**Clinical case**

**McCune-Albright syndrome revealed by hyperthyroidism at advanced age**

**Révélation tardive d’un syndrome de McCune-Albright dans les suites d’une hyperthyroïdie**

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**Résumé**


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**Abstract**

We report a case of a 38-year-old woman admitted to our service for diagnosis of osteolytic lesions. She suffered from back, lumbar and costal pain at the time a hyperthyroidism, related to multinodular goiter, was diagnosed. The pain remained despite the cure of hyperthyroidism. Cutaneous examination revealed café au lait skin spots. Analysis of the phosphocalcic metabolism allowed the diagnosis of phosphate diabetes. X-ray showed lytic lesions involving the ribs with thinning of the cortex and vertebral fractures of the dorsal spine. The computed tomography revealed lytic lesions with a typical “ground glass” appearance involving the spine, ribs, sternum, iliac bones and sacrum. The presence of this clinical triad allowed the diagnosis of McCune-Albright syndrome (MAS). The treatment consisted in vitamin D supplementation, and high doses of both oral phosphate and calcitriol to treat the phosphate diabetes as well as cycles of intravenous pamidronate administration to relieve bone pain. We report an uncommon case of the diagnosis of MAS at an advanced age following hyperthyroidism. We believe that the disease was revealed by an increase in bone turnover due to hyperthyroidism.

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1. **Introduction**

Originally, the McCune-Albright syndrome (MAS) was defined as the presence of the triad of polyostotic fibrous dysplasia (FD) of bone, café-au-lait skin pigmentation and precocious puberty [1,2]. Later, other endocrinopathies including hyperthyroidism [3], growth hormone excess and Cushing syndrome were included in this syndrome. These endocrinopathies are related to peripheral endocrine secretion, free of hypothalamic pituitary control. The typical time of appariation is before ten years of age.

2. **Case report**

A 38-year-old woman from Guadeloupe was admitted to our service in April 2010 for diagnosis of vertebral fractures associated with lytic lesions. She was treated in the endocrinology department of our hospital for a hyperthyroidism for two years. Her hyperthyroidism was diagnosed when she was 36 years old after noticing weight-loss, palpitations and trembling. She had
no previous thyroid function evaluation. Thyroid peroxidase, thyroglobulin and thyroid stimulating hormone receptor antibodies were negative. Ultrasonography of the thyroid revealed a heterogeneous asymmetric goiter (left > right). Thyroid scintigraphy showed a nodular goiter with hot nodules on the apex of the left and the right lobes (Fig. 1). The disease remained active despite medical treatment. Therefore, the patient underwent surgery in 2009. During one interview with the endocrinologist in 2009, she reported that she suffered from back, lumbar and costal pain; this pain was appeared at the same time as other manifestations of hyperthyroidism. She had never previously suffered from lumbar pain. Following the thyroid surgery, the pain remained despite the treatment for hyperthyroidism and the use of morphine. X-ray was performed showing lytic lesions involving the ribs with thinning of the cortex (Fig. 2) as well as vertebral fractures of the dorsal spine. Consequently, she was hospitalized in our unit for diagnosis. The interview revealed that her puberty occurred when she was 13 years old and that she had two children. No familial medical history was recorded. There was neither fever nor weight-loss. There was no neurological deficiency. Cutaneous examination revealed café au lait skin spots on the left side involving the back and the trunk, which were on the same side as the radiographic lytic lesions (Fig. 3). Laboratory investigations revealed no blood inflammation and protein electrophoresis was normal. Thyroid stimulating hormone was equal to 5.37 mUI/L (normal range: 0.4–4.5), whereas the level of free T4 in the blood was normal (equal to 11.3 pM). Blood analysis also showed normal creatinine level, hypocalcaemia at 2.16 mM with low ionized serum calcium (1.18 mM). Urinary analysis revealed hypocalciuria at 0.8 mg/kg per day. There was also frank hypophosphatemia (0.55 mM). However, except the pain, no other symptom of hypophosphatemia was reported by the patient. Examination of phosphocalcic metabolism had never been performed before this hospitalization. So it was not possible to determine the date of appearance of these abnormalities. The tubular reabsorption of phosphate (TRP) was 76.7% and the maximal tubular reabsorption of phosphate per glomerular filtration rate (TmPO4/GFR) was 0.44 allowing the diagnosis of phosphate diabetes. The FGF-23 level was normal at 64 reference unit (RU)/mL (normal range: 1-120). The 25 OH D3 concentration was low, equal to 19 ng/mL and parathyroid hormone was elevated at 62 pg/mL (normal range: 10–46), related to secondary hyperparathyroidism; 1–25(OH)2D3 was also higher than normal (68 pg/mL) (normal range: 15–60) but was low in view of the hypophosphatemia, suggesting suppression of its secretion. Vitamin D supplementation allowed the normalization of the ionized serum calcium level; however phosphate level remained low at 0.69 mM. Osteocalcin and C-telopeptid, biochemical markers of bone turnover, were normal. The T-score was + 3.5 for the lumbar spine and +1.6 for the total hip. The computed tomography (CT) (Fig. 4) revealed lesions with a typical “ground glass” appearance involving the spine, ribs, sternum, iliac bones and sacrum. There were no such lesions in the limbs. Bone scintigraphy showed increased tracer uptake at affected skeletal sites. Magnetic resonance imaging revealed cystic lesions on the spine.

