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EDITORIAL

"Slow and steady wins the race": the importance of perseverance in the management of oncogenic osteomalacia

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Despite the recent advances in understanding the pathogenesis of oncogenic osteomalacia, a rare paraneoplastic syndrome related to an excessive production of the phosphaturic hormone fibroblast growth factor 23 (FGF-23) by the tumor, the clinical diagnosis of this entity is still to be considered a clinical challenge, with an usual delay in the identification and treatment of affected patients that may lead to severe consequences for the individual's quality of life.

In this issue, Mathilde M. Bruins Slot-Steenks and colleagues report on a typical case of oncogenic osteomalacia in which a long delay from symptoms onset to correct clinical diagnosis had occurred, as well as a long time before tumor was identified and therefore an effective treatment could be established [1].

From a clinical point of view, it could be hard to suspect an osteomalacia in the initial phases of the disease, since most patients report only nonspecific symptoms such as weakness or diffuse pain, that could be identified as related to muscle or joint involvement, thus mimicking other common clinical conditions. The occurrence of fractures could highly help in the diagnosis, but a low bone mineral density at presentation may be lacking in some patients [2].

Laboratory findings suggestive of oncogenic osteomalacia are hypophosphatemia associated with renal wasting of phosphate, and inappropriate normal or low levels of 1,25OH vitamin D despite normal or mildly elevated parathyroid hormone values. These features are directly related to the effect of FGF-23, which inhibits on one hand tubular phosphate reabsorption, and on the other 1α-hydroxylase activity [3]. However, serum phosphate is frequently not included in routine blood chemistry testing, and hypophosphatemia, when detected, is frequently not regarded as relevant in the clinical judgment. Moreover, renal phosphate wasting is not always evident and it can be often revealed only after a specific evaluation, as in the case reported in this issue. Furthermore, 1,25OH vitamin D level is not routinely assessed and usually it is looked for only when a specific diagnostic hypothesis has been formulated.

The dosage of circulating FGF-23 has been performed in some cases as a further help in the diagnosis of oncogenic osteomalacia. This assay however is currently not easily available in everyday clinical practice. Moreover, other phosphatonines have recently been postulated to be implicated in the pathogenesis of phosphaturic osteomalacia related to the tumor, such as fibroblast growth factor 7 [4].

Once the disease has been suspected based on clinical and laboratory findings, and after having ruled out other possible genetically determined renal phosphate-wasting syndromes due to FGF-23 excess, tumor detection is essential to confirm the diagnosis. Tumors responsible for oncogenic osteomalacia are often small, difficult to locate and slowly growing (strange tumors in strange places). Nowadays most osteomalacia-associated tumors are classified under a single histopathologic entity and referred as phosphaturic mesenchymal tumor-mixed connective tissue variant. Due to the high expression of receptors for somatostatin in most of these neoplasms, imaging techniques involving these receptors have been utilized for tumor localization. Whole-body scintigraphy with a radiolabelled somatostatin analogous (Tc-99 octreotide or In-111 pentetreotide) was the first choice in the past, but it provides only

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bi-dimensional images and has a relatively low sensitivity. Now other tri-dimensional techniques, such as Gallium-68-DOTA-Octreotate somatostatin receptor positron emission tomography/computed tomography imaging, have demonstrated a higher accuracy in identifying the tumor, due to a higher selectivity for specific receptors expressed in these mesenchymal tumors [5]. Combining different imaging techniques and selective venous FGF-23 sampling may further help to better localize the tumor [6, 7].

Tumor removal is the only definitive cure for the disease, since it completely and rapidly normalizes the previously altered phosphate metabolism. If tumor localization or complete eradication is not possible, pharmacological treatment should be started with phosphate and 1,25OH vitamin D supplementation. However, this approach is not definitively effective and tumor localization must be pursued over time since slowly growing tumors could become evident years after the symptoms onset, as in the case reported in this issue. Novel treatment options have been suggested for cases in which surgical removal of the tumor is not achievable, such as treatment with monoclonal antibodies against FGF-23 [8] or peptide receptor radionuclide therapy [9], but at the moment their real efficacy is to be proven.

The important lesson that comes from oncogenic osteomalacia is that clinical diligence and perseverance are the main weapons in the management of this rare but potentially debilitating clinical entity.

Compliance with Ethical Standards

Ethical Approval This article does not contain any studies with human participants performed by any of the Authors.

Conflict of interest Luigi Sinigaglia has received speaker honoraria from Eli Lilly, Amgen, Abbvie, Bristol Meyers Squibb. Maria Manara declares that she has no conflict of interest.

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