Curative surgical treatment after inefficient long-acting somatostatin analogues therapy of a tumor-induced osteomalacia

Efficacité du traitement chirurgical après échec des analogues de la somatostatine dans l’ostéomalacie oncogénique

Oncogenic osteomalacia (OOM), also known as tumor-induced osteomalacia, is a rare paraneoplastic syndrome characterized by hypophosphatemia related to tubular leakage of phosphorus, and acquired osteomalacia. Tumors responsible for OOM are predominantly mixed connective tissue variants of benign phosphaturic mesenchymal origin [1].

The urinary phosphorus loss is the consequence of an abnormal secretion by the tumor of phosphaturic factors termed phosphatoin. Several phosphatokinases have been described: fibroblast growth factor 23 (FGF23), matrix extracellular phosphoglycoprotein (MEPE), secreted frizzled related protein 4 (sFRP4), dentin matrix protein 1 and osteopontin [2]. The only routinely measurable phosphatonin is FGF23. When it is found elevated in OOM, it decreases dramatically after the surgical removal of the causative tumor [3,4].

Resection of the responsible tumor is obviously the treatment of choice, since it relieves all symptoms and normalizes FGF23 level [3,4]. In unresectable tumors or when the tumor cannot be localized, medical treatments have been tested but are not yet codified. Medical therapy with calcitriol and oral phosphate gives symptomatic improvement, although osteomalacia has been shown to persist even with the maintenance of a near-normal phosphate level [5]. Oral phosphate therapy is generally well tolerated, although 5–10% of treated patients develop gastrointestinal symptoms, including nausea, vomiting, diarrhea or abdominal pain. In a case of OOM in which hyperparathyroidism was induced by oral phosphate therapy, intravenous infusion contributed to improvement in biochemical and clinical parameters [6]. Nevertheless, this therapy remains constraining and comprises considerable side effects, in particular when central catheterization is needed.

Some authors suggested that phosphate wasting might be relieved by treatment with somatostatin analogues, provided that the tumor expresses somatostatin receptors.

We used long-acting somatostatin analogues in a patient with OOM, but without any remission, requiring surgical removal.

Case report

A 86 years old woman was referred to our Endocrine Unit with a history of goiter. Her past medical history was remarkable for mild chronic renal impairment caused by repetitive urinary infections. There was no family history of bone disease, hypophosphatemia or Fanconi disease. For a few years she was complaining of asthenia with muscle weakness and bone pain. She experienced rib and vertebral fractures. For a few months, walk had become difficult, responsible for falls, limiting her autonomy. A 3 cm soft painless lump was noted in the submaxillary area, known for ten years. Initial biochemical evaluation revealed hypophosphatemia, which was unexpected in the context of renal impairment, and 1.25-dihydroxyvitamin D concentration was inappropriately low (table I, supplementary material). Her serum creatinine level was elevated as previously known (19 mg/L). Phosphatasia was high, the threshold for tubular phosphate reabsorption was decreased to 12% (N > 85%). Elevated serum alkaline phosphatase, telopeptide and osteocalcin levels were also noted. Serum parathyroid hormone (PTH) [solid phase, two-site chemiluminescent enzyme-labeled immunometric assay, Architect] was increased despite normal 25-hydroxyvitamin D. The serum values for calcium, calcitonin, thyroid-stimulating hormone (TSH) were normal. Serum FGF23 level was elevated to 137 pg/mL (normal range 6–22 pg/mL) (Human Intact FGF-23 ELISA kit, Immuno-technics, USA) (table I, supplementary material) and (figure 1). Radiological studies showed generalized osteopenia (figure 2), several ribs and vertebral fractures. Osteodensitometry showed reduced bone density in both lumbar spine (T-score, –3.20) and left femoral neck (T-score, –3.10). CTscan confirmed a 28 × 25 × 22 mm enhancing soft tissue mass in the submaxillary area. Whole body scintigraphy with octreotide (Octreoscan®) revealed focal enhancement in the cervical mass (figure 3).

A treatment with intramuscular long-acting octreotide was initiated and continued for 3 months (10 mg on month 1, increased to 20 mg on month 2, and 30 mg on month 3). She developed gastrointestinal symptoms including abdominal pain and diarrhea. No clinical nor biochemical improvement was observed after three months course of treatment. Serum phosphatemia and FGF23 levels were not modified under the octreotide treatment.
**Figure 1**
Serum phosphorus and fibroblast growth factor 23 (FGF23) changes with long-acting somatostatin analogues and after tumor resection.

