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TUMOR-INDUCED HYPOPHOSPHATEMIC OSTEOMALACIA : Report of Three Cases

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CONTENTS

Ⅰ. INTRODUCTION

Hypophosphatemic osteomalacia secondary to osseous or soft tissue tumor is an unusual metabolic disease consisting of loss of body weight and height, diffuse skeletal pain, muscular weakness, and pathologic fractures [1-4]. Related tumor is usually reported mesenchymal origin except one case which was originated from prostatic carcinoma[2]. Radiographically, patients with osteomalacia show overall radiolucent appearance in the skeletal system and pseudofractures in the weight bearing bones. Within the jaws, there may be an overall radiolucent appearance, sparse and coarse trabeculae, thinning of the inferior mandibular border, and thinning or loss of the walls of mandibular canal and alveoar lamina dura on the radiograms[3-5]. Laboratory features are characterized by decreased serum phosphorous concentrartion, normal serum calcium concentration, elevated serum alkaline phosphatase level, and decreased renal tubular reabsorption of phosphorus[1,3,4,5].

Tumor-induced hypophosphatemic osteomalacia is interesting since surgical resection of a coexisting tumor has resulted in reversal of the clinical, radiographic, and labolatory features of the osteomalacia. A few cases on the healing of osteomalacia by excision of a coexisting osseous or soft tissue tumor have been published. However, reports of such a phosphaturic tumor being found in the jaws[1] are extremely rare.

Thus we reviewed the literature related to the tumor-induced hypophosphatemic osteomalacia and report three cases of hypophosphatemic osteomalacia induced by the mesenchymal tumor of the jaw.

Ⅱ. REPORT OF THREE CASES

Case 1

A 32-year-old woman was admitted to our hospital with chief complaints of diffuse skeletal pain and generalized muscular weakness.

Fig. 1. Intraoral photograph demonstrating teeth displacement and soft tissue mass on the lower left molar area.

Fig. 2. Panoramic radiograph demonstrating newly formed bony shadow on the lower left molar area and generalized wispy trabeculation.

Eight years prior to our examination, the patient was diagnosed with hyperparathyroidism and managed, but the symptoms got worse.

On physical examination, she was in severe distress with diffuse skeletal pain and not able to stand by herself. Body weight was 35 kg, and height was 145 cm. Intraorally, soft tissue mass on the lower left molar area was noticed(Fig. 1).

On radiographic examination, panoramic radiograph revealed generalized wispy trabeculation, newly formed bony shadow, and teeth displacement on the lower left molar area(Fig. 2). Periapical radiographs showed complete loss of alveolar lamina dura around maxillary teeth and left mandibular teeth and partial loss around right mandibular teeth. However, there is no evidence of involvement on the tooth structure on the entire dentition (Fig. 3). Occlusal radiograph showed destruction of lingual cortical plate, displacement of teeth, and newly formed bony shadow(Fig. 4). Radiograph of the hands demonstrated thinning of cortical bone, wispy trabeculation, and multiple pathologic fractures(Fig 5). Axial computerized tomograms demonstrated radiopaque foci within the soft tissue mass on the lower left molar area(Fig. 6).

Bone scan using ^{99m}Tc-MDP revealed increased uptake and scoliosis(Fig. 7). Total body bone mineral density was markedly decreased.

An incisional biopsy was performed. In the biopsy specimen, interlacing fascicle of proliferating fibroblastic spindled cells with scattered woven bone and rounded/irregular shaped bony spicules, which were partly interconnected, were seen(Fig. 8).

The biochemical examination showed that the hemoglobin concentration, erythrocyte count, total leukocytes, differential counts, blood urea, serum creatinine, chloride, and potassium values were all within normal limits. Other biochemical findings showed hypophosphatemia with a serum phosphorous concentration of 1.0 to 1.5 mg/dl(normal range: 2.5-5.5), associated with a normal serum calcium concentration of 8.7 to 9.9 mg/dl(normal

