Case Report

Femoral fracture and iatrogenic hyperthyroidism in spinal cord injury

E Valayer-Chaleat, P Calmels, P Giraux and I Fayolle-Minon

Service de Médecine Physique et Réadaptation, Hôpital Bellevue - CHU de Saint-Etienne, F. 420055 Saint-Etienne Cedex 2, France

Analysis of the clinical case of a male aged 30 years, presenting with T6 complete paraplegia in 1991, demonstrated the existence of aggravating factors for disuse osteoporosis of spinal cord injury, possibly leading to bone density values below the fracture threshold with the risk of spontaneous fractures. This patient was admitted to hospital for multiple pressure sores requiring prolonged local dressings before and after plastic surgery performed in July 1995. In January 1996, following exercise, he developed a fracture of the femoral diaphysis with a cystic demineralized appearance of the bone. The etiologic work-up demonstrated hyperthyroidism due to iatrogenic iodine overload secondary to Betadine®. A review of the literature revealed numerous cases of thyroid dysfunction secondary to iatrogenic iodine saturation. This case justifies regular surveillance of thyroid function tests during prolonged treatment with Betadine® and identification of patients with a clinical predisposition.

Keywords: fracture; pressure sores; iodine overload

Introduction

Disuse osteoporosis is the most frequently observed bone metabolism disorders in spinal cord injury (88% of subjects according to Chantaine)¹ and different factors as age, sex, level of the lesion, spasticity, verticalization have been analyzed.^{1–7} According to Minaire,⁶ disuse osteoporosis is related to local vascular changes and loss of bone stimulation and insufficient mechanical stimulation. One of the clinical manifestations of osteoporosis is spontaneous fracture^{2,4} but with a moderate incidence: 4–6%.^{8–11} As these fractures are associated with increased morbidity and complications,¹² their prevention is essential.

Case report

Mr. JE, 30 years old, presented with post-traumatic T6 complete paraplegia in 1991. He was treated by osteosynthesis of the spine, followed by management in a rehabilitation unit. Rehabilitation enabled him to regain an autonomous life at home. In October 1994, he presented with multiple sacral, trochanteric and bilateral malleolar pressure sores, due to negligence, requiring prolonged local dressings initially administered on an outpatient basis. However, in view of the unfavorable course, he was admitted to hospital for local dressings and reconstructive plastic surgery in July 1995. Severe septic complications, particularly involving bone, considerably delayed healing. Resec-

tion of the right femoral neck was necessary with resumption of local Betadine® dressings and prolonged bed rest.

In January 1996, during an exercise, the patient felt a crack in the left thigh. He subsequently experienced general malaise. X-rays demonstrated a fracture of the left femoral diaphysis, with a demineralized appearance and bone cysts (Figure 1). He was treated by an endomedullar nail. The bone was described by the surgeon as being friable but biopsy was not carried out. For several weeks, this patient also presented general manifestations with weight loss, emaciation of the face, asthenia, tachycardia, excessive sweating, gastrointestinal manifestations such as frequent stools and moderate jaundice, associated with psychoaffective instability and relational difficulties.

Laboratory results revealed the features of hyperthyroidism and elevated alkaline phosphatase (154), decreased cholesterol (2.9 mmol/L–4.4 < N < 5.3), normal serum calcium, but masked by hypoalbuminaemia of 30 g/L, increased urinary calcium (7.82 mmol/24 h–1.8 < N < 7), normal urinary and blood phosphorus balance, raised urinary hydroxyproline (619–160 < N < 290), moderately elevated blood glucose (6.9 mmol/L), decreased TSH (< 0.05 mIU/L–0.2 < N < 4.5), T3 at the upper limit of normal, and elevated T4 (28.4 mmol/L–11.5 < N < 23).

Bone mineral densitometry demonstrated osteopenia (T score = –1.57) of the vertebrae, (not performed in the femur because of the osteosynthesis on

Figure 1 The illustrative X-ray shows femoral fracture and osteoporosis with some bone cyst

the left side and the resection of the femoral neck in the right side).

Radioactive iodine thyroid scan showed a thyroid gland of normal size and very low uptake of radioactive tracer, suggesting iodine overload confirmed by 24-h urinary iodine assay ($3019 - N < 590$) and serum iodine levels ($1528 - 315 < N < 630$).

This iodine overload was iatrogenic reported to dressing of the pressure sores with Betadine® for several months. This hyperthyroidism with thyrotoxic bone disease was considered as aggravating the disuse osteoporosis.

The treatment consisted of Neomercazol 30 mg, from February 15 to October 1996, with a significant resolution of the laboratory tests after 4 months (TSH $1.8 - 0.25 < N < 5$; T4 $10.3 - 8.4 < N < 22$ in May) and a normalization in September. All the clinical symptoms regressed, and the subject was discharged at the end of March. Sequential treatment for osteoporosis with Diphosphonats, Calcium, Vitamin D was carried out.

