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**Objective** To report a series of patients with Paget's disease of bone that is rarely diagnosed in the Chinese, and to describe their presentations and clinical characteristics.

**Design** A retrospective case series and literature review.

**Setting** A regional public hospital in Hong Kong.

**Patients** Patients with a diagnosis of Paget's disease of bone (or osteitis deformans) documented in the Clinical Management System of the Hospital Authority and being followed up in the medical endocrine clinic of the Pamela Youde Nethersole Eastern Hospital were identified in July 2011. This was performed using the Clinical Data Analysis and Reporting System of the Hospital Authority. Corresponding case notes and radiological imaging data were retrieved and reviewed. Patients with diagnostic X-ray or computed tomography findings of Paget's disease of bone were included in this series. The demographic data, clinical features, and investigation results of the cases were retrieved, recorded, and analysed.

**Results** Seven Chinese patients (5 men and 2 women; mean age, 66 years) diagnosed to have Paget's disease of bone from 2000 to 2010 were identified. All but one were asymptomatic and presented as an incidental finding (isolated raised serum alkaline phosphatase level or abnormal X-ray). The most commonly involved sites were the skull and pelvis. The majority (71%) of the patients had polyostotic disease. During follow-up, there were no disease-related complications, nor was malignant transformation identified. None reported positive family history.

**Conclusion** In this series of seven Chinese patients with Paget's disease, most were asymptomatic and presented with an isolated raised serum alkaline phosphatase level during routine testing. The disease was predominantly found in males and the elderly, and commonly involved the skull and pelvis.

#### New knowledge added by this study

- Paget's disease of bone in this Chinese series is usually diagnosed in elderly males, who are incidentally found to have isolated raised serum alkaline phosphatase levels.
- In this series of patients, the disease was mostly polyostotic, with involvement of the skull and pelvis being the most common.

#### Implications for clinical practice or policy

- Paget's disease of bone should be considered in asymptomatic and elderly males with isolated raised serum alkaline phosphatase levels. Radiological investigations such as skeletal surveys and bone scans are useful for diagnosing and detecting polyostotic involvement.

#### Key words

Alkaline phosphatase; Bone neoplasms;  
Osteitis deformans

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## Introduction

Paget's disease of bone was first described by Sir James Paget as "osteitis deformans" in 1877.<sup>1</sup> It is a chronic progressive metabolic bone disorder, characterised by rapid bone resorption and deposition that leads to a woven pattern of lamellar bone with extensive local vascularity and fibrous tissue in the marrow.<sup>2</sup> The aetiology remains unclear, and there are conflicting claims as to whether slow viruses are involved in its pathogenesis.<sup>3-8</sup> A strong family history in some cases implies a possible genetic or hereditary basis for its development.<sup>9</sup>

The frequency of Paget's disease varies markedly among different ethnic groups and in different geographic areas.<sup>10</sup> Most cases have been reported in Caucasian

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populations, especially of European descent.<sup>10,11</sup> Among individuals age 50 years or more, the reported prevalence in England is 3 to 4%, while in the United States it is approximately 3% in Caucasian individuals older than 55 years.<sup>12</sup> Interestingly, Paget's disease is uncommon in Africa and Asia, and is rarely diagnosed in Chinese.<sup>12,13</sup> The exact reason for this ethnic discrepancy is unknown. Till now, no more than 10 Chinese patients with Paget's disease of bone appear to have been reported in the English literature.<sup>14-18</sup> Owing to such a low prevalence, there is only scanty information about the clinical features of this disease in the Chinese.

