Virchows Arch. Abt. A Path. Anat. 356, 119—126 (1972)

Osteomyelitis of Both Femora in a Patient on Maintenance Hemodialysis with Severe Uremic Osteopathy*

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Received March 13, 1972

Summary. The case is reported of a 29 y. old woman with chronic renal failure and severe azotemic osteopathy treated by maintenance hemodialysis. At autopsy bilateral symmetrical osteomyelitis of the medial corticalis of both femoral diaphyses was found. Osteomyelitis was associated with large, partially penetrating cortical sequesters, and the formation of involucra and cloaca. The coincidence of azotemic osteopathy with osteomyelitis in patients kept on maintenance hemodialysis has not been reported so far. An increased rate of bone remodelling and an enhanced skeletal blood flow as a consequence of uremic metabolic bone disease is thought to raise the risk of hematogenous osteomyelitis. The symmetrical localization in both femora may be due to a local increase of bone remodelling where the riders muscles insert (caused by an altered tonus of riders muscles in uremic myopathy) or in stress zones from bending stress of the femora.

Zusammenfassung. Bei einer 29 Jahre alt gewordenen Frau mit chronischer Niereninsuffizienz und schwerer azotämischer Osteopathie wurde unter Langzeithämodialyse eine doppelseitige symmetrische Osteomyelitis beider Oberschenkeldiaphysen beobachtet. Die Osteomyelitis hatte auf beiden Seiten zu einer partiell penetrierenden Sequesterbildung mit Totenlade und Cloace geführt. Das Zusammentreffen von urämischer Osteopathie und Osteomyelitis ist bislang nicht mitgeteilt worden. Die Entstehung der Osteomyelitis wird auf die metabolische Osteopathie bei chronischer Niereninsuffizienz mit Steigerung des Skeletumbaues und der Skelettdurchblutung zurückgeführt. Als Ursache der symmetrischen Lokalisation osteomyelitischer Herde in beiden Oberschenkeldiaphysen wird eine lokale Steigerung des Knochenumbaues diskutiert, hervorgerufen durch die urämische Myopathie mit einer Tonusänderung der Adduktorenmuskulatur im Bereich ihrer Insertion und/oder durch die Biegebelastung der Oberschenkelbeine im Bereich der Biegungsmaxima.

Although histological, roentgenological and clinical signs of bone disease are rather frequent in patients undergoing chronic hemodialysis (Krempien *et al.*, 1971; Ritz *et al.*, 1971), gross skeletal destructions or deformities are distinctly rare. In the following we report the case of a 29 years old female patient in terminal renal failure who was kept on hemodialysis for two years. At autopsy severe azotemic osteitis fibrosa and osteomalacia was found. In addition, however, both femora were partially destroyed by chronic osteomyelitis and showed symmetrical gross sequesters in the diaphyseal region with typical involucra and cloaca formation. Since in uremia similar cases have not been described so far, etiology and pathogenesis of this rather unusual skeletal finding shall be discussed.

Case Report

a) History. 29 years old female. 1955 in the age of 15 scarlet fever and nephritis. Chronic renal insufficiency since march 1966. Maintenance hemodialysis since february 1968. Bilateral