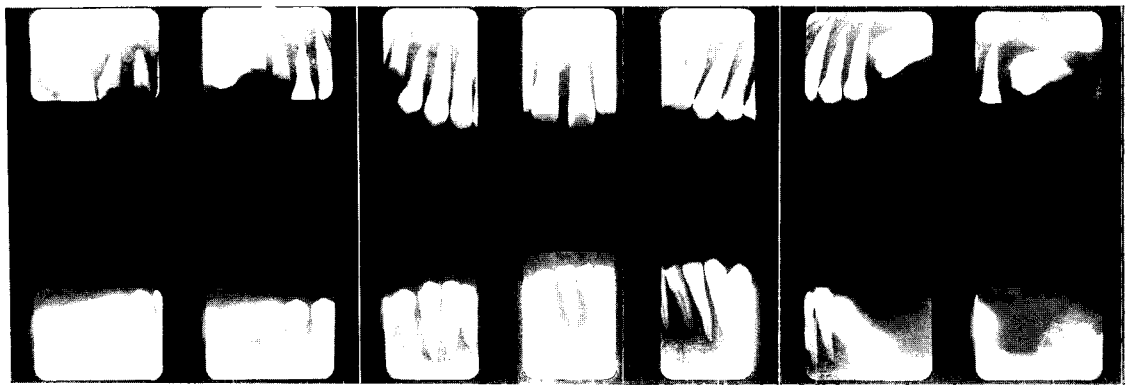

Fig. 3. Periapical radiographs demonstrating loss of alveolar lamina dura on entire dentition.

Fig. 4. Occlusal radiograph demonstrating destruction of lingual cortical plate and displacement of teeth.

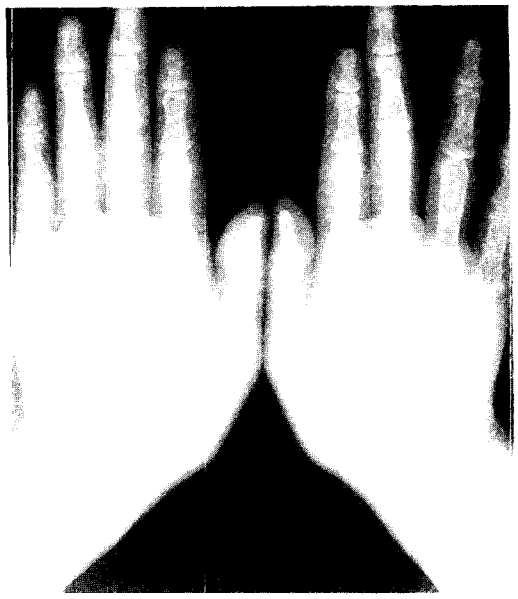

Fig. 5. Radiograph of hands demonstrating thinning of cortical bone, wispy trabeculation, and multiple pathologic fractures.

range: 8.4-10.2). The serum alkaline phosphatase level was 432-548 IU/L(normal range : 56-176). Renal tubular reabsorption of phosphorous was 62-69%(normal range: 91%). A further study of bone metabolism revealed normal serum levels of immunoactive parathryoid hormone. These features led to a diagnosis of osteomalacia and ruled out hyperparathyroidism. In view of the diagnosis, the jaw tumor was removed surgically. Three weeks after removal of the tumor mass, serum phosphorus concentrations began to rise from

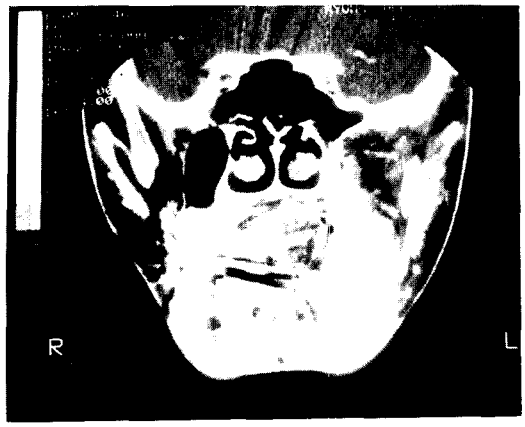

Fig. 6. Axial computed tomogram demonstrating radiopaque foci within the soft tissue mass on the lower left molar area.

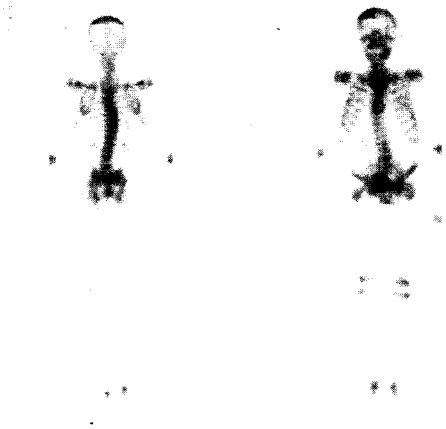

Fig. 7. Total body bone scan demonstrating multiple increased uptake and scoliosis.