**Figure 2**
Lumbar spine radiological evaluation of the patient showing a marked osteopenia [2A: lumbar spine, (lateral view); 2B: lumbar spine, (anterior view) (service de radiologie, Pr Ernst, CHRU, Lille)]
The tumor was thus surgically removed using locoregional anesthesia. Pathological examination of the tumor revealed a proliferation of small, ovoid or spindle shaped tumor cells with a hemangiopericytoma pattern. Moderate anisocaryosis and rare mitotic figures were seen. Occasional osteoclast-like giant cells and hemorrhage were noted while tumoral cartilage/bone was absent. Immunohistochemical analyses performed against cytokeratin, desmin, smooth muscle actin and chromogranin were negatives. Somatostatin receptors (SSTRs) expression analysis was realized using Taqman PCR assay as previously reported [7]. A high expression of somatostatin receptor 2 (7.92 copy/copy b-Gus) was noted, while somatostatin receptors 1, 3 and 5, as well as dopamine receptors were not detected. Biological evaluations 3 days and 2 months after surgery revealed a complete normalization of phosphoremia and vitamin D levels. The postoperative serum FGF23 decreased to 34.2 pg/mL (table I, supplementary material) and (figure 1). The patient also responded clinically with resolution of the bone pain and improvement in the muscle strength. Within 3 months after surgery she was able to ambulate without assistance. Four months after surgery, osteodensitometry showed a spectacular improvement in bone density (T-score in lumbar spine, −2.2 and in left femoral neck −2.6), representing a 15.5% rise in the vertebral area, and whole body scintigraphy with octreotide was negative. At that time, we also observed a new increase in serum FGF23 level to 101.1 pg/mL, reaching 157 pg/mL after 10 months, without any decrease neither in phosphoremia nor in 1.25-dihydroxyvitamin D level after a 17 months follow-up. No sign of tumor recurrence was observed on clinical examination, ultrasonography or scintigraphy one year after surgery. She was reviewed else 17 months after surgery, and phosphorus levels remained stable. Despite the stability of phosphoremia, she died about 2 years after surgery aged of 88 years.

Discussion

Diagnosis of OOM remains difficult and is often delayed for several years. The clinical picture is unspecific, characterized by asthenia, generalized pain and muscle weakness evolving in chronic mode, mimicking physical alterations due to aging. The diagnosis should be evoked in front of chronic hypophosphatemia, even if moderate, associated with reduced renal tubular phosphate reabsorption, low serum levels of 1.25-dihydroxyvitamin D, and in the absence of malabsorption, vitamin D deficiency and family history of hypophosphatemia.

The main differential diagnosis of OOM are X-linked hypophosphatemia (XLH) and the autosomal dominant hypophosphatemic rickets (ADHR) [1]. OOM is biochemically indistinguishable from these inherited hypophosphatemic rickets and in both, serum FGF23 can be elevated. X-linked hypophosphatemia and ADHR typically appear in childhood, although age of onset is variable and can be delayed in ADHR. In OOM, the average age of onset is more than 30 years old. For unknown reasons, muscle weakness is not a feature of XLH and ADHR. The presence of family history helps to distinguish the inherited forms of hypophosphatemic rickets. FGF23 can also be elevated in familial tumoral calcinosis, kidney impairment, hypoparathyroidism and Mac Cune Albright syndrome [1]. Hyperparathyroidism is unusual in OOM, and serum PTH level is usually normal. It can occur after long-term phosphorus supplementation or immediately after surgical removal, then explained by rapid uptake of calcium by bone (“hungry bone”) [8,9]. In the present case, high PTH level is probably explained by the existence of mild chronic renal impairment. “Hungry bone” mechanism could also explain the initial elevation of serum PTH followed by a progressive reduction in the months following surgery. Another reason for transient hyperparathyroidism in our patient could be the normalization of serum phosphorus levels desinhibiting the secretion of parathyroid hormone [10].

Some mesenchymal tumors express SSTRs [11,12], and therefore can be detected with a scanning technique that uses a radiolabeled somatostatin analogue, indium In111-pentetreotide scintigraphy (Octreoscan®). This imaging is particularly
indicated when conventional imaging such as magnetic resonance imaging or computed tomography have failed to locate the tumor [10,13,14]. The presence of high expression of somatostatin receptor 2 could explain the hyperfixation by cervical tumor seen on Octreoscan® imaging in our case. Successful tumor location has also been reported with F-18 FDG FART/CT scan [15]. Continuous oral supplementation with 1-25-dihydroxyvitamin D and phosphate gives symptomatic improvement, although osteomalacia has been shown to persist even with the maintenance of a near-normal phosphate level [5]. In addition, their long term use, apart from not tolerable side effects, can cause secondary hyperparathyroidism.