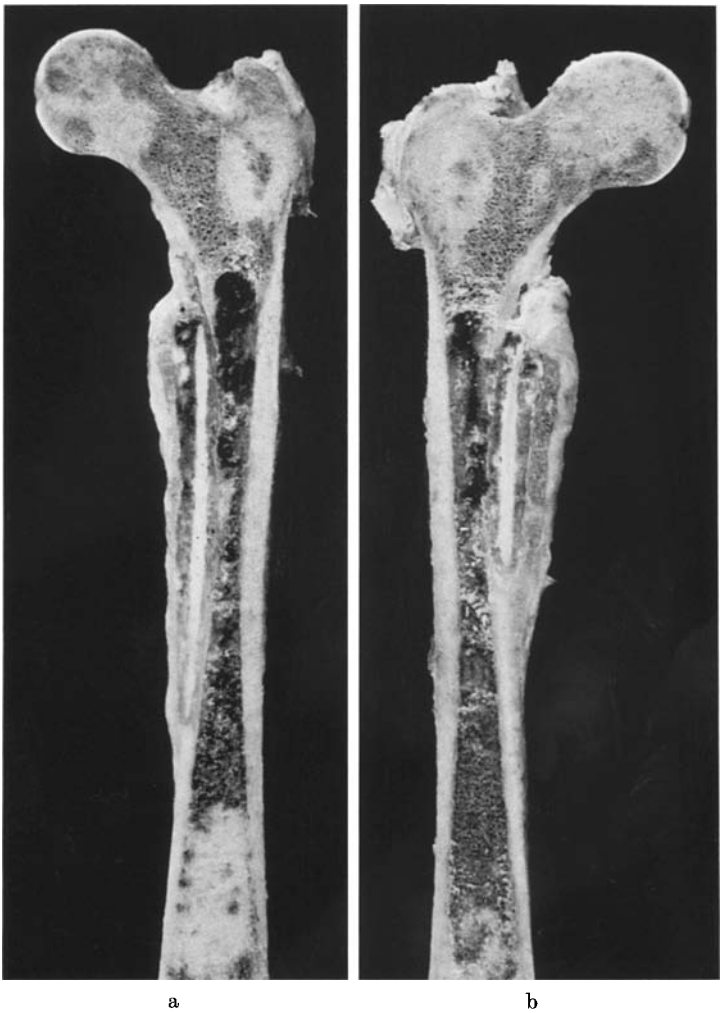
* Supported by Deutsche Forschungsgemeinschaft.

nephrectomy on 8. 5. 1969. At this time severe secondary hyperparathyroidism. On 12. 3. 1970 subtotal parathyroidectomy because of extreme skeletal changes. On histology the parathyroid glands showed diffuse hyperplasia.

On 3. 4. 1970 kidney homotransplantation with acute rejection. Nephrectomy on 14. 4. 1970. Death in cardiac insufficiency on 28. 4. 1970 as a result of gram-negative septicemia.

b) Gross Pathologic Findings. Fibrinous pericarditis and ulcero-hemorrhagic enterocolitis due to chronic uremia. Severe renal osteopathy. Concentric hypertrophy of the left cardiac ventricle with dissiminated cardiac muscle scars after longstanding renal hypertension. Wound infection and septicemia after nephrectomy of an unsuccessful renal homotransplant.

c) Skeletal Changes. In the proximal diaphysis of both femora we found symmetrical, partly penetrating cortical sequesters with involucra and cloaca formation (Fig. 1a and b). The large cortical sequesters were totally necrotic and were partially resorbed by multinucleated osteoclasts. Foci of chronic osteomyelitis were found in both femora in fibrous scar tissue. The vital compacta showed extreme spongiosation (Fig. 2 and 3). Iliac crest biopsy, obtained



a b

Fig. 1a and b. Longitudinal section of the right (a) and left (b) femur. Symmetrical gross cortical sequesters of both femora with formation of involucra and cloacae due to bilateral partially penetrating osteomyelitis of the proximal diaphyses

Fig. 2. Partly emptied abscess-cavity of the diaphysis surrounded by fibrous scar tissue. Subtotally resorbed sequester covered by numerous Howship's lacunae. Spongiosation of the vital cortical bone. HE-staining after decalcification. Microphotograph, 1:10

prior to parathyroidectomy gave evidence of severe azotemic osteopathy with fibrosis of the endosteum, increased osteoblastic and osteoclastic activity, marked periosteocytic osteolysis and defective mineralization with an increase of osteoid.

Discussion

In the literature available to us we were unable to find a report on comparable skeletal changes in dialysed patients. Although septicemia is not uncommon in dialysed patients osteomyelitis apparently is extremely rare. The symmetrical localization of the osteomyelitic foci in our case is particularly intriguing and suggests that systemic factors were involved.