## Methods

Patients with a diagnosis of Paget's disease of bone (or osteitis deformans) documented in the Clinical Management System of the Hospital Authority and being followed up in the medical endocrine clinic of the Pamela Youde Nethersole Eastern Hospital were identified in July 2011. This entailed recourse to the Clinical Data Analysis and Reporting System of the Hospital Authority. Relevant case notes, radiological reports, and radiological imaging data (including X-rays, computed tomography [CT], and bone scans) were retrieved. The latter were reviewed by radiologists. For X-rays that had been destroyed due to the storage policy of the Radiology Department, the previously documented radiological findings in the X-ray reports were accepted. Patients with some or most of the following diagnostic radiological findings of Paget's disease of bone were included in the current case series. These were: expansion of bone size, thickened and disorganised trabeculae as well as thickened and expanded bone cortices, osteosclerosis, and bone deformity. Cases lacking the above diagnostic radiological findings were excluded. Bone scans were reviewed by nuclear medicine specialists to confirm the sites of involvement. The case notes of those being included for reporting were reviewed. The demographic data of the patients, the year of presentation, their symptoms and complications on presentation and during follow-up, and their serum alkaline phosphatase levels on presentation and during follow-up were retrieved, recorded, and analysed. The levels of serum albumin, adjusted calcium and phosphate levels on presentation, the radiological and bone scan findings, the treatments received, the side-effects experienced, and any family history of the disease were also retrieved, recorded, and analysed. A literature review was undertaken to identify previous case reports of Paget's disease of bone in Chinese and Caucasian patients. The clinical characteristics of our current patients and those reported previously in the Chinese, as well as data derived from Caucasian epidemiological data were compared.

## 佩吉特氏病（變形性骨炎）華籍患者的 病例系列報告

- 目的** 報告佩吉特氏病（變形性骨炎）華籍患者的病例，並描述其發病及臨床症狀。
- 設計** 病例系列報告及文獻回顧。
- 安排** 香港一所分區公立醫院。
- 患者** 於2011年7月利用醫院管理局臨床資料分析及報告系統，找出在醫院管理局臨床醫療管理系統中，記載現於東區尤德夫人那打素醫院內科部內分泌科門診跟進的佩吉特氏病（變形性骨炎）患者。本研究檢索和審視其病歷紀錄及放射影像數據，把X光片或電腦斷層攝影結果確診為佩吉特氏病的患者列入研究範圍；並將其人口學數據、臨床症狀及檢驗結果作紀錄及分析。
- 結果** 於2000至2010年期間，共有7名華籍患者（分別為5男2女，平均年齡66歲）確診佩吉特氏病。除1名患者外，其餘於確診時均無症狀，他們只是偶然被發現血清鹼性磷酸酶水平上升或有異常的X光片影像。大部份（71%）患者有多發性骨疾病，最經常受影響的部位為顱骨和盆骨。於跟進期內，患者並無任何與此病有關的併發症，亦無轉化惡性的現象。此外，全部患者均無家族病史。
- 結論** 本病例系列報告發現7名患佩吉特氏病的華籍患者中，大多為男性及老年人。大部份於確診時沒有症狀，只是在常規檢查中發現血清鹼性磷酸酶水平上升。此病一般涉及患者的顱骨和盆骨。

## Results

Seven Chinese patients with Paget's disease of bone were identified, and their clinical features are summarised in Table 1. They were diagnosed over a 11-year period from the year 2000 to 2010. Interestingly, half of them were diagnosed in 2009 and 2010, which was probably a random finding, as they were referred from different sources. None of the patients reported a positive family history. Their mean age at diagnosis was 66 years, and five (71%) of them were male. One patient presented with low back pain. The rest were asymptomatic and identified owing to an incidental raised serum alkaline phosphatase level or abnormal X-ray. The serum alkaline phosphatase level at diagnosis ranged from 157 to 716 IU/L, with a mean level of 370 IU/L, which was nearly 3-fold the upper limit of normal (141 IU/L). In all the patients, the diagnosis was also supported by typical X-ray or CT findings (including bony enlargement or expansion with focal cortical thickening and coarsening of bone trabeculae). Only one patient had a bone biopsy to rule out a malignant

TABLE 1. The clinical characteristics and investigation results of the seven patients reported in this series\*