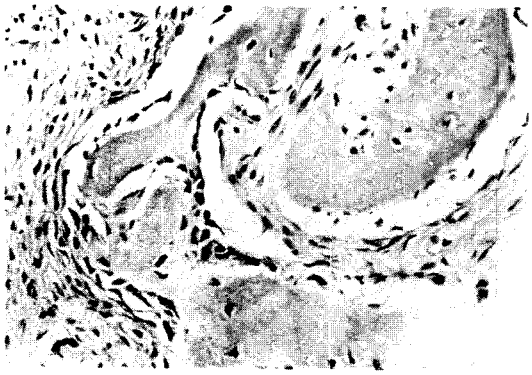

Fig. 8. Interlacing fascicles of proliferating fibroblastic cells with scattered bony spicules(Hematoxylin-eosin stain:original magnification, X200)

1.3 to 3.0 mg/dl and renal tubular reabsorption of phosphrous returned to normal. Three months after operation, radiographic examination revealed some evidence of regeneration of alveolar lamina dura around affected teeth (Fig 9). Seven months later, her physical condition had improved dramatically with no additional treatment.

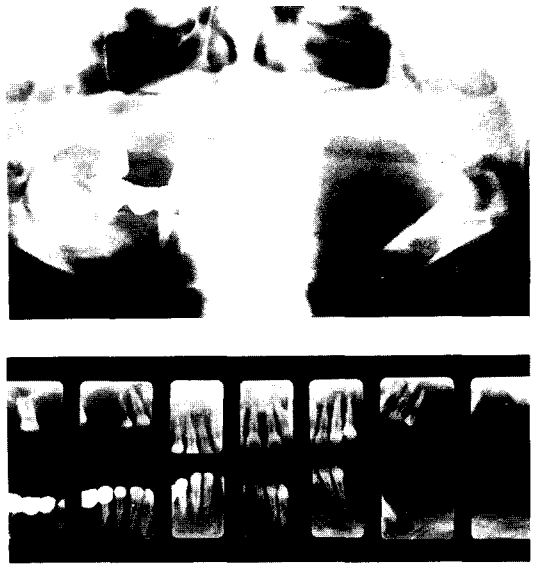

Fig. 9. Panoramic(A) and periapical radiographs(B) demonstrating regeneration of alveolar lamina dura and trabeculae.

Case 2

A 43-year-old man who had a 4-year history of back pain was examined. Body weight

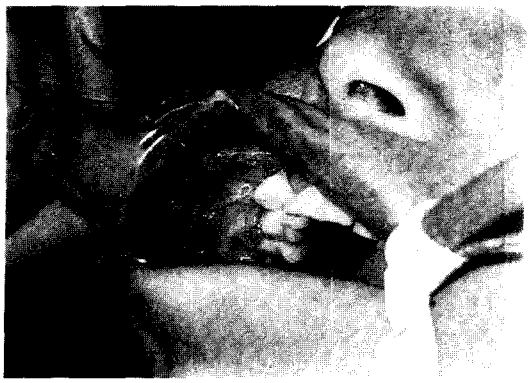

Fig.10. Soft tissue mass on the upper right vestibular area.

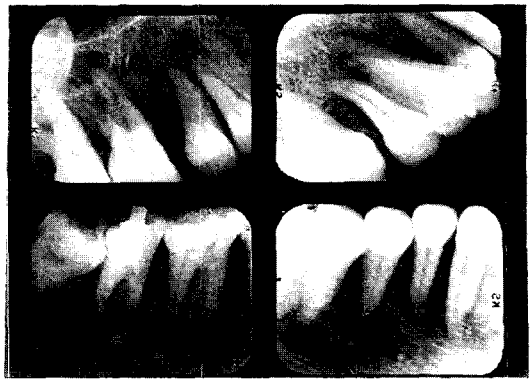

Fig.11. Periapical radiographs demonstrating increased radiolucency and loss of alveolar lamina dura.

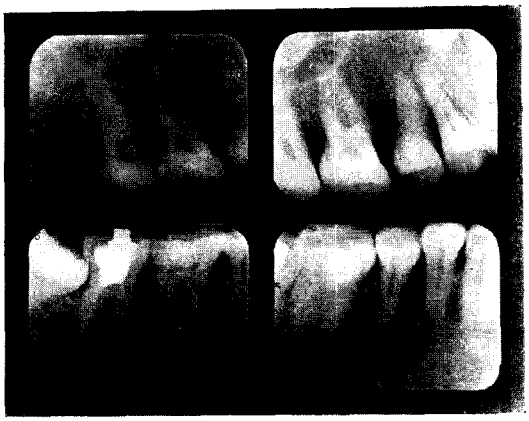

Fig.12. Periapical radiographs demonstrating regeneration of alveolar lamina dura and trabeculae.

was 30 kg, and height was 142 cm. There was a soft tissue mass on the buccal gingiva of upper right premolar and molar area(Fig.10).

