoplasmic organelles detectable at places on the surface, the CD31 positivity of some flattened cells lining the aneurysmal spaces, as well as the concentrically appearing S-actin positivity around the aneurysmal spaces, similarly to the smaller dilated venous structures.

The trigger point for the etiology of aneurysmal bone cysts is presumably on the venous side of the cysts. This is supported by the high increase in intracystic pressure, the hinderance to venous flow, and also the appearance of dilated, undulating veins in the environment of the cysts following the direct intracystic administration of contrast medium. This is the main cause of the hemodynamic disturbance, resulting in the clinico-pathological alteration so characteristic to aneurysmal bone cysts. Hence the aneurysmal cysts of the bones may develop by means of a pathomechanism similar to the venous malformation of the viscera.

Apart from surgical treatment, more attention is given to methods which alter the circulation of the cysts, substantiating that a hemodynamic disturbance, venous malformation is at issue, rather than a real tumor. The supersc elective embolisation of the supplier arteries could lead to connective tissue formation, then bony healing of the cysts.\(^13\) A further, non-surgical approach is the sclerosing treatment of aneurysmal bone cysts by means of direct intracystic puncture.\(^1\) This method provides good results similar to those obtained with the sclerosing treatment of the venous malformations of the viscera.\(^24\)

References


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