Pa-tient No.	Sex	Age at diagnosis (years)	Presentation and year	Symp-toms	Sites	ALP level (IU/L)	adj Ca and PO <sub>4</sub> level (mmol/L)	X-ray findings	Bone scan	SPECT/CT	Com- plication	Treat- ment	Family history	Sar- coma	Latest ALP level
1	F	75	Raised ALP in routine blood test in 2009	Nil	Skull	275	2.33, 1.23	Y <sup>†</sup>	Y	Y	Nil	Yes	Nil	Nil	86
2	M	59	KUB findings in 2001	Nil	Right femur	238	2.47, 0.85	Y <sup>‡</sup>	Y	ND	Nil	Yes	Nil	Nil	47
3	M	73	Raised ALP in routine blood test in 2009	Nil	Skull, pelvis	573	2.28, 1.16	N	Y	Y <sup>**</sup>	Nil	Yes	Nil	Nil	150
4	M	54	Raised ALP in routine blood test in 2010	Nil	Right femur, pelvis	157	2.39, -	Y <sup>§</sup>	Y	Y	Nil	Yes	Nil	Nil	114
5	M	69	Raised ALP in routine blood test in 2000	Nil	Skull, left femur, L3 vertebra	716	2.51, 1.06	Y <sup>†</sup>	ND	ND	Nil	Yes	Nil	Nil	144
6	M	53	Raised ALP in routine blood test in 2010	Nil	Skull, humerus, T12-L1 vertebrae, pelvis	165	2.3, 1.18	Y <sup>¶</sup>	Y	Y	Nil	No	Nil	Nil	162
7	F	76	Abnormal X-ray finding for back pain in 2003	Back pain	Pelvis, T8 vertebra	464	2.43, 1.41	Y <sup>#</sup>	Y	ND	Nil	Yes	Nil	Nil	269

\* ALP denotes serum alkaline phosphatase (reference range, 53-141 IU/L); KUB kidney, ureter and bladder; adj Ca adjusted calcium (Ca + 0.02 x [40 - serum albumin level (g/L)]); PO<sub>4</sub>, phosphate; SPECT single-photon emission computed tomography; CT computed tomography; ND not done; Y positive findings; and N negative findings  
<sup>†</sup> Mild sclerotic changes and thickening of occipital bone  
<sup>‡</sup> Coarsening of trabeculae at right femoral neck and intertrochanteric region, cortical thickening at proximal and mid femur (Fig 1a)  
<sup>§</sup> Sclerosis in right acetabulum and right pubic bone; coarsening of trabeculae at right pubic bone (Fig 1b)  
<sup>†</sup> Bony expansion, focal cortical thickening and coarsening of trabeculae at left proximal femur and medial shaft; multiple sclerotic foci over skull, bony expansion and thickening of occipital bone, sclerosis changes of sphenoid and petrous bone; minimal expansion with coarsening of vertical trabeculae of L3 vertebra  
<sup>¶</sup> Thickening of left iliopectineal line with trabecular coarsening and bone expansion of left ilium  
<sup>#</sup> Thickening of right iliopectineal line with sclerosis, bony expansion and coarsening of trabeculae in right hemipelvis; coarsening of trabeculae in T8 vertebra  
<sup>\*\*</sup> Bony expansion, mixed osteolytic and sclerotic changes in skull vault

lesion. The positive imaging findings of each patient are described in Table 1. All but one patient had bone scans to search for polyostotic involvement. In our series, the bones involved included: the skull (n=4), the pelvis (n=4), thoracic or lumbar vertebrae (n=4), the femur (n=3), and the humerus (n=1). None of the patients with skull involvement had radiological features of osteoporosis circumscripta, but the majority (71%) had polyostotic features. All except one of the patients received intermittent intravenous infusions of pamidronate or zoledronic acid that were well tolerated, though one of them developed severe flu-like symptoms following pamidronate. These patients had been followed up between 1 and 11 years since diagnosis, and according to their latest blood tests, the serum alkaline phosphate level had normalised in three of them. Nor was malignant transformation or any other disease-related complication detected during the follow-up of these seven patients. One patient subsequently developed bilateral sensorineural hearing loss, but CT evaluation revealed no abnormality of the internal auditory canal or temporal bone.

## Discussion

### Diagnosis and management of cases in this series

It is well recognised from epidemiology studies that

Paget's disease of bone is very rare in the Chinese.<sup>19,20</sup> To our knowledge, the case series we are describing herein is the largest reported so far in the Chinese. By contrast, this disease is quite common in Caucasians of European descent, especially from the United Kingdom. The exact reason for such ethnic discrepancy is not well understood, though variable genetic susceptibility in different ethnic groups has been postulated.