Periapical radiographs revealed loss of density of alveolar bone, complete loss of alveolar lamina dura on entire dentition, and complete loss of mandibular canal(Fig.11).

Initial laboratory studies showed a serum phosphorus concentration of 1.5 mg/dl associated with inappropriate phosphaturia(494 mg/24 hours). Serum alkaline phosphatase concentrations were higher than normal limits, but other biochemical studies including parathyroid hormone were all within normal limits.

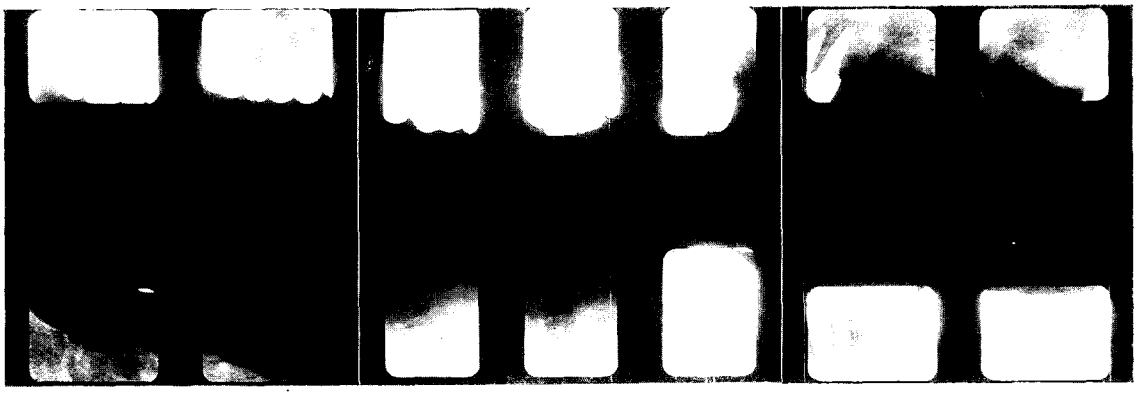

Fig.13. Periapical radiographs demonstrating wispy trabeculation and loss of alveolar lamina dura.

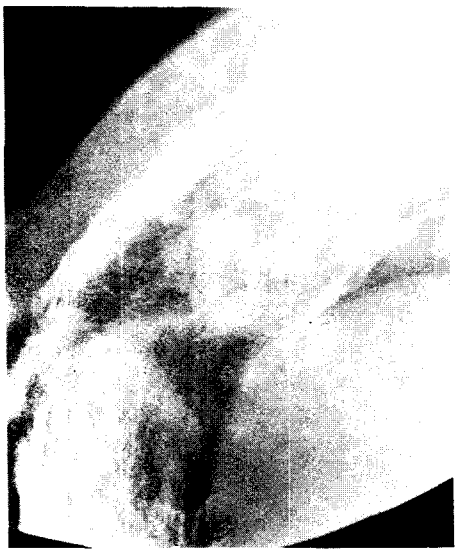

Fig.14. Occlusal radiograph demonstrating destruction of cortical plate and pathologic fracture.

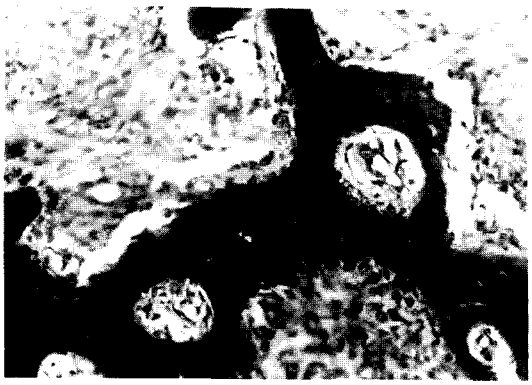

Fig.15. Interlacing fascicles of proliferating fibroblastic spindle cells with scattered bony spicules which were partly interconnected and surrounded by active osteoblasts (Hematoxylin-eosin stain: original magnification, X200)

After radical resection of the tumor mass composed of fibroblasts containing scattered osteoclast-like giant cells, serum phosphorus concentration dropped to within normal limits.

