

NEW ASPECTS IN JOINT AND BONE PROCESSES IN PSORIATIC ARTHRITIS (PSA)

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Corresponding to the clinical-radiological peculiarities PSA demonstrates also a morphological profile which diverges from other joint diseases. Following our observations morphological characteristics are found in synovial tissue as well as in joint cartilage and juxta-articular bone.

In contrast to the alterations in rheumatoid arthritis (RA) and osteoarthritis (OA), the following morphological features are characteristic for PSA: the synovial villi are longer and thinner. Depending on the actual inflammatory activity, the lining cells may be either high-cylindrical and multi-layered or inconspicuously flat and single-layered. A multi-layered proliferation of the lining cells is transitory and merely an expression of an actual but uncharacteristic inflammatory reaction which is observable in every joint disease. The fibrosis of villous stroma is denser than in OA but not as compact as in RA. From our observations, the pattern of vascularization is the most reliable feature^{1,2}. Within the synovial stroma, mainly in the periphery, closed to the lining cell layer, there is an unusually high number of narrow, thin-walled blood vessels (Fig. 1). These

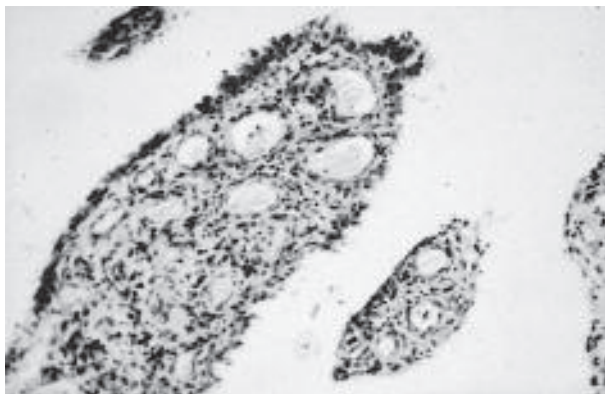


Fig. 1: Synovial villi in arthropathia psoriatica. Characteristic are the wide, thin-walled blood vessels.

can best be seen in the early stages of synovitis. We presume that after each episode of inflammation these vessels disappear due to the ensuing increased density of collagen fibres. Thus, diagnosis becomes more difficult. Danning and his co-workers³ believe that increased expression of alphavbeta3 integrin is one explanation for the neovascularization in early phases of PSA. Fearon and his co-workers⁴ believe that the increase in blood vessels in the villi, compared to patients with RA, is due to higher levels of TGFB-1 and increased VEGF expression in the synovial membrane. These thin-walled, newly formed blood vessels adjacent to the lining cell layer should not be confused with the coarser blood vessels that form after the infection has ceased.

The infiltration of the villous stroma by lymphocytes is generally of medium density. In between, plasma cells are often found. Occasionally, lymphocytes can aggregate focally. True lymph follicles with germinal centres, however, are never observed. In rare cases, we found proper lawn-like aggregates of plasma cells. Neutrophils are not a part of the inflammatory cell components of PSA.

High levels of lymphocytes of the subgroups CD28, CD69, and lower levels of CD25 lymphocytes were found.

The clinical and radiological changes, particularly in areas near the phalangeal joints, i.e. osseous ankylosis, osteolysis and ossification in the capsule region outside the joint cavity would predict a bone process of a special kind which differs qualitatively from other joint diseases.

We have examined juxta-articular bone tissue from 168 patients with PSA and we could detect an unusual process in the spongy and cortical bone, the stepwise progress of which we divided into 4 phases^{5,6}:

The first phase is characterized by a focal loss of the aggrecan and calcium apatite substance in the lamellar bone of the spongiosa. The exposed collagen fibre network is preserved and still indicates the original pattern of the

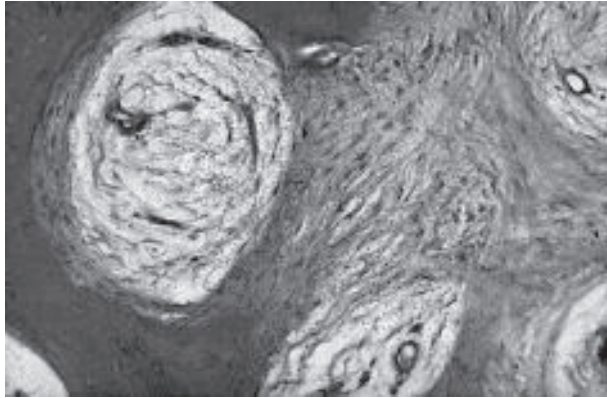


Fig. 2: Denudation of the collagen fibres in the region of the spongy bone in arthropathia psoriatica.