Interestingly, many cases in this series were first suspected based on bone scan findings rather than X-rays. As Paget's disease of bone is so rare in this locality, it is likely that the disease is seldom considered early in the differential diagnosis of an isolated raised serum alkaline phosphatase level. Thus, most of the cases in this series were initially being worked up for biliary disease or occult bone metastasis. Heat stability is sometimes useful to distinguish bone and liver isoenzymes of alkaline phosphatase. The typical clinical features of Paget's disease of bone include: focal bone deformity or pain, fracture, neurological symptoms, and rarely malignant transformation. In this series, however, six out of seven of the patients were asymptomatic on presentation, at which time they either had an incidental finding of an isolated raised serum alkaline phosphatase level or an abnormal X-ray. This has also been observed in Caucasians, among whom up to 95%

of those affected are asymptomatic at presentation. In this series, the final diagnosis depended on X-rays, single-photon emission computed tomography/CT or dedicated plain CT of affected sites with marked tracer uptake in bone scans. It is known that there are three phases of pagetic bone activity with different corresponding X-ray features, as follows: (1) the initial hyperactive bone resorption phase has an osteolytic appearance in radiographs; (2) the mixed phase manifests co-existing bone osteolysis and sclerosis, in which activities of osteoblasts gradually prevail, consistent with markedly increased serum alkaline phosphatase levels; and (3) the inactive phase, which yields osteosclerotic lesions in radiographs.<sup>21,22</sup> Diagnostic radiological features of Paget's disease of bone include: bony expansion with cortical thickening, disorganised and coarsening of trabeculae, and osteosclerosis (Fig 1a). There may also be bone deformity, and osteoporosis circumscripta (a skullcap-shaped area of resorption of the skull) that is pathognomonic of the disease. However, such features were not found in our case series. On the other hand, several patients with pelvic bone involvement had thickening and sclerosis of the iliopectineal line in the ilium (Fig 1b), which is also a typical feature. Notably, X-rays may not reveal abnormalities at sites of involvement detected by bone scans, as illustrated by some of our cases, whilst CT is more sensitive and can be used to detect abnormalities in bone structures.

Bone biopsy is rarely used to diagnose the disease in the presence of typical radiological findings. It was performed in one of our patients to exclude osteosclerotic bone metastases. It is

also indicated when malignant transformation to osteosarcoma is suspected in the presence of Paget's disease of bone. Typically, the histology shows thickened bone trabeculae with irregular cement lines, demarcating randomly oriented lamellar bone, in a mosaic pattern. The reticulin stain can be used to highlight the disorganisation of lamellar bone, and the presence of fine fibrosis in the marrow.

In asymptomatic Paget's disease of bone, the use of anti-resorptive therapy is debated. Outcome studies in the prevention of disease complications by these agents are scanty, and their effectiveness in this respect remains unknown. Although the risk of developing complications from the disease in asymptomatic individuals is generally considered very low, some clinicians advocate the use of bisphosphonates when weight-bearing bones near major joints or nerve roots are affected, and so long as these agents are well tolerated. They are also used to treat patients with concomitant osteoporosis. In our series, five out of six asymptomatic cases received intermittent infusions of bisphosphonates with the aim of reducing disease progression and avoiding disease-related complications. Subsequently, one patient started regular oral alendronate after being diagnosed with osteoporosis. Her serum alkaline phosphatase level entered the low normal range. Currently, three of our cases are in remission after treatment, as judged by normalisation of their latest serum alkaline phosphatase levels (Table 1). However, bisphosphonates can have rare but debilitating side-effects, namely: osteonecrosis of the jaw in certain high-risk groups, and possibly atypical femoral fractures. Hence, the risks and benefits of treating

