

# Osteoporosis with lymphoid nodules and hematopoietic marrow hyperplasia

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Received on October 6, 1998; accepted in revised form on February 1, 1999.

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## Key words:

Osteoporosis, lymphoid nodules.

## ABSTRACT

### Objective

In 1983 Vigorita reported 3 cases of osteoporosis associated with intra-medullary lymphoid nodules. We present 8 patients with osteoporosis and lymphoid nodules (LN) in whom we studied the clinical, biological and histological features and the course of the disease.

### Methods

Three men (mean age 52 yrs., range 43 - 68 yrs.) and 5 women (mean age 60 yrs., 49 - 66 yrs.), 6 of them with osteoporosis with fracture and 2 with osteoporosis on bone densitometry (T score < -2.5 SD) were enrolled in this study. The following parameters were studied: immunobinding with IG determination, phosphorus and calcium levels, PTH, 25 and 1-25 OH D3, osteocalcin, urinary deoxypyridinoline, histomorphometry, tests for autoanti-bodies, HIV, HTLV, EBV and CMV serology. The results were compared with those of 20 patients with osteoporosis but without LN. Five patients underwent a second BMB a mean of 2 years after the first.

### Results

Five patients had asthenia, 4 had joint pain and 3 had hyperlymphocytosis. Immunologic and virologic investigations were negative in all cases. Bone marrow was hypercellular ( $59.9 \pm 5.3$  vs  $40.1 \pm 13\%$ ,  $p: 0.001$ ). At the second BMB, LN were absent but bone marrow was still hypercellular. In all cases, no cause of demineralization was found and osteoporosis progressed rapidly (an average of 3 vertebral compression fractures in three months, with increased resorption ( $ES\ 6.5 \pm 1.6$  vs  $3 \pm 1.2$ ,  $p: 0.05$ ) with decreased calcification rate ( $CR\ 0.62 \pm 0.07$  vs  $0.79 \pm 0.1$ ,  $p: 0.04$ ).

### Conclusion.

Some interesting questions are raised by this study. Did an undiscovered viral infection cause the asthenia and joint pain via cytokines or PTHrp in our patients, and can activated lymphocytes perhaps modify bone remodeling?

## Introduction

In 1983 Vigorita *et al.* (1) reported three patients who had lymphoid nodules, bone marrow hyperplasia and osteoporosis. Since that publication, the pathophysiological mechanisms which regulate bone remodeling have been partially elucidated and several works have demonstrated multiple interactions between lymphocytes, macrophages and bone cells via cytokines (2, 3).

We report eight new cases of osteoporosis associated with intramedullary lymphoid nodules and bone marrow hyperplasia and explore the possible links between bone mineral loss and lymphoid nodules.