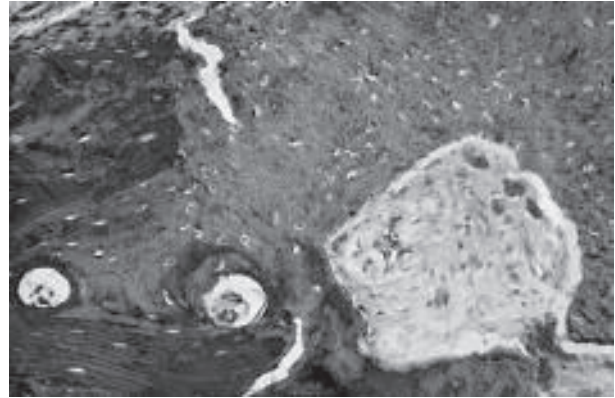


Fig. 3: New accumulated fibrous bone in the region of the spongiosa in arthropathia psoriatica.

bone structure. The delineation between the intact bone and the demasked collagen fibre network is sharp. The exposed collagen fibres are initially still fine. However, in the course of time, they become coarser under the deposition of fibrocytes. Instead of Haversian canals one sees expanded blood vessels which also have survived the process (Fig. 2).

The loss of the proteoglycan-containing interstitial substance of these circumscribed bone sections is not disregarded by the surrounding connective tissue. The sharply defined areas resulting from loss of aggrecan are reactively settled by osteoblast chains. The osteoblasts position themselves between the remaining collagen bundles and use these so to speak as a building frame for the remodeling which subsequently starts. Depending on the age of the osteoblast chains newly formed osteoid is found here which smoothly covers the rough disrupted surface between the fibres. Also in this second phase not the slightest evidence of an inflammatory reaction is found.

The third phase is characterized by the new formation of fibrous bone in the region of the aggrecan loss zones. In contrast to the specific structural pattern of the original lamellar spongiosa, this newly formed bone shows an unarranged matrix. The bone cells of this fibrous bone, in contrast to the lamellar bone, are larger and tend to be round. The preserved collagen fibre frame indeed functions largely shaping in bone remodeling. In fact, however, these newly formed fibrous bone areas are significantly coarser and bulkier and only a caricature of the genuine structure.

Probably the aggrecan loss described above and the new fibrous bone formation processes occur in rare and probably short episodes, since we saw situations in which nei-

ther an indication of acute collagen fibre unmasking, osteoblast activity, nor the formation of new fibrous bone were observable, but only a gravel-like, pagetoid course of disordered fusion lines and an irregularly arranged surface indicating a partial or completely healed condition. These pagetoid final stages, however, achieve neither qualitatively nor quantitatively the structure of the original spongy or cortical bone (Fig. 3). The provisional fibrous bone will, in the course of time, be remodeled into definite lamellar bone. The irregular path of the fusion lines remains as a witness of the newly formed bone and the remodeling process. On the other hand, these gradually progressing processes can lead to a negative balance in the bone structure and can result eventually in osteolyses (fourth phase).

Since phases I and II (fibre unmasking and remodeling) are probably of short duration, histological examinations are most likely to encounter the longer lasting phases III and IV. In cases of doubt the following characteristics verify the diagnosis: Smooth, round spongiosa break-offs and polarization optical proof of bone remodeling whereby the trabeculae, in addition to the old lamellar bone, contain newly formed fibrous bone areas. It is of importance, however, that in these areas all indications of an acute or expired inflammation are excluded.

In cortical compact bone the process is quite different. In a few cases we have had the opportunity to investigate abarticular corticalis from patients with PSA in the initial stages. So, we could observe proliferation of the periosteum during a highly active stage: Between the outer surface of the corticalis and the periosteum, we found an approximately 1-3 mm zone of densely packed cells (Fig. 4). These cells increase in number proceeding from the periosteum

on the guideline of collagen fibres and at first exhibit the characteristics of fibroblasts. But, towards the cortical bone, they increasingly undergo transformation into osteoblasts, forming a compact cell layer between periosteum and cortical bone, a cambium layer. In this way, duplicates of the external cortical contour may be formed, occasionally also bud-shaped forms or fierce formation of new, bizarrely shaped fibrous bone may develop, the latter are almost pathognomonic.

As our observations serve to exclude an inflammatory cause of the pathological formation of new bone in PSA and other seronegative spondarthritides (SSA), we believe that bone modeling proteins (BMP) play a role in the osteoblastic transformation process. We could identify e.g. analogous benign new formation of fibrous bone in the shoulder girdle and pelvic girdle of BMP-6 transgenic mice⁷. The cambium layer contains neither lymphocytes, plasma cells, macrophages, nor neutrophils. It is the prototype of ossification without any interfering inflammation mechanism and characteristic not only of PSA but also of the ossifying processes in SSA.