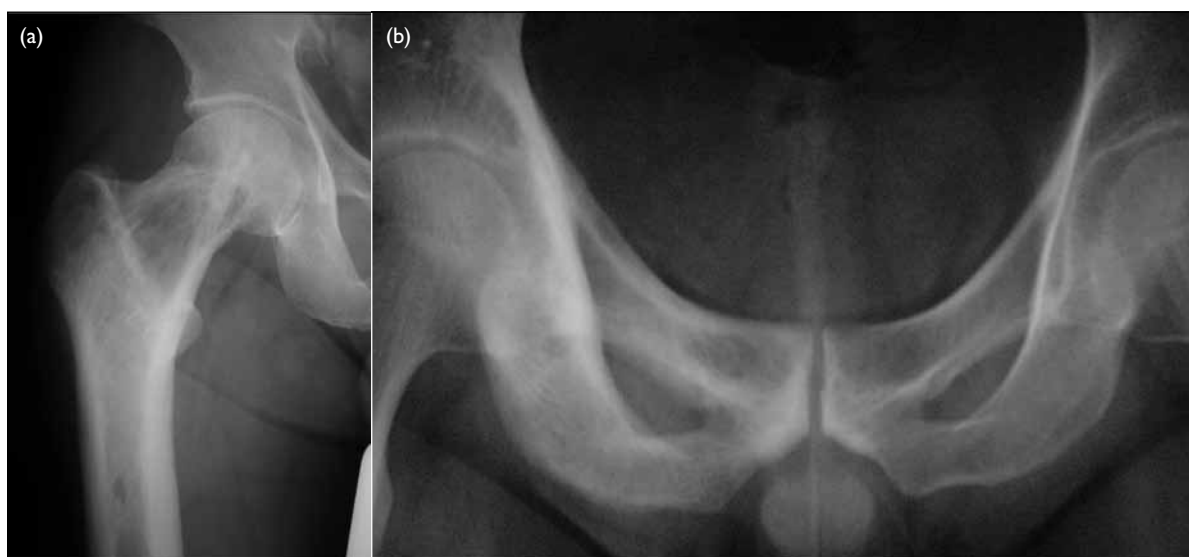


FIG 1. (a) The X-ray of right femur of patient 2 showing typical features of Paget's disease of bone. There is trabeculation coarsening and bony enlargement at the right femoral neck and intertrochanteric region. The bone cortex is thickened at the proximal right femur. (b) The X-ray pelvis of patient 4 showing diagnostic radiological features of Paget's disease of bone. There is thickening of the right iliopectineal line, together with bony expansion, cortical thickening and trabecular coarsening involving the right superior and inferior pubic ramus, as well as the right acetabulum

asymptomatic patients should be balanced carefully in every individual.

### Comparison of patient clinical characteristics in this and other Chinese series

Wang et al<sup>23</sup> reported a case of Paget's disease of bone in 2005 and reviewed another eight Chinese cases reported in the literature. The clinical features in our seven patients and the nine that were previously reported<sup>14-18,23</sup> are shown in Table 2. Owing to the small sample sizes as well as selection and reporting biases, significance testing of differences between the groups may not be valid and hence was not performed. In both groups, males were more commonly affected, the mean age at diagnosis was around 65 years, and the three most commonly involved sites were the skull, pelvis, and spine. Polyostotic features were evident in 71% of our cases and 56% in the other group. Moreover, the majority of our subjects were asymptomatic on presentation, whilst in the other series they were mostly symptomatic.

Till now, we are not aware of any instance of malignant transformation in a Chinese patient. This very rare complication occurs in less than 1% of affected patients, but may be even rarer.<sup>24</sup> As Paget's disease of bone itself is very rare in the Chinese, it is hardly surprising that this has not been documented to date in Chinese patients. Lifelong follow-up of a larger cohort of cases appears necessary to determine whether malignant transformation ensues in Chinese patients. The same caveat applies to having a positive family history,<sup>25</sup> having bone-deforming disease, and diagnosis at an early age.<sup>26</sup>

### Comparison of clinical characteristics in the Chinese and in Caucasians

Table 3<sup>14-18,21,23,27-35</sup> shows the clinical characteristics of Paget's disease of bone in Chinese patients (current series and previously reported cases combined) and in Caucasian patients reported in the literature. The series of Chinese patients was small compared to the Caucasian group, indicating a degree of selection bias, rendering statistically significant testing

TABLE 2. Comparison of the clinical features of current series with other Chinese cases reported in literature<sup>14-18,23</sup>

Clinical feature	Current series (7 cases)	Previously reported in literature (9 cases) <sup>14-18,23</sup>
Mean (range) age (years)	65.5 (53-76)	64.9 (44-91)
Male-to-female ratio	5:2	5:4
Sites of involvement	Skull (57%), pelvis* (57%), lumbar or thoracic spine (43%), femur (43%), humerus (14%)	Skull (44%), pelvis (44%), lumbar or thoracic spine (44%), tibia (33%), jaw (22%), clavicle (11%), rib (11%), femur (11%)
Monostotic	29% (2/7)	44% (4/9)
Asymptomatic cases	86% (6/7)	22% (2/9)
Symptoms and signs in symptomatic patients	Bone pain	Bone pain, deformity, neurological symptoms
Familial cases	No	No
Malignant transformation	No	No