Radiographically, alveolar lamina dura and trabeculae were regenerated gradually(Fig. 12).

Case 3

A 40-year-old man who had a 17-year history of generalized skeletal pain was admitted to our hospital. Fifteen years prior to our examination, resection of the mandibular tumor mass diagnosed with fibrous dysplasia was performed, and then the symptoms disappeared temporarily. After two years, the mandibular tumor mass and the symptoms recurred.

Radiographic examination revealed generalized wispy trabeculation, destruction of cortical bone, pathologic fracture, and partial loss of alveolar lamina dura around all the remaining teeth(Fig. 13, 14). Total body bone mineral density was markedly decreased.

Laboratory findings showed hypophosphatemia with a serum phosphorus concentration of 1.1 to 1.6 mg/dl, associated with a normal serum calcium concentration of 10.6 to 11.4 mg/dl. The serum alkaline phosphatase level was found to be elevated.

After radical resection of the coexisting tumor mass consisting of interlacing fascicles of proliferating fibroblastic spindle cells with scattered bony spicules(Fig. 15), the clinical and laboratory features were improved dramatically.

Ⅲ. DISCUSSION

Osteomalacia in adults, persons in whom linear bone growth can no longer occur, is a metabolic disease[3-5]. It is related with vitamin D deficiency, disorders of vitamin D metabolism, acidosis, gastrointestinal disturbance, chronic renal failure, and prolonged anticonvulsive drug therapy[3-5]. In rare cases, osteo-

malacia has been reported to be induced by osseous or soft tissue tumor[1-3,5-15]. It is referred to the tumor-induced hypophosphatemic osteomalacia.

The pathogenesis of tumor-induced hypophosphatemic osteomalacia is unknown. However, the probability that these tumors elaborate an active humoral substance has been increased. Such a substance could act directly on the kidney to reduce the efficiency of its phosphate reabsorption, or it might mediate its influence through alterations in the metabolism of vitamin D. Although McCance[6] reported the first case of tumor-induced hypophosphatemic osteomalcia, Prader and his associates[7] first recognized the etiologic role of a tumor.

Aschinberg and his associates[8] performed the experimental study on the homogenate of the phosphaturic mesenchymal tumor. They assumed that such a phosphaturic mesenchymal tumor releases an active humoral substance responsible for the development of the bone disease. Such a substance might act primarily on bone or on the gastrointestinal tract by altering the absorption of calcium and phosphorus or by interfering with normal vitamin D metabolism.

Clinically, the patient with tumor-induced hypophosphatemic osteomalacia demonstrates loss of body weight and heght, diffuse skeletal pain, and muscular weakness. According to Linovits and his associates[16], eleven patients with tumor-induced hypophosphtemic osteomalacia had symptoms with a duration ranging from five months to four years(average 2.5 years). In our three cases, patients had a duration of symptoms of 8 years in case 1, 4 years in case 2, and 17 years in case 3, respectively. In general, radiographic features of osteomalacia demonstrate loss of alveolar lamina dura, thinning of cortical bone, reduced number of trabeculae, bowing of weight-bearing bones, and pathologic fractures. In our three cases, the degree of alveolar lamina dura loss was various. It is generally accepted that the degree of alveolar lamina dura loss depends on the duration and severity of the disease[4]. In the present three cases, severity of loss of the alveolar lamina dura was not proportional to the duration of disease. It may be proportional to the severity of disease. Loss of alveolar lamina dura is not a specific sign and may occur in fibrous dysplasia, Paget's disease, Cushing's syndrome, or hyperparathyroidism. Therefore, differential diagnosis with clinical, laboratory and histopathological examination is essential to rule out such diseases. Also, complete loss of mandibular canal was observed in all three cases. It may be suggested that alveolar lamina dura is more resistant to bone resorption than the cortical plate of the mandibular canal. The resistance of the alveolar lamina dura to bone resorption might be partially influenced by mechanical forces, induced by the occlusal function of teeth[17].

Laboratory features of osteomalacia characterized by decreased serum phosphorus concentrations, normal serum calcium concentrations, elevated serum alkaline phosphatase levels, and decreased renal tubular reabsorption of phosphorus are essential for differential diagnosis from hyperparathyroidism, which has similar laboratory features to osteomalacia. In contrast to hyperparathyroidism, patients with osteomalacia show normal concentrations of parathyroid hormone and normocalcemia.