The irregular and excessive new bone formation offers an explanation for the radiological phenomena (including the capsular ossification) which appear in the region of the phalanges, particularly in PSA (Fig. 5). The remodeling processes at the diaphyseal corticalis cause inflammation of the surrounding soft tissues and are the reason for the dactylitis ("sausage finger" and "sausage toe").

Two questions remain to be answered:

1. How do bony bridges (ankyloses) between articular cavities develop in patients with PSA and other SSA?

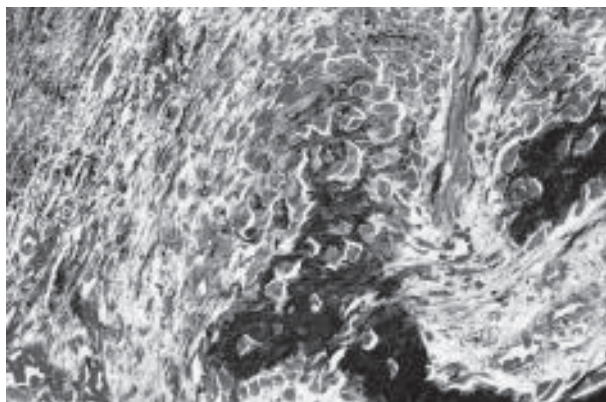


Fig. 4: Arthropathia psoriatica. New formation of bone between periosteum and corticalis. Fibroblasts change to osteoblasts and form new fibrous cartilage.

2. How does arthritis develop in PSA and other members of the SSA family?

Our studies confirm Ball's clinical concept, dating from 1971, which states that one pathogenetic mechanism is common to all the skeletal processes in the SSA group, namely the enthesopathy. Enthesis designates a transitional zone, where sinews and bony tissue are interwoven. Such transitional zones also exist between cortical bone and periosteum, between bone and articular cartilage, as well as between vertebrae and anulus fibrosus.

Bone and adjacent tissues, with the exception of articular cartilage, are basically made of collagen type I fibres. With the help of microscopic studies done with polarization technique, these fibres can be visualized radiating into the respective adjacent tissue. Of decisive importance for the progress of the process is the proliferation of regional fibroblasts and their transformation into osteoblasts. With varying degrees of intensity, the osteoblasts begin to form fibrous bone. Hereby the collagen fibres radiating into the neighbouring tissue serve as a guiding structure. Primary structure borders between tissues, such as between bone and collagenous connective tissue, are thus transgressed without any inflammatory interference. Therefore, zones of ossification form in areas of tendon insertions, and bone remodeling develops along the remaining collagen fibre framework within the spongiosa. These processes duplicate when bony structures stand face-to-face, as they do in the following case:

Finger joints: the formation of new bone leads to a bridging of the interarticular space and to osseous ankylosis (Fig. 6).

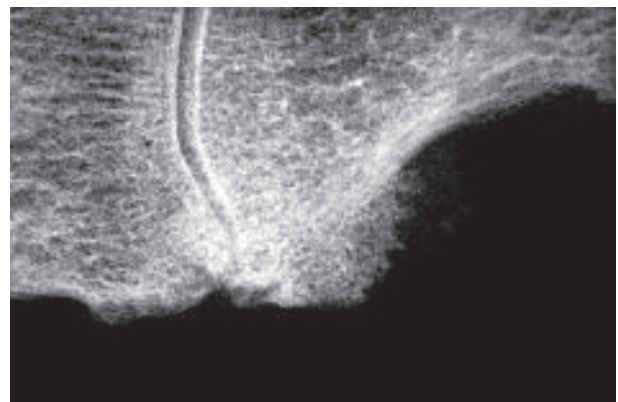


Fig. 5: Arthropathia psoriatica. X-ray. New formation of bone in the region of the corticalis, „protuberances“.

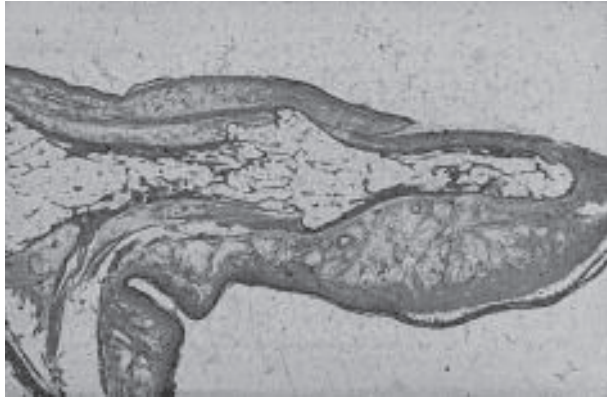


Fig. 6: Bony ankylosis of finger joint in arthropathia psoriatica.