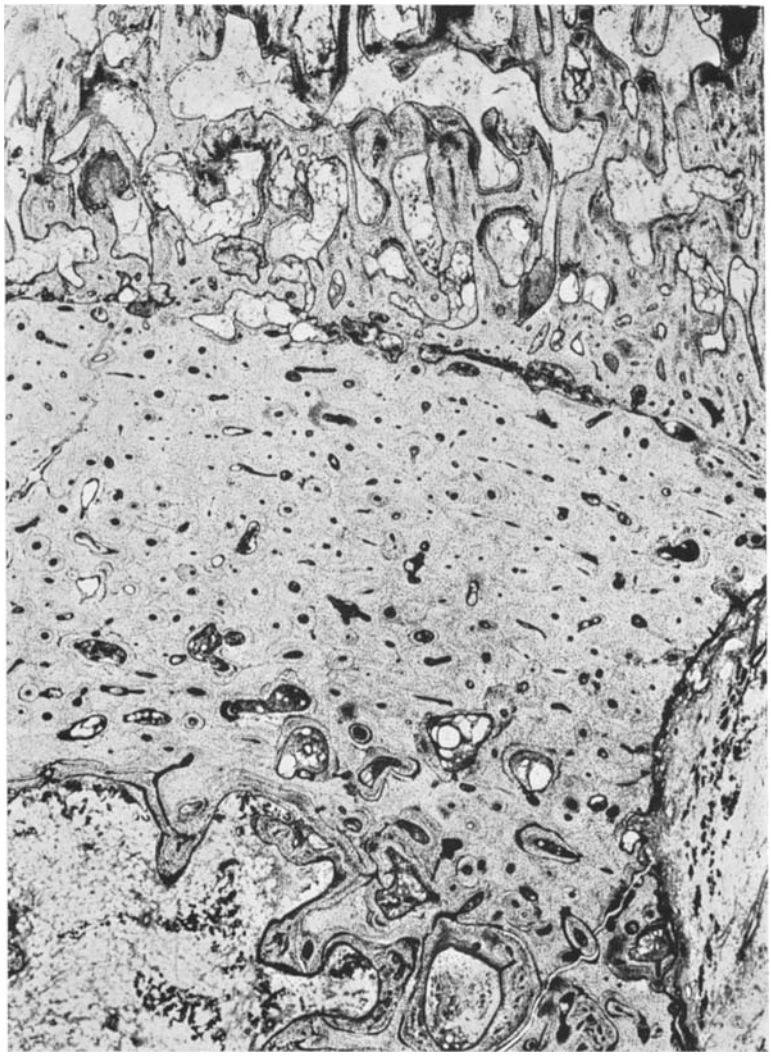


Fig. 3a. Transverse ground section of the femoral cortex with endosteal (below) and periosteal (above) new bone formation and gross destruction by sequestration (on the right hand).

Symmetrical defects of the skeleton are wellknown in Milkman's syndrome, which according to Uehlinger (1943, 1959) are caused by a so called "Umbauzone" (Looser, 1920). Symmetrical pseudofractures or Looser's zones are a characteristic feature of osteomalacia both in nutritional vitamin D deficiency and in renal insufficiency, where osteomalacia is due to a pecurliar inefficiency of physiological doses of vitamin D (uremic vitamin D resistance). The presence of Looser's zones in our case could be excluded, since histological examination of both femora showed bilateral osteomyelitis of both femoral diaphyses with formation of symmetrical partially penetrating sequesters of the medial femoral corticalis associated with the formation of involucra and cloacae (Fig. 1a and b, 2 and 3a).