Fig. 1. Thyroid scintigraphy: hyperfunctioning nodules at the apex of the right and left lobes (arrows). There was also a hypofunctioning area involving the base of the left lobe.

Fig. 2. Thoracic radiography: lytic lesions on the left side involving the ribs with thinning of the cortex.

Fig. 3. Café au lait skin spots on the left side involving the back.
Fig. 4. Computed tomography: multiple lytic lesions of the dorsal and lumbar spine associated with vertebral fractures in the dorsal spine (white arrows), lesions with a typical “ground glass” appearance involving the sacrum (black arrows).

The presence of this clinical triad allowed the diagnosis of MAS, which was then confirmed by a biopsy. No other hyperfunctioning endocrinopathy was detected: Prolactin, Growth hormone, Insulin-Like Growth Factor 1, plasma and urinary cortisol levels were normal. CT of the abdomen and pelvis and pelvic sonography revealed ovarian cysts considered as no pathologic by radiologist. There was no adrenal adenoma. The treatment consisted in vitamin D supplementation, and high doses of both oral phosphate and calcitriol to treat the phosphate diabetes. Cycles of intravenous pamidronate administration (60 mg/day on three successive days every six months), were used to relieve bone pain. After six months of treatment, phosphate level was normal at 0.80 mM. Bone pain remained despite the first cycle of intravenous pamidronate.

3. Discussion

The current definition of MAS is FD of bone combined with at least one of the typical hyperfunctioning endocrinopathies and/or café-au-lait spots [4]. Almost 50% of patients with MAS present renal phosphate wasting due to overproduction of the phosphaturic factor, fibroblast growth factor-23 (FGF 23), by fibrous dysplastic tissue [4,5]. Our patient presented the triad with polyostotic FD of bone, café-au-lait skin pigmentation, hyperthyroidism and phosphate diabetes. However the level of FGF 23 was normal, suggesting that other phosphaturic factors were possibly involved.

The histological characteristic of this bone disease is extensive proliferation of fibrous tissue within the bone marrow. The sites most commonly involved are the base of the skull and the proximal femur with the classic “shepherd’s crook”. Although FD is a disease of the osteoblastic lineage, there is evidence of increased bone resorption in affected bone [6]. In our patient, we suppose that high bone density was related to involvement of osteoblastic lineage, whereas involvement of osteoclast lineage was reflected by osteolytic lesions. Surprisingly biochemical markers of bone turnover were normal.

The sites of FD involvement are established early. Hart et al. found that 90% of the lesions in the axial skeleton were already present at the age of 15.5 years [7]. Dysplastic bone lesions seem to stabilize after puberty and the subsequent appearance of new lesions is uncommon [8]. The occurrence of fractures peaks between six and ten years of age and declines thereafter. Nevertheless, the risk of fracture persists into adulthood. Fractures occur earlier and more frequently in the presence of phosphaturia, with a fracture rate almost twice as high, or higher, in patients with renal phosphate wasting [9]. Our patient was 38 years old, had phosphate diabetes and her disease remained asymptomatic until the emergence of hyperthyroidism, which is uncommon. She had no previous history of either fracture or pain. Whereas worsening of FD during pregnancy, due to the presence of oestrogen receptors in bone of MAS patients has been reported [10], our patient had had two pregnancies and two deliveries without any pain. Nevertheless, her lesions were undoubtedly already present at that time. Indeed, dysplastic bone lesions may have occurred before or during puberty and have stabilized subsequently. Thus we believe that her disease was revealed at the time of the hyperthyroidism. Nevertheless no previous blood analysis was available, therefore a misdiagnosis could not be ruled out.

Hyperthyroidism is commonly associated with MAS: 38% of patients in Mastorakos’s review suffer from this symptom [3]. It is generally due to multinodular toxic goiter. The clinical expression of hyperthyroidism is highly variable [11]. Spontaneous resolution of hyperthyroidism is very rare, and consequently a definitive treatment, like surgery or radiation, is frequently needed. Likewise, our patient had hyperthyroidism related to multinodular goiter requiring radical treatment. Hyperthyroidism has deleterious effects on the normal skeleton, including especially increased bone resorption [12], and may therefore have a direct effect on the fibrous dysplastic skeleton. Despite the common association of hyperthyroidism and phosphaturia with MAS, there is no report on the risk of fractures or discovery of the disease associated with the coexistence of these two conditions. We suggest that the discovery of the disease and the occurrence...
of fractures in our patient were a consequence of increased bone resorption related to hyperthyroidism. Surgical cure of hyperthyroidism did not relieve the pain and symptoms linked to MAS after one year of follow-up. Thus hyperthyroidism was probably a triggering factor for MAS by increasing bone turnover.

Bisphosphonates are used in cases of MAS and FD to relieve bone pain and reduce bone turnover [13–15]. In our patient, pain remained despite the first cycle of pamidronate. This may be explained by the absence of evidence of bone resorption in our patient at the time of the treatment (i.e. normal level of markers of bone turnover, high bone density).

4. Conclusion

We report an uncommon case of the diagnosis of MAS following hyperthyroidism. We believe that the disease was revealed by an increase in bone turnover due to hyperthyroidism. Our patient had had two pregnancies and deliveries without either pain or diagnosis of her disease, despite her lesions having undoubtedly already been present. Indeed, dysplastic bone lesions may have occurred before or during puberty and have stabilized subsequently.

Thus, we suggest that hyperthyroidism may reveal pre-existing asymptomatic bone disease by increasing bone turnover. Oral informed consent was obtained from the patient.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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References