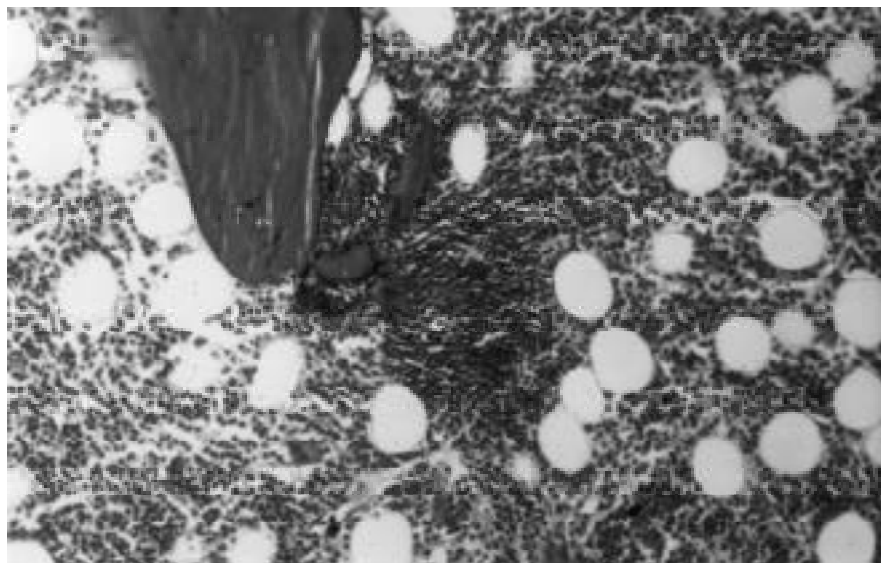
## Patients and methods

Since 1984 we have been carrying out bone biopsies with histomorphometric study for osteoporosis in the rheumatology department of our institution. During this period we have found lymphoid nodules in 8 of 420 biopsies done. The patients concerned were 3 men, mean age 52 years (range 43 - 68 years) and 5 women, mean age 60 years (range 49 - 66 years). The records of 3 patients were reviewed retrospectively; those of 5 patients were re-examined and a second bone biopsy and further complementary investigations were carried out.

### Methods

All patients had osteoporosis with fracture: the presence of at least one compressed vertebra, defined as a > 25% reduction in the anterior or middle vertebral height after minimal trauma (4) or a T score < 2.5 SD at bone densitometry (5). Lymphoid nodules were defined according to Rylwin (6) (Fig. 1).

All patients had the following tests done: ESR, C-reactive protein (CRP), protein electrophoresis, immunobinding of the blood and urine, phosphorus and calcium tests, determination of 25(OH)D3, 1,25(OH)D3, intact PTH, osteocalcin and urinary deoxypyridinoline (Pyrilinks®). The patients underwent transiliac bone biopsy: quantitative bone histomorphometry was carried out on cancellous bone using a semi-automatic system and the measurements were expressed according to the recommendations of the American Society for Bone and Mineral Re-



**Fig. 1.** Bone marrow biopsy (patient 6); taken from the iliac crest of patient no. 6, showing a lymphoid nodule (Goldner stain, magnification  $\times 50$ ).

search (7). Bone marrow cellularity (the percentage of the surface occupied by hematopoietic cells) and the percentage of the surface occupied by adipocytes were determined using an integrated eyepiece.

Five patients had a second BMB with study of the marrow, lymphocyte immunolabeling and histomorphometry done a mean of 2 years after the first biopsy (range 1-3 yrs.). The following tests were also carried out in these patients: search for rheumatoid factor, antinuclear antibodies, anti-granulocyte cytoplasm antibodies, study of serum lymphocyte subpopulations, search for antibodies to cytomegalovirus and Epstein-Barr virus, HIV and HTLV1. X-ray absorptiometry (DEXA) (DPXL Lunar) was done at the times of the first and second bone biopsy. The parameters of these patients were compared with those of 20 age- and sex-matched patients with osteoporosis but without lymphoid nodules.

#### Statistical analysis

The parameters of the patients at the time of the first BMB and the parameters of the control subjects with osteoporosis but without lymphoid nodules were compared using Wilcoxon's test for small matched series.

#### Results

Six of the 8 patients had osteoporosis with fracture, and the 2 others had osteo-

porosis confirmed by bone densitometry. Of the six patients with fractures, all had vertebral compression: one patient experienced 6 vertebral compression fractures in 4 months; three patients had 3 fractures in 2 months; one patient had 3 in 3 months; and the last had 3 in 7 months. Their osteoporosis was thus progressing rapidly. In patient no. 7, who had undergone gastrectomy and who had a reduced dietary calcium intake and low vitamin D levels, the osteoporosis could be explained. In the other cases, a search for the possible cause of the bone mineral loss was negative.

The mean calciuria in the 8 patients with lymphoid nodules was higher than that of the patients with osteoporosis without lymphoid nodules (Table I). The 8 patients also had, in comparison with the disease controls, a non-significant increase of urinary deoxypyridinoline and osteocalcin. Resorption surfaces were significantly increased ( $6.5 \pm 1.6$  vs  $3.0 \pm 1.2$ ,  $p = 0.05$ , as was the osteoid volume ( $6.4 \pm 4.7$  vs  $2.5 \pm 1.3$ ,  $p = 0.05$ ), whereas the mineralization rate was lower ( $0.62 \pm 0.07$  vs  $0.79 \pm 0.10$ ,  $p = 0.04$ ).