Somatostatin analogues were used in few cases to repair phosphate wasting, provided that the tumor expresses somatostatin receptors. Seufert used subcutaneous octreotide during 13 days (50 µg three times a day on days 1 through 5 and 100 µg three times a day on days 6 through 13), and this therapy led to normalization of serum phosphorus levels, phosphate clearance, and the threshold for renal tubular re-absorption of phosphate [10]. Yoshioka et al. treated a patient with subcutaneous octreotide during 7 days (100 µg three times a day), but did not observe any effect on the biochemical nor clinical parameters [16]. Paglia et al. described a case in which intravenous octreotide was used during 6 days (600 µg per day), without any improvement in serum phosphorus level [17]. The same result occurred in the case described by Elston with subcutaneous octreotide during 5 days (0.1 mg three times a day). However in this last case, for the first time a reduction in the level of FGF23 was noted after somatostatin analogues treatment [18].

In our case, because of tumor detection by Octreoscan® and patient age, somatostatin analogues were used first. Due to the constraints related to the daily use of the immediate somatostatin analogues, a long-acting form was tested. However, no clinical nor biochemical improvement was noticed after 3 months, in spite of dose increase. SSTRs2 had a high expression, similar to the expression observed in acromegaly and could justify the use of somatostatin analogues in our case. As speculated by Paglia et al., lack of response in the present case could be attributed to the heterogeneous distribution of somatostatin receptors among tumor cells, or to the prevalence of cells lacking somatostatin receptors [17]. Among growth hormone (GH) adenomas, a variable SSTR2 expression was noted and the degree of GH inhibition was highly correlated with the levels of SSTRs2 mRNA expression [19]. It is also possible that the SSTRs were expressed, but unable to modulate the secretion of FGF23.

Another hypothesis could be that, since the patient did not receive previous pre-treatment with immediate release somatostatin analogues, we did not obtain a sufficient saturation of somatostatin receptors.

The patient was complaining of asthenia and muscle weakness for several years and walking became impossible. A dramatical clinical improvement occurred following tumor resection, and biochemical abnormalities were normalized within few days as it is usually reported in literature [3,4]. Few weeks postoperatively, the patient was able to walk short distances without aid, and after 4 months, she recovered a nearly normal bone mineral density. The locoregional anesthesia used in our patient can be interesting in elderly subjects because of eventual associated diseases, and feasible because the tumor is usually small, situated in superficial craniofacial location and in the extremities.

However, 4 month after surgery, the serum FGF23 level started to increase again. No modifications of phosphorus and of 1-25-dihydroxyvitamin D levels were noted after 17 months of monitoring, and renal function remained stable. An asymptomatic tumor recurrence could be raised, but phosphorus, 1-25-dihydroxyvitamin D and PTH levels, as well as radiological evaluation remained normal. The important variations of FGF23 could also be related to the assay. We used an enzyme-linked immunoabsorbent assay, with intra-essay variation coefficients of 2.6% to 4.4%, and inter-essay coefficient of 6.1% to 6.5%. In our patient, supplementary FGF23 measurements were performed after progressive plasma dilutions and we observed gradually increasing FGF23 concentrations. These inconsistencies in results after dilution could be explained, according to the manufacturer, by the coexistence, in normal and pathological serum, of multiple FGF23 isoforms and fragments. Assuming that the ratio of FGF23 isoforms and fragments is stable for a single patient, we decided to use only assays performed on undiluted plasma. However, that ratio could have been modified after the tumor removal and consequently explain the increase in FGF23 level contrasting with clinical and biochemical remission.

Conclusion

We report for the first time a case of OOM in which a medical treatment with long-acting somatostatin analogues was tested, without any efficacy in spite of the strong SSTRs2 expression by the responsible tumor. Although OOM is exceptional, it should be known because the surgical treatment usually allows a clinical and biochemical relief, as it was described for our patient.

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References


Arsene Mékinian1, Miriam Ladsous1, Anne-Sophie Balavoine1, Bruno Carnaille2, Sebastien Aubert3, Benoit Soudan4, Jean-Louis Wémeau1

1CHRU de Lille, service d’endocrinologie et des maladies métaboliques, 59037 Lille cedex, France
2CHRU de Lille, service de chirurgie endocrinienne, 59037 Lille cedex, France
3CHRU de Lille, laboratoire d’anatomopathologie, 59037 Lille cedex, France
4CHRU de Lille, Laboratoire de Biochimie, France

Correspondence: Jean-Louis Wémeau, Hôpital Claude-Huriez, clinique endocrinologique Marc-Linquette, rue Polonoswki, 59037 Lille cedex, France. jw-wemeau@chru-lille.fr

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