Paget Bone Disease and Heredity: A Case Report

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Recommended Citation
Agnusdei, Donato; Civitelli, Roberto; Camporeale, Angelo; and Gennari, Carlo (1988) "Paget Bone Disease and Heredity: A Case Report," Henry Ford Hospital Medical Journal : Vol. 36 : No. 3 , 150-152.
Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol36/iss3/7

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Evidence on familial aggregation of Paget disease of bone shows that the trait is controlled by a single dominant gene. Due to the late onset of the disease, the primary biochemical abnormalities leading to the characteristic roentgenographic features are still unknown. We report the case of a 24-year-old woman who had an elevated serum alkaline phosphatase on routine analysis. Family history revealed that her father and paternal grandmother had Paget bone disease. This pattern is compatible with an autosomic dominant inheritance. Complete laboratory workup confirmed high heat labile alkaline phosphatase values, along with high serum osteocalcin and urinary hydroxyproline excretion. Skeletal x-ray and bone scan were negative. The 24-hour body retention of 99mTc-methylenediphosphonate was elevated, suggesting high bone turnover. Dual photon densitometry of distal radius, femoral shaft, and lumbar spine revealed lower than normal bone density at all sites. The existence of a high bone turnover disease and osteopenia in a member of a family with high incidence of Paget disease might represent an abnormality linked to the "Pagetic trait," although an occasional association cannot be ruled out. (Henry Ford Hosp Med J 1988;36:150-2)

Sir James Paget, in his original description of osteitis deformans, wrote in 1889: "I have tried in vain to trace any hereditary tendency to the disease. I have not found it twice in the same family" (1). However, the observations of familial aggregation reported from even before that time are fairly numerous, and the role of heredity in the production of this disease has been stressed repeatedly (2-13). Familial history of the disease has been identified in several instances, with reports indicating that several members of a family in various generations and identical twins may be affected (11,14,15).

There is no agreement regarding the mode of inheritance. In general the data are consistent with the view that the trait for Paget disease is controlled by a simple autosomal Mendelian dominant gene (9,16). However, some authors suggested that it is inherited as a sex-linked recessive or incompletely dominant gene (10,14,17).

Case Report

A 24-year-old white woman (weight 53 kg [116.6 lb], height 164 cm [65.6 in]) was referred to us because she had an elevated serum alkaline phosphatase on routine analysis. Family history revealed that her father, her paternal grandmother, and two brothers of her grandmother were affected by Paget bone disease. Details of the family are depicted in the genealogical diagram shown in Fig 1.

The patient was asymptomatic and did not complain of bone pain. Clinical evaluation was unremarkable. No bowing or deformities of extremities were present. No areas of increased skin temperature were noted. Her calcium intake was calculated at about 800 to 1,000 mg/day. The neurologic examination was negative, and no Trousseau or Chvostek signs were present.

Complete metabolic laboratory workup revealed reduction of total serum calcium with normal values of ionized calcium, normal levels of phosphate, and increased parathyroid hormone circulating levels suggesting a secondary hyperparathyroidism associated with a slight increase in 1,25(OH)2D, serum levels. An elevated alkaline phosphatase was confirmed along with increased hydroxyproline/creatinine ratio excretion, serum osteocalcin, and 24-hour whole-body retention of 99mTc-methylenediphosphonate, suggesting a high turnover bone disease.

An important decrease in urinary calcium/creatinine ratio excretion and severe impairment of intestinal calcium absorption, evaluated by calcium-47 oral test, were also observed. Bone mineral content, measured by dual photon absorptiometry at three different sites—lumbar spine, femoral shaft, and distal radius—showed a reduction of bone mineral below the normal range of normal, age-matched women. Functional and biochemical features are shown in the Table.

A complete skeletal x-ray survey was performed. No bone lesions were observed in the axial skeleton and upper limbs. X-rays of both femurs showed a "lance-like" appearance of distal extremity (Fig 2). Although not diagnostic, this radiographic finding may be suggestive of initial "Pagetic" osteodystrophy.

A bone scan with 99mTc-methylenediphosphonate revealed an increased uptake of the radioactive tracer, especially in the long bones. There was no evidence of localized areas of increased uptake. Whole-body retention was 48%. This picture is compatible with high bone turnover.
Fig 1—Pedigree of four generations.

### Table

**Functional and Biochemical Features**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMC: Lumbar spine (g/cm²)</td>
<td>0.69 (0.85-1.11)</td>
</tr>
<tr>
<td>BMC: Femoral shaft (g/cm²)</td>
<td>1.20 (1.35-1.55)</td>
</tr>
<tr>
<td>BMC: Distal radius (mg/cm²)</td>
<td>307 (411-529)</td>
</tr>
<tr>
<td>Ca²⁺ Intestinal absorption (fx)</td>
<td>0.092 (0.220 ± 0.040)</td>
</tr>
<tr>
<td>24-hour ⁴⁷⁹Tc-MDP WBR (%)</td>
<td>48 (34 ± 7)</td>
</tr>
<tr>
<td>Serum total Ca (mg/dL)</td>
<td>7 (8.6-10.4)</td>
</tr>
<tr>
<td>Serum Ca²⁺ (mEq/L)</td>
<td>2.20 (2-2.30)</td>
</tr>
<tr>
<td>Alkaline phosphatase (UKA)</td>
<td>33.5 (5.14)</td>
</tr>
<tr>
<td>Urinary Ca/Cr (mg/g)</td>
<td>10.8 (35-160)</td>
</tr>
<tr>
<td>Urinary PTH/Cre (mg/g)</td>
<td>82.2 (1-19)</td>
</tr>
<tr>
<td>PTH C-ter (ng/mL)</td>
<td>0.70 (0.0-0.88)</td>
</tr>
<tr>
<td>PTH MM (ng/mL)</td>
<td>0.40 (0.05-0.31)</td>
</tr>
<tr>
<td>Osteocalcin (ng/mL)</td>
<td>14 (2.2-6.6)</td>
</tr>
<tr>
<td>25(OH)D₃ (ng/mL)</td>
<td>71.2 (50-90)</td>
</tr>
<tr>
<td>1,25(OH)₂D₃ (pg/mL)</td>
<td>41.7 (29.4 ± 6.5)</td>
</tr>
</tbody>
</table>

An iliac crest bone biopsy was also performed. Undecalcified 1 micron thick slices were stained with Azur II, methylene blue, which stains the osteoid and leaves the calcified matrix unstained. Histological examination showed several trabeculae almost completely surrounded by a large osteoid seam (Fig 3) and resorption lacunae with active osteoblasts inside. The electron microscopy evaluation showed no evidence of viral inclusions in the nuclei of osteoclasts examined.

### Discussion

Although the clinical findings do not allow a precise diagnosis in this case, the radiologic findings and the family history of Paget disease may be indicative of a disease in the initial phase. The high turnover bone disease might be the consequence of the extremely reduced intestinal calcium absorption with associated hypocalcemia.

Reduced calcium bioavailability may partly explain the mineralization defect which was present in this patient despite normal serum phosphate and slightly elevated 1,25(OH)₂D₃ serum levels. The reasons for impaired intestinal calcium transport and its possible link with the “Pagetic trait” are obscure. Regarding the inheritance of Paget bone disease, further genetic studies are needed to clarify the primary biochemical abnormalities leading to the characteristic roentgenographic features of the disease.

### References