Endocrinol Nutr. 2016;63(4):181–186

ENDOCRINOLOGÍA Y NUTRICIÓN

www.elsevier.es/endo

REVIEW ARTICLE

Tumour-induced osteomalacia: An emergent paraneoplastic syndrome☆

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Received 13 September 2015; accepted 26 October 2015
Available online 23 April 2016

KEYWORDS
Tumour-induced osteomalacia;
Oncogenic osteomalacia;
Hypophosphatemia;
Fibroblast growth factor 23;
Phosphaturic mesenchymal tumour

Abstract Endocrine paraneoplastic syndromes are distant manifestations of some tumours. An uncommon but increasingly reported form is tumour-induced osteomalacia, a hypophosphatemic disorder associated to fibroblast growth factor 23 (FGF-23) secretion by tumours. The main biochemical manifestations of this disorder include hypophosphatemia, inappropriately low or normal tubular reabsorption of phosphate, low serum calcitriol levels, increased serum alkaline phosphatase levels, and elevated or normal serum FGF-23 levels. These tumours, usually small, benign, slow growing and difficult to discover, are mainly localized in soft tissues of the limbs. Histologically, phosphaturic mesenchymal tumours of the mixed connective tissue type are most common. Various imaging techniques have been suggested with variable results. Treatment of choice is total surgical resection of the tumour. Medical treatment includes oral phosphorus and calcitriol supplements, octreotide, cinacalcet, and monoclonal antibodies.
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PALABRAS CLAVE
Osteomalacia tumoral;
Osteomalacia oncogénica;
Hipofosfatemia;

Osteomalacia tumoral: un síndrome paraneoplásico emergente

Resumen Los síndromes paraneoplásicos endocrinos constituyen manifestaciones a distancia de algunas neoplasias. Una forma infrecuente, pero cada vez más descrita, es la osteomalacia tumoral (OT), un trastorno hipofosfatémico secundario a la pérdida renal de fosfatos inducida por la secreción tumoral del factor de crecimiento fibroblástico 23 (FGF-23). Sus principales manifestaciones bioquímicas son la hipofosfatemia, la reabsorción tubular de fosfatos inadecuadamente normal o baja, los niveles bajos de calcitriol, la fosfatasa alcalina elevada y el

☆ Please cite this article as: Alonso G, Varsavsky M. Osteomalacia tumoral: un síndrome paraneoplásico emergente. Endocrinol Nutr. 2016;63:181–186.

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Factor de crecimiento fibroblástico 23; Tumor mesenquimal fosfatúrico

FGF-23 sérico elevado o normal. Los tumores asociados a la OT suelen ser pequeños, benignos, de lento crecimiento, de difícil localización y con predominio en las partes blandas de los miembros. La histología más frecuente son los tumores mesenquimales fosfatúricos tipo tejido conectivo mixto. Se han propuesto varias técnicas de imagen para su identificación con resultados variables. El tratamiento de elección es la resección quirúrgica completa de la lesión. Otras alternativas terapéuticas son las sales de fósforo, el calcitriol, la octreótida, el cinacalcet y los anticuerpos monoclonales.
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Introduction

Paraneoplastic syndromes include a constellation of signs and symptoms occurring as a consequence of the distant effects of a tumour on different organs and systems. Such effects may be mediated by molecules with hormonal action, growth factors, cytokines, the development of autoimmunity, and other unknown factors. The term 'ectopic' refers to the secretion of a hormone by tissues which physiologically do not exert such a function. However, hormones secreted by tumours are generally present in non-malignant precursor cells, usually in small amounts. Thus, most endocrine manifestations of tumours are caused by eutopic hormone secretion by cells previously programmed to secrete hormones.

Inappropriate hormone secretion in neoplasms is characterized by its being rarely suppressible. The generation of abnormal or incompletely processed molecules with limited biological activity and, occasionally, peptides related to certain hormones (e.g. insulin-like growth factor type II (IGF-II), parathyroid hormone-related peptide) is also common. Table 1 lists the main hormones involved in paraneoplastic syndromes.

Osteomalacia is a metabolic bone disease characterized by a defect in bone matrix mineralization. This disorder is called rickets in childhood, when growth cartilage is also altered. The mineralization process requires adequate calcium and phosphate levels, and preserved cell function and bone matrix structure. Thus, the two main causes of osteomalacia are impaired vitamin D and phosphate metabolism. There are other uncommon conditions that may interfere with bone mineralization, including changes in alkaline phosphatase, some drugs, and bone matrix disorders (Table 2). Among hypophosphatemic osteomalacias, an uncommon aetiology is tumour-induced osteomalacia [TIO]), also called oncogenic osteomalacia.[1,2] TIO is a paraneoplastic syndrome caused by renal loss of phosphorus. It was first described by McCance in 1947,[3] although its link to a humoral factor is attributed to Prader in 1959. The term phosphatonins was later used to refer to phosphaturic humoral factors, and at the beginning of this century, the central role of fibroblast growth factor 23 (FGF-23) in hypophosphatemic osteomalacia was identified.[4] Less than 400 cases have been reported in the medical literature, which reflects its low incidence, its difficult identification and, probably, its underdiagnosis.[5] TIO may occur at any age, but is more common in adults aged 50–70 years.[6]

Table 1 Main molecules involved in endocrine paraneoplastic syndromes.

Factors for hypercalcemia
Parathyroid hormone-related peptide (PTHrp)
1-25-dihydroxycolecalciferol (calcitriol)
Tumour necrosis factor (TNF)
Prostaglandins
Parathyroid hormone (PTH)
Adrenocorticotropic hormone (ACTH)
Vasopressin
Human chorionic gonadotropin (HCG)
Erythropoietin
Calcitonin
Insulin-like growth factor type II (IGF-II)
Somatotropin-releasing hormone (GHRH)
Human placental lactogen (hPL)
Growth hormone (GH)
Corticotropin-releasing hormone (CRH)
Atrial natriuretic peptide (ANP)
Endothelin
Renin
Gastrointestinal hormones (somatostatin, gastrin-releasing peptide, etc.)
Fibroblast growth factor 23 (FGF-23)

Pathophysiology

Chronic variants of hypophosphatemia are associated with clinical muscular (myalgia, weakness, proximal myopathy) and bone signs (rickets in children and osteomalacia in adults). Three main pathophysiological mechanisms have been reported: redistribution (from the internal environment to the inside of cells), decreased intestinal absorption, and increased renal excretion of phosphorus. The main regulators of phosphorus metabolism are parathyroid hormone (PTH), 1-25 dihydroxyvitamin D or calcitriol (1-25$[OH]_2$D), and FGF-23. FGF-23 is normally expressed by osteocytes and regulates phosphorus metabolism and vitamin D through binding to the Klotho-FGF receptor complex.[7] In the kidney, it acts by decreasing tubular reabsorption of phosphate through the inhibition of expression of

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