In the present three cases, typical clinical, radiographic, and laboratory features of tumor-induced hypophosphatemic osteomalacia were noticed. However, the patients had been incorrectly diagnosed as hyperparathyroidism in case 1 and fibrous dysplasia in case 3. So

proper management was delayed.

Related tumors were found in the femur[6], rib[7], knee[9], groin[10], pharynx[11], radius[12], toe[13], ulna[14], and mandible[1]. The histological diagnosis of these tumors has been reported variously as degenerative osteoid tissue[6], giant cell reparative granuloma[7], benign cavernous hemangioma[9], sclerosing hemangioma[10], ossifying mesenchymal tumor[11], non-ossifying fibroma[12], mesenchymal tumor[13], benign ossifying mesenchymal tumor[14], and giant cell variety[1]. Because many of these tumors have had an undifferentiated mesenchymal origin, making a diagnosis was difficult.

These phosphaturic mesenchymal tumors are classified into four morphologic groups by Weidner and associates[15]. One group is composed of a peculiar form of mixed connective tissue tumor that occurred predominantly in soft tissues and contained variably prominent vascularity and osteoclast-like giant cells. Tumors of the remaining three groups occur in bone and are grouped as osteoblastoma-like tumor, nonossifying fibroma-like tumor, and ossifying fibroma-like tumor according to their close resemblance to tumors known to occur in bone. According to the classification by Weidner and associates[15], the tumors found in our cases were classified as mixed connective tissue tumor in case 2 and osteoblastoma-like tumor in case 1 and Case 3, respectively. However, the histological findings of the tumor in Case 3 were consistent with fibrous dysplasia.

The average elapsed time from tumor resection to clinical response was 16 weeks (range 1 day to 17 months)[16]. In our cases, the elapsed time was 7 months in case 1, 6 weeks in case 2, and 3 weeks in case 3, respectively.

The average interval for a chemical response from the removal of the tumor was 6 weeks[16]. In our cases, the interval from removal of the tumor mass for recovery of serum phosphorus level was 3 weeks in case 1, 6 weeks in case 2, and 2 weeks in case3, respectively. Radiographic examination revealed evidence of alveolar lamina dura regeneration in 3 months in case 1, 6 weeks in case 2, and 4 months in case 3, respectively. In our three cases, recovery of all patients was relatively rapid.

Ⅳ. SUMMARY

Tumor-induced hypophosphatemic osteomalacia has been rarely reported. The clinical and radiographic features of tumor-induced hypophosphatemic osteomalacia are similar to that of hyperparathyroidism, but it is distinguished from hyperparathyroidism on the basis of its different biochemical features, such as normal serum calcium concentration, decreased serum phosphorus concentration, and elevated serum alkaline phosphatase level[1].

The importance of laboratory features of the metabolic disease is emphasized. Since resection of a coexisting tumor without additional treatment lead to prompt a increase in serum phosphorus, recovery of clinical symptom, and remineralization of bone, an accurate diagnosis should be established as quickly as possible.

We have recently experienced three cases of tumor-induced hypophosphatemic osteomalacia. The clinical, radiographic, and laboratory features were dramatically improved after resection of the coexisting tumors.

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-국문초록-

종양유발성 골연화증의 3예

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종양유발성 골연화증은 종양에 의하여 생성된 활동성 펩티드호르몬과 유사한 물질이 골이나 위장관에 작용하여 칼슘대사와 인대사의 변화를 일으키거나, 정상적인 비타민 D 대사에 장애를 일으킴으로써 2차적으로 발생되는 대사성 질환으로 알려져 있다. 이의 발생빈도는 매우 낮으며, 임상적으로는 체중과 신장의 감소, 전신적인 골격의 동통 및 근무력증과 병적 골절이 동반되어 나타난다. 방사선사진에서는 골소주의 전반적인 소실, 피질골의 비박, 위골절, 치조백선의 소실등을 보이고, 실험실 소견에서는 혈청 인의 농도와 신세뇨관에서 인의 재흡수율의 감소 및 혈청 알칼리성 인산화효소 농도의 상승이 관찰된다. 본질환은 종양이 제거되면 별도의 부가적인 치료없이도 임상적, 방사선학적 소견 및 실험실 소견의 뚜렷한 개선을 보이므로 이의 치료에 있어서 정확한 진단이 매우 중요하다.

저자들은 전신적인 동통과 근무력증을 주소로 내원한 환자들에게서 발생된 종양유발성 골연화증 3예를 경험하였기에 문헌고찰과 함께 이를 보고하는 바이다.