Five of the 8 patients had asthenia for a mean of 6 months duration before the onset of signs of osteoporosis. Three patients had lost weight. One patient had low grade fever. Four patients had arthralgia of a mean duration of one year. The search for autoantibodies was nega-

tive in all patients. In all cases, the serum immunobinding of urine and determination of the immunoglobulin molecular weight was normal, viral serology (HIV, EBV, CMV, HTLV1) was negative or showed residual levels of IgG, and the lymphocyte subpopulations showed homogeneous distribution of B and T lymphocytes.

All patients had lymphoid nodules and bone marrow hyperplasia which was abnormal for their age. The surface occupied by hematopoietic cells was  $59.9 \pm 5.3\%$  vs  $40.1 \pm 13\%$  for the subjects with osteoporosis without lymphoid nodules ( $p = 0.04$ ). At the second biopsy, which was carried out in 5 of the 8 patients, lymphoid nodules were no longer found but hyperplasia was still present.

The histological appearance was that of reactionary marrow, as may be seen in the chronic inflammatory syndromes, but without tumor infiltration or any suggestion of a blood disorder. Immunolabeling showed no monoclonal lymphoplasmacyte proliferation and the distribution of B and T lymphocytes was normal.

Four of the 5 patients received cyclical etidronate and calcium, and one woman underwent replacement estrogen therapy. After 2 years of follow-up no new vertebral or appendicular fracture had occurred. However, in 2 patients the bone mineral density decreased after two years: by -1% at the spine and by -1.8% at the femoral neck in one patient; and by -2.6% at the spine, remaining unchanged at the femoral neck, in the other.

After a mean of 2 years follow-up, no signs suggesting a blood or autoimmune disorder were found on clinical examination. Three of 5 patients were still asthenic and 2 still had arthralgias without radiographic signs. Weight loss and fever were no longer present.

#### Discussion

Benign lymphoid nodules (BLN) have occasionally been reported in association with osteoporosis. These nodules can measure from 0.08 to 1.2 mm, are round to oval, and are often sharply circumscribed with serrated edges created by an extension of the lymphocytes into the spaces between fat cells (6). The reported incidence of BLN has varied in different studies: 1% for Rywlin (6), and 8%

**Table I.** Biological, phosphorus and calcium, hormonal and histomorphometric parameters of the patients with osteoporosis with lymphoid nodules at the first (B1) and second bone biopsies (B2), compared with those who had osteoporosis without lymphoid nodules.

	Patients B1	Patients B2	Osteoporosis	p (Anova)
Age (years)	54 ± 10	56 ± 10	55 ± 7	0.2
Postmenopausal years	3 ± 1	5 ± 1	3.5 ± 0.5	0.8
Weight (kg)	64 ± 10	66 ± 9	62 ± 11	0.7
Height (cm)	161 ± 7	161 ± 7	159 ± 8	0.75
ESR (mm)	10 ± 8.3	6.8 ± 5	2.5 ± 2	0.09
CRP (mg/l)	6.2 ± 7.8	2 ± 1.2	2.5 ± 1	0.04*
Lymphocytes/mm <sup>3</sup>	2374 ± 674	2120 ± 1377	1850 ± 730	0.4
Marrow hyperplasia (%)	59.9 ± 5.3	53.4 ± 12.8	40.3 ± 10	0.04*
Ca (mmol/l)	2.3 ± 0.1	2.3 ± 0.1	2.31 ± 0.08	0.85
Calciuria (mmol/24 hr)	6 ± 1.8	4.3 ± 2.6	3.7 ± 1	0.2
Ca/Cr	0.23 ± 0.11	0.16 ± 0.05	0.12 ± 0.04	0.04*
BGP (ng/ml)	10.1 ± 3.1	8.8 ± 3.2	7.3 ± 2.1	0.4
Pyrlinks (nmol/mmol cr)	6.2 ± 3	5.4 ± 2.5	4.1 ± 2	0.2
25(OH)D3 (ng/ml)	33 ± 22	43 ± 12	27 ± 12	0.5
PTH	30 ± 11	28 ± 13	36 ± 8	0.5
T-score (L2 - L4)	- 3.1±0.3	-3 ± 0.2	-2.9±0.4	0.8
Trab bone vol. (%)	13.7 ± 2.8	14.2 ± 2.5	12.4 ± 2.8	0.6
Eroded surface (%)	6.5 ± 1.6	4.7 ± 2.2	3.1 ± 1	0.05*
Osteoid surface (%)	22.8 ± 15	17.7 ± 8	15.8±4	0.3
Osteoid volume (%)	6.4 ± 4.7	5.1 ± 3.9	2.3 ± 1.2	0.05*
Calc. rate (µ/day)	0.62 ± 0.07	nd	0.77 ± 0.08	0.04*