Discussion

The commonest causes of iodine overload are pharmacological, with radiological contrast agents,

iodinated drugs, iodide-containing drugs (as Betadine®) and certain bronchodilators or antispasmodics. Secondary hyperthyroidism may be observed in two situations. Iodine-induced hyperthyroidism may occur in the context of a pathological thyroid: this is the commonest, with a female predominance, with a long-standing, more or less nodular and autonomous goiter. There are no means of prevention, apart from avoiding prescription of slowly eliminated iodinated products. Iodine-induced hyperthyroidism can also occur in the presence of a normal thyroid gland: this situation has a male predominance (sex ratio: 1/6). Amiodarone is the agent responsible in the majority of cases (1–5% of all cases of hyperthyroidism).¹³

Hyperthyroidism starts during the months following excess iodine intake, sometimes very early (several days) or very late (several years) after onset of the overload. The patient presents with weight loss, asthenia, arrhythmia or angina, absence of ophthalmoplegia, and varying degrees of thyrotoxicosis.¹⁴

The diagnosis is established on the basis of the clinical interview (history of iodine use), clinical examination and laboratory signs with a decreased ultrasensitive TSH, increased T3 and T4, normal or increased serum thyroglobulin, normal or increased antithyroid antibodies.^{14,15} Iodine overload is evaluated by total blood iodine and by the 24-h iodide excretion, which reflects even moderate iodine overload. Radioactive iodine thyroid scan is either white, in favor of iodine-induced hyperthyroidism with an apparently normal thyroid, or contrasted, in favor of Graves' disease incidentally associated with iodine overload, or heterogeneous and slightly contrasted, in favor of hyperthyroidism either induced or facilitated by iodine in a multinodular goiter.

The prognosis of iodine-induced hyperthyroidism is usually good.^{13,16} It has a slowly favorable course in response to Neomercazole® antithyroid treatment in the context of a pathological thyroid. Improvement of iatrogenic hyperthyroidism is very variable in the presence of a normal thyroid gland (not correlated with the severity of hyperthyroidism or the rapidity of elimination of the iodine overload). Neomercazole® is not very effective, PTU (propylthiouracil) is inconsistently effective and potassium perchlorate is sometimes useful.¹³

Hyperthyroidism is rarely associated with bone manifestations (less than 10% of cases on the basis of clinical and radiological criteria).^{15,16} But systematic analysis of calcium-phosphorus metabolism or bone mass determination shows that bone metabolism is always altered.^{15–20} The bone mass is decreased, due to a reduction of bone remodeling in favor of osteoclastic resorption.^{16,20,21} The clinical and radiological features resemble those of common osteoporosis.¹⁶ Laboratory assessment reveals moderate hypercalcemia, an increase of serum phosphorus, alkaline phosphatase, urinary hydroxyproline and osteocalcin, a decrease of serum, $1,25(\text{OH})_2\text{D}_3$ and variable circulating PTH levels. Radiological assess-

ments show rapidly progressive osteoporosis, with thinning of the cortical bone in the long bones, a porous appearance, sometimes associated with bone cysts.¹⁶ Bone biopsy reveals increased osteoclastic resorption with bone marrow fibrosis and an increased number of osteoid margins. Histomorphometric analysis reveals a reduction of trabecular bone volume and global stimulation of cortical bone turnover with an increased rate of osteoblastic apposition, increased Haversian canals, accelerated mineralization, osteoclastic resorption and increased cortical porosity.^{22,23} Bone densitometry shows a moderate, but significant reduction of lumbar and femoral bone mineral density.

The clinical course consists of normalization of laboratory signs within 4–6 weeks, (exception of alkaline phosphatase and 24-h urinary hydroxyproline, reflecting persistence of overactive bone remodeling for several months). Restoration of bone mass is slow and inconstant,²⁴ despite restoration of normal thyroid function. We did not find any clinical data in the literature concerning iatrogenic hyperthyroidism or thyrotoxic bone disease responsible for fracture in spinal cord injury, and also no cases of spontaneous fractures due to a combination of thyrotoxic bone disease and disuse osteoporosis. Most authors attribute such fractures to disuse osteoporosis^{4,9–12} but certain factors can accentuate disuse osteoporosis: infections, pyelonephritis, renal failure, etc.⁴

In our case of a young spinal cord injury patient, the combination of a major risk factor, disuse osteoporosis, with a less common risk factor, iatrogenic hyperthyroidism, responsible for thyrotoxic bone disease, induced a reduction of the bone mineral density to below the fracture threshold.