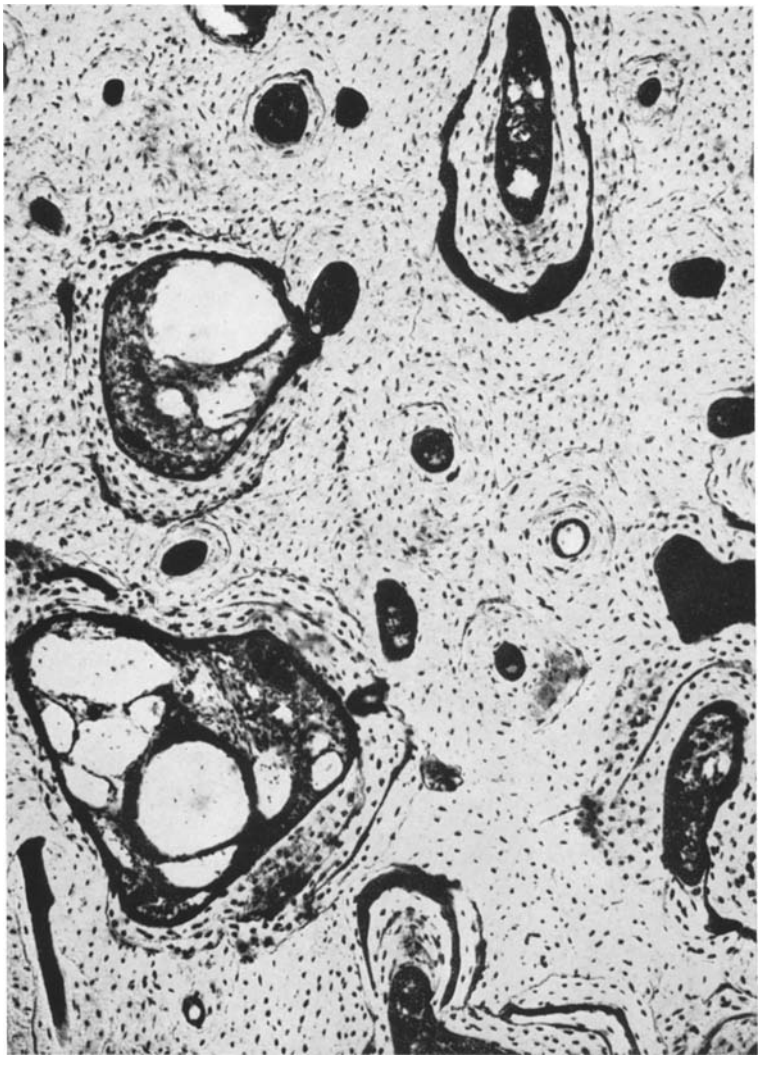


Fig. 3 b. Higher magnification of the same region. Severe azotemic osteopathy with microcysts, marrow fibrosis, enlarged osteoid seams, augmented osteocytic lacunae and periosteocytic osteolysis of cortical bone. Undecalcified ground section (50 μ), basic fuchsin-staining (5%). Microphotograph, a 1:15, b 1:48

This form of destructive osteomyelitis in adults is rarely observed today (Doerr, 1955, 1957). The extensive formation of sequesters resembles osteomyelitis in childhood, where separation of the loose periosteal layer is responsible for ischemic sequestration of cortical bone (Trueta, 1959). A similar situation may have been present in our case, where an increased cellularity and vascularity of the periosteum has developed as a consequence of azotemic bone disease.

Apart from the report of Pfeifer and Donath (1969) who described unilateral osteomyelitis of the femoral diaphysis in an 11 y. girl with primary hyperparathyroidism we have been unable to find further reports of hyperparathyroidism

associated with osteomyelitis in literature. Pfeifer and Donath did not see a causal relationship between hyperparathyroidism and osteomyelitis. The symmetrical localization of osteomyelitic foci in our case suggests that azotemic bone disease as an underlying systemic factor might be causally related to the development of the bilateral osteomyelitis.

Osteomyelitis usually is localised in the femoral metaphysis. It is encountered much less frequently in the diaphysis as in our case (Lauche, 1939). Hematogenous osteomyelitis is primarily a disease of the growing skeleton. Most of all cases start before the age of 25 (Garre, 1897; Schinz *et al.*, 1952; Waldvogel *et al.*, 1970). Osteomyelitic foci are typically localised underneath the epiphyseal plate in the metaphysis of long bones. This is probably due to the high vascularity of the metaphysis (Lexer, 1896; Lauche, 1939; Trueta, 1959). Multiple bone involvement occures in less than 10% of all patients (Schinz *et al.*, 1952; Waldvogel *et al.*, 1970). The age of multiple foci is usually different (Garre, 1897). The present case with synchronous development of osteomyelitis in atypically symmetrical localization in an age beyond the age maximum is distinctly unusual.