\*Significant p value, nd: not done.

of 7080 biopsies for Bartl (8). BLN occur more frequently in older patients. Their clinical significance remains unknown: many researchers consider them to be a normal finding, but Faulkner (9) showed that some patients with BLN were later diagnosed as having lymphoproliferative disease.

The association between BLN and osteoporosis could be a coincidence, but certain characteristic peculiarities of the osteoporosis in our patients and those of Vigorita (1) led us to search for a link between BLN and bone mineral loss. No specific etiology or risk factor could be found in 7 of our 8 patients, who comprised both men (n = 3) and pre-menopausal (n = 1) or recently menopausal women (n = 4). The osteoporosis progressed rapidly; in six patients several vertebral fractures occurred within a few months. Their osteoporosis was marked by increased resorption; osteoid parameters were also increased but paradoxically the mineralization rate was low, whereas 7 of the 8 patients had no biological markers of osteomalacia and

25(OH)D3, 1,25di-(OH)D3 and parathyroid hormone levels were normal. Like Vigorita, we observed increased bone resorption and a decreased calcification rate.

In 5 of our 8 patients, two years of follow-up allowed us to exclude an autoimmune disorder or a lymphoproliferative disease. A lymphocytotropic virus could lead to the formation of lymphoid nodules and to mild circulating lymphocytosis. Our virological investigations were negative but serology was carried out in only 5 patients and our sampling was not exhaustive. Numerous viruses are still unknown and others, such as HHV8 which was recently found in myeloma stromal cells (10), are only revealed by PCR techniques in hematopoietic marrow. The Epstein-Barr virus has been implicated in certain polyclonal B lymphocyte disorders (11). These activated lymphocytes also could then stimulate bone resorption: parathyroid hormone-related peptide (PTHrp), which can stimulate bone resorption, has been found in lymph nodes (11). In pa-

tients with HIV, 20% of the lymphocytes are marked for PTHrp and are thus probably capable of synthesizing far larger quantities than the lymphocytes of healthy subjects (12).

Stock speculates that lymphocytes could be involved in the pathophysiology of demineralizing bone disorders, in particular in chronic inflammatory syndromes, via lymphokine secretion. Certain activated lymphocytes inhibit the production of osteocalcin by osteoblasts stimulated by 1,25di(OH)D3 (13). The increased resorption observed after menopause probably results from an indirect mechanism via the increase, secondary to the estrogen deficit, of hyper-resorptive cytokines (IL1, IL6, TNF alpha) (14).

It is also known that IL6 increases the number of granulocyte precursors and the level of neutrophils in the peripheral circulation in mice. The increase in granulocyte and monocyte precursors is correlated with the increase in the number of osteoclasts and in resorption surfaces. This cytokine thus acts on bone cells and on hematopoiesis (15). Other cytokines are also involved both in bone remodeling and in hematopoiesis: macrophage colony stimulating factor (MCSF) and granulocyte colony stimulating factor (GCSF) can be synthesized by osteoblastic lines and stimulate both bone resorption and the production of macrophages and granulocytic cells.

The osteoporosis in our patients was of a particular nature: rapidly progressive and occurring in men or in premenopausal or recently menopausal women, it was associated with increased resorption and a decreased calcification rate. The association of this osteoporosis with lymphoid nodules and bone marrow hyperplasia raises a number of questions. Could such patients be suffering from a lymphocytotropic virus, responsible for the asthenia and arthralgia which affected the majority in our series? Could activated lymphocytes, through the action of cytokines or PTH-rp, modify bone remodeling? These issues definitely merit further investigation.

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