\* Pelvis includes sacrum, ilium, pubic and ischium bone

TABLE 3. Comparison of clinical features of Paget's disease of bone in Chinese and Caucasians<sup>14-18,21,23,27-35</sup>

Clinical feature	Chinese series (7* + 9 <sup>14-18,23</sup> cases)	Western series
Mean (range) age (years)	65.2 (44-91)	>40 <sup>28</sup>
Male-to-female ratio	5:3	1:1 <sup>29</sup> , 3:1 <sup>30</sup>
Sites of involvement	Skull (50%), pelvis (50%), spine (44%), femur (25%), tibia (19%), humerus (6%), jaw (13%), rib (6%), clavicle (6%)	Pelvis (67%), <sup>27</sup> spine (34%), <sup>27</sup> femur (32%), <sup>27</sup> tibia (25%), <sup>27</sup> skull (23%), <sup>27</sup> jaw (17%), <sup>28</sup> humerus (11%), <sup>27</sup> rib (7%), <sup>27</sup> clavicle (3.8%) <sup>29</sup>
Monostotic	37.5% (6/16)	17-31% <sup>21</sup>
Asymptomatic cases	50% (8/16)	67%, <sup>31</sup> 80%, <sup>21</sup> 95% <sup>30,32</sup>
Symptoms and signs in symptomatic patients on presentation	Bone pain, deformity, neurological symptoms	Bone pain, deformity, neurological symptoms
Familial cases	No	Yes, 14% of cases <sup>33</sup>
Malignant transformation	No	Yes <sup>34,35</sup>

\* 7 Cases in this report



between the groups unreliable. In both ethnic groups, there was a male predominance, the age at diagnosis was usually more than 40 years, and most cases were polyostotic. The pattern and prevalence of involved sites in the two groups seemed to differ (Fig 2). The skull was the most common site affected in the Chinese (about 50%), in contrast to only about 20% in Caucasians. The pelvis was affected in two thirds of Caucasian cases, but only half of the Chinese cases. Vertebral involvement was present in more than one third of the cases in both ethnic groups. The femur was more commonly affected than the tibia in both the Chinese and in Caucasians; the former was involved in a quarter of the Chinese and one third of the Caucasian cases. Asymptomatic cases constitute the majority among Caucasians, but only half of all the reported Chinese cases, and just around one fifth of the cases previously reported in the 1990s. In that sense, as in the Caucasians the majority (86%) of our series were asymptomatic when diagnosed. Reasons for such secular changes in symptoms at presentation in the Chinese series remain unclear. Conceivably, increased accessibility to X-ray examination may have led to identification of more asymptomatic cases than in the past, or could simply be a random finding.

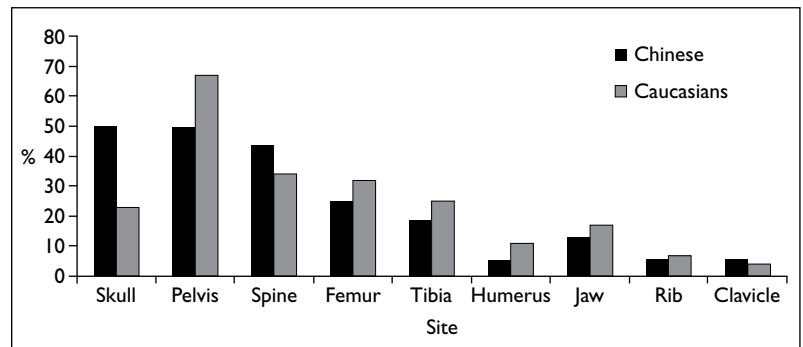


FIG 2. Comparison of the percentage of patients at different sites of involvement in Chinese and Caucasians

### Conclusion

Paget's disease of bone is very rare in Chinese. This series reported seven such patients with the disease. Most were diagnosed while asymptomatic, and presented with isolated increased serum alkaline phosphatase levels from routine blood tests. The mean age at diagnosis was about 65 years and there was a male predominance. The majority of cases were polyostotic, with the skull and the pelvis being the most commonly affected. Neither familial cases nor malignant transformation were identified in this series.

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