Lexer (1903) could clearly show experimentally that the regional blood flow is an important determinant for the establishment of osteomyelitic foci. Hyperparathyroidism leads to spongiosation of cortical bone as a consequence of an increased rate of bone remodelling (Haslhofer, 1937). Extensive spongiosation of the femoral bone cortex in the present case is demonstrated by Fig. 2 and 3. Increased bone remodelling is associated with increased blood flow in osseous tissue. This has been well documented in Paget's disease, where the local increase of bone remodelling is accompanied by increased vascularisation and increased blood flow of the diseased bone (Rutishauser *et al.*, 1954; Deuxchaisnes and Krane, 1964). Similarly increased blood flow in bone has been shown when bone resorption was enhanced by immobilization (Imig *et al.*, 1953; Geiser and Trueta, 1958; Hulth and Olerud, 1960). Metabolic bone disease presumably alters regional blood flow in bones too (Copp and Suiker, 1962; Rokoff *et al.*, 1969). Severe azotemic osteopathy with hyperparathyroidism and osteomalacia could be clearly demonstrated in the present case. Therefore increased blood flow in the skeleton due to azotemic osteopathy might have been a *general* risk factor for the development of osteomyelitis in our case.

A possible *local* factor that might explain the development of bilateral symmetrical foci in the femoral diaphyses may well be a local increase of bone remodelling rate in the medial bone cortex of the femora. It seems significant to us, that both sequesters were found in the medial cortex of the femora, i.e. in that part of the femur, where the musculi adductores insert. Myopathy and enhanced tonus of riders muscle is a feature of osteomalacia and hyperparathyroidism (Wernly, 1959; Smith and Stern, 1967). Patients with chronic renal insufficiency are often found to suffer from myopathy which can be cured by vitamin D (Stanbury, 1965). Therefore it might be assumed, that in the present case an increased tone of the riders muscles has caused a local increase of bone remodelling. It is also conceivable, that bone remodelling rates were locally elevated in the medial corticalis due to local maximum of bending stress in a malacic skeleton. An increased blood flow in these remodelling zones might well have favored the establishment of osteomyelitic foci in the course of septicemia.

Subperiosteal bone formation is kown to occur when blood flow to the skeleton is augmented (Ginzberg, 1959; Mendlowitz and Leslie, 1962). Subperiosteal bone formation of the femoral compacta has been repeatedly described in hyperparathyroid bone disease (Heath and Martin, 1970). In the present case, however, subperiosteal bone formation is probably caused by an inflammatory irritation of the periosteal tissue as usually seen in osteomyelitis (Lauche, 1939).

It is remarkable, that osteomyelitis is uncommon in patients on maintenance hemodialysis although bacteremia and hematogenous infections are rather frequent due to shunt infections or repeated canulation of the arteriovenous fistula. On one hand the discrepancy between the relative frequency of staphylococcal bacteremia and the scarcity of osteomyelitis might be due to the disturbance of immunological mechanisms that have been demonstrated in renal insufficiency. According to Grundmann (1953) a specific state of hyperergy is a possibly prerequisite for the localization of staphylococci in the terminal vessels of bone. On the other hand phagocytosis plays a prominent role in the clearance of staphylococci by the reticulo-endothelial cells of the sinusoids of bone. Phagocytosis induced stimulation of the pentose cycle in leucocytes is impaired in uremia. The scarcity of osteomyelitis in uremic patients undergoing chronic hemodialysis is therefore still more puzzling, because quickly dividing endothelial cells of high turnover bone are unable to phagocytose due to their immaturity (Hobo, 1921; Lennert, 1964).

Since traumatic hematomata were shown to predispose to the development of osteomyelitis, hemorrhagic microfractures or bleeding in microcysts caused by osteitis fibrosa might also have playd a significant role in trapping staphylococci in the present case. This possibility is somewhat supported by the finding of multiple hemosiderotic foci in resorption cavities of the femoral cortical bone (Fig. 3b). However, macroscopically recognizable cysts or brown tumors were not seen. According to Waldvogel *et al.* (1970) it is a matter of speculation, whether the high frequency of involvement of long bones by hematogenous osteomyelitis is due to increased exposure to trauma. Nevertheless, it remains still puzzling how apparently trivial trauma can precede the development of clinical or experimental osteomyelitis. In our observation neither case history nor anatomical findings suggests major trauma as the cause of the osteomyelitis.

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