What remains to be clarified is the question of the origin of the synovitis, that, long before the specific bone processes become apparent, characterizes the clinical symptomatology in arthritis. The morphological similarity between the synovitis in PSA and that in other members of the SSA family suggests that the synovitis in PSA is most likely a concomitant phenomenon caused by a systemic immunological disorder. On the other hand, according to our observations, it could be argued that the spreading of the primary, non-inflammatory bone lesion into the articular space causes inflammatory reactions in the synovial membrane (Fig. 7). The irritability of the synovial membrane is obvious, we observed that even the slightest trauma may induce reactive hyperplasia of the villi. If the synovitis is triggered by a mechanical cause, the inflammation in PSA could be considered to be analogous to the synovitis accompanying OA or following intra-articular injuries, that is, the inflammatory mechanism in PSA would be a reaction to structural damage in cartilage or bone and to the ensuing biochemical consequences. Depending on the degree and activity of the disease, the synovial membrane in PSA may contain lymphocytes and plasma cells. This, however, is not conducive to an answer, because lymphocytes, plasma cells, and even sometimes true lymph follicles are also seen in the synovial membrane in patients with OA or synovitis following intra-articular injuries, both of which certainly do not result from immunological reactions. At the present time, the problem of the origin of synovitis in PSA, whether it arises from immunological reactions as it does in reactive arthritis (REA), or whether it is induced by mechanical processes spreading from adjacent bone, remains to be investigated. Whatever the origin of joint destruction may be, the morphological features do not offer anything indicative of either mechanism.

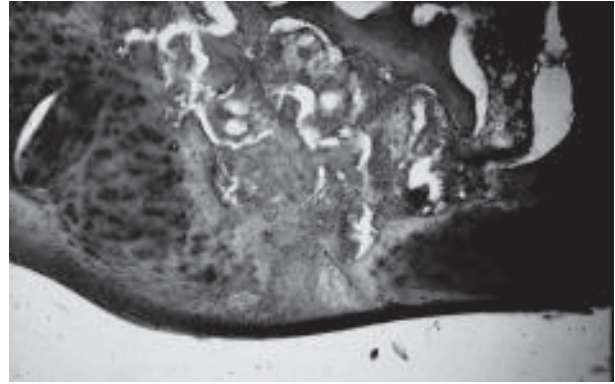


Fig. 7: Transgression of the spongy bone under destruction of the subchondral osseous lamella and the articular cartilage.

From what we know today, two possible mechanisms responsible for the joint destruction ought to be taken into consideration: the enzymatic degradation of cartilage and bone by proteases released by neutrophils, as is the case in bacterial arthritis (BA), and destruction caused by the invasion of "aggressive" proliferated synovial cells and their proteases, as is the case in RA. No evidence of either mechanism is found in the synovial membrane of patients with PSA: we never observed synovial aggression upon cartilage. Nor did we see caving in of granulation tissue into cartilage, bone or marrow space - which would be present were the destructive lesions inflammatory in origin - nor infiltration of synovial tissue by neutrophils, the enzymes of which can destroy cartilage and bone, as they do in BA. Even though the mechanism that triggers the synovitis in PSA cannot yet be identified, any claim that the synovitis may be responsible for the destructive lesions characteristic of PSA is certainly to be dismissed. Consequently, antiphlogistic medication, while it may well influence the inflammatory processes, will be ineffective in controlling the bone process. On the other hand, it is plausible that cytostatic substances seem to be a promising therapeutic option as they influence the proliferation of osteoblasts. While the bone lesions can be visualised with the help of radioactive isotopes, they cause pain only when they encroach on the periosteum and induce secondary inflammation of neighbouring soft tissues ("sausage finger").

The skeletal scintigraphic studies of Holzmann and coworkers^{9,10}, Haydl and coworkers¹¹ as well as Hahn and coworkers¹² who used ^{99m}Tcchnetium can offer elucidation on the connection of bone processes and arthritis in PSA. Holzmann and coworkers found in 3% of patients with PSA not only an accumulation of the tracer in the area of manifest joint processes, but also in the neighbourhood

of clinically intact joints and, moreover, also in the skeletal system distant from the joints as well as in the area of the cranium and the ribs. Haydl and coworkers¹¹ describe corresponding findings in the vertebral column in 60% of their patients with PSA. These results correlate with our findings in that extraarticular pathological processes were detected. The concentration of radionuclides can be explained by the osteoblast proliferation and new bone formation.

Taking into account our observations and these findings we recommend the term "Osteoarthropathia psoriatica" which includes the generalized bone process, which, only by spreading to the neighbouring joint, causes a secondary synovitis.

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