Although the classical form of thyrotoxic bone disease is uncommon, the major aggravating role of subclinical hyperthyroidism in common osteoporosis, but also in disuse osteoporosis of spinal cord injury patients, must be emphasized. The literature indicates that the presence of hyperthyroidism must be systematically investigated in apparently normal subjects presenting with severe, progressive demineralizing bone disease. The present clinical case emphasizes the fact that the iodine intake could be underestimated in spinal cord injury, although iodinated products are frequently used to dress pressure sores or during repeated radiological examinations. It therefore seems legitimate to propose regular surveillance of TSH in these patients to determine the presence of a predisposing clinical context (goiter, Graves' disease,...) in order to limit the aggravating factors of this disuse osteoporosis.

References

- 1 Chantaine A, Nusgens B, Lapierre CM. Bone remodeling during the development of osteoporosis in paraplegia. *Calcif Tissue Int* 1986; **38**: 323–327.
- 2 Chantaine A, Minaire P. *Les troubles du métabolisme de l'os*. In: Maury M (ed). *Paraplegie*. Flammarion: Paris, 1981, pp 136–144.
- 3 Biering-Sorensen F, Bohr H, Schaadt O. Bone mineral content of the lumbar spine and lower extremities years after spinal cord lesion. *Paraplegia* 1988; **26**: 293–301.
- 4 Guttman L. Spinal Cord Injuries. Comprehensive management and research. Blackwell Scientific Publications: Oxford, 1973.
- 5 Minaire P et al. Quantitative histological data on disuse osteoporosis. Comparison with biological data. *Calc Tissue Res* 1974; **17**: 57–73.
- 6 Minaire P. *Effets de l'immobilisation sur l'os: mise à jour et approche thérapeutique*. In: Simon L (ed). *Actualités en Rééducation Fonctionnelle et Réadaptation*. Masson: Paris, 1983, pp 90–96.
- 7 Minaire P. Pathologie de l'immobilisation. *Ann Med Phys Réadapt* 1986; **28**: 409–424.
- 8 Comarr AE, Hutchinson RH, Bors E. Extremity fractures of patients with spinal cord injuries. *Am J Surg* 1962; **104**: 732–739.
- 9 Eichenholtz SN. Management of long-bone fractures in paraplegic patients. *J Bone Joint Surg (Am)* 1963; **45A**: 299–310.
- 10 Ragnarsson KJ, Sell H. Lower extremity fractures after spinal cord injury: a retrospective study. *Arch Phys Med Rehabil* 1981; **62**: 418–423.
- 11 Ingram RR, Suman RK, Freeman PA. Lower limb fractures in the chronic spinal cord injured patient. *Paraplegia* 1989; **27**: 133–139.
- 12 Freehafer AA, Hazel CM, Becker CL. Lower extremity fractures in patients with spinal cord injury. *Paraplegia* 1981; **19**: 367–372.
- 13 Gayne JP, Houlbert D. Pathologie thyroïdienne iatrogène. *Rev Prat* 1987; **37**: 40.
- 14 Orgiazzi J, Mornex R. *Hyperthyroïdies, signes et symptômes de la thyrotoxicose*. In: Lecler et Rousset. (ed). *La thyroïde*. Expansion Scientifique Française: Paris, 1992, pp 346–350.
- 15 Wartofsky L, Ingbar SH. *Maladies de la Thyroïde*. In: Harrison TR (ed.) *Principes de Médecine Interne*, Flammarion: Paris, 1992.
- 16 Meunier PJ. Hyperthyroïdie et ostéoporose. *Ann Endocrinologie*, 1995; **56**: 57–59.
- 17 Fallon MD et al. Exogenous hyperthyroidism with osteoporosis. *Arch Intern Med* 1983; **143**: 442–444.
- 18 Meunier PJ et al. Bone manifestations of thyrotoxicosis. *Orthop Clin North Am* 1972; **3**: 745–774.
- 19 Mosekilde L et al. Bone changes in hyperthyroidism: interrelationships between bone morphometry, thyroid function and calcium-phosphorus metabolism. *Acta Endocrinol* 1977; **85**: 515–525.
- 20 Menezes-Ferreira M-M, Torresani J. Mécanismes d'action des hormones thyroïdiennes au niveau cellulaire. *Ann Endocrinol* 1983; **44**: 205–216.
- 21 Mundy GR et al. Direct stimulation of bone resorption by thyroid hormones. *J Clin Invest* 1976; **58**: 529–534.
- 22 Linde J, Friis Th. Osteoporosis in hyperthyroidism estimated by photon absorptiometry. *Acta Endocrinol* 1979; **21**: 437–448.
- 23 Naveau B, Caroit M. Os et thyroïde. *Acta Rhum* 1993; **31**: 119–129.
- 24 De Vernejoul MC, Miravet L, Ryckewaert A. Ostéose thyroïdienne. *Actualités rhumatologiques* 1988; **6**: 209–214.