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Digital clubbing as an unusual complication of the secondary hyperparathyroidism associated with atypical neutrophils: a case report

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Abstract. – Digital clubbing is a rare clinical finding and usually represents a sign of underlying disease.

There are only few cases of digital clubbing in patients with primary hyperparathyroidism or with secondary hyperparathyroidism (SHPT) during long-term hemodialysis. We haven't come across papers dealing with the relation of digital clubbing and SHPT caused by vitamin D deficiency.

In this article, we report a case of 43 year-old female patient with prominent clubbing of the fingers and toes, and 22 year history of SHPT caused by vitamin D deficiency. Current radiographic findings of the hands and feet are actually uncommon, and they show massive osteolytic lesions of numerous phalanges, which is the consequence of long-time untreated SHPT.

Besides, our patient has a rare case of neutrophils with bilobed nuclei and decreased cytoplasmic granularity.

This paper for the first time describes digital clubbing as an unusual complication of the SHPT caused by vitamin D deficiency associated with atypical neutrophils.

Key Words:
Digital clubbing, Secondary hyperparathyroidism, Vitamin D deficiency, Neutrophils.

Introduction

Digital clubbing is a rare clinical sign characterized by bulbous enlargement of the distal segments of the fingers and toes[1,2]. It's usually acquired and is associated with a number of pulmonary, cardiovascular, gastrointestinal, neoplastic, infectious, endocrine, psychiatric, and multisystem diseases[1-3].

Digital clubbing was described as an unusual clinical finding or an unusual complication in some patients with secondary hyperparathyroidism (SHPT) during long-term hemodialysis. One of the most common causes of SHPT is renal failure, but SHPTmay occur in association with vitamin D deficiency or intestinal malabsorption. The absorption of calcium and phosphate across gut is significantly impaired in the presence of vitamin D deficiency[4]. As vitamin D deficiency progresses, the parathyroid glands are maximally stimulated, causing SHPT, because there is no feedback of parathyroid hormone (PTH) by vitamin D. Low vitamin D and calcium levels result in increased secretion of PTH by parathyroid glands[4,5].

One of the principal radiological features of SHPT is the evidence of subperiosteal bone resorption, most often seen involving the hands and the feet. The earliest lesions often appear at the radial aspects of the second and third middle phalanges[6,7]. Terminal tuft resorption can also be seen, and hyperparathyroidism should be considered in the differential diagnosis for acro-osteolysis[7].

Here, we report a patient with prominent digital clubbing and massive osteolytic lesions of numerous phalanges as a complication of the long-time untreated SHPT caused by vitamin D deficiency. Besides, our patient has a rare case of neutrophils with bilobed nuclei and decreased cytoplasmic granularity.

Case Report

A 43 year-old female patient with 22 year history of SHPT admitted to the Rheumatology Department with enlargement of the fingertips,

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complains of weakness, fatigue, strength loss, difficulty in walking, intermittent pain in the lumbar spine area lasting for several months. For the last 19 years she hasn't had any difficulties and she hasn't taken any medications for SHPT, and neither visited her doctor during this period.

Her previous medical documentation showed that she had recurrent respiratory infections, conjunctivitis, otitis media, and diarrhea. In the third year of her life hypogammaglobulinemia was diagnosed, as well as neutrophils with a hyposegmented bilobed nuclei on peripheral blood smear. At the age of 21 a complete testing was done due to digital clubbing and the SHPT caused by vitamin D deficiency was diagnosed, while radiographs of the hands and feet was described as soft-tissue expansion of the fingertips with diffuse resorption of the distal phalanges and the incipient osteolytic lesions of the phalanges. Calcium and vitamin D supplementation was applied then. Control peripheral blood smear confirmed the finding of neutrophils with bilobed nuclei.

Neither anamnesis nor the insight in earlier medical documentation could provide the data when the digital clubbing started.

There was no family history of digital clubbing, endocrine or metabolic bone diseases. The patient comes from the family of modest educational and socio-economic status with the dominant nutrition that lacks vitamin D. She spends most of her time in the house, without the exposure to the sun.

Physical examination showed prominent clubbing of the fingers (Figure 1) and toes (Figure 2), thorasic spine kyphoscoliosis, proportional short stature (height 149 cm, weight 36 kg, body mass index 16.2), teeth loss, tread wearily, and diminished mental abilities. The neck palpation didn't find the enlarged parathyroid glands.

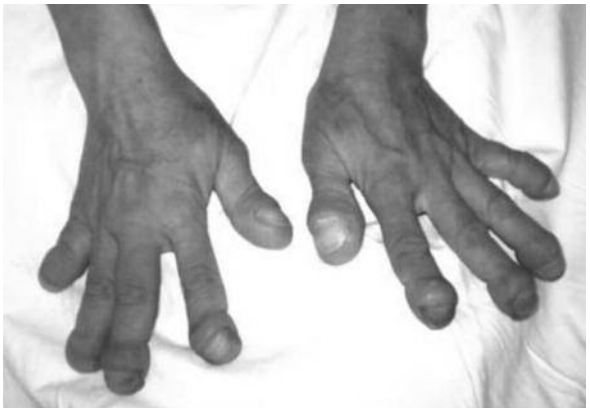

Figure 1. Photograph of the hands shows prominent clubbing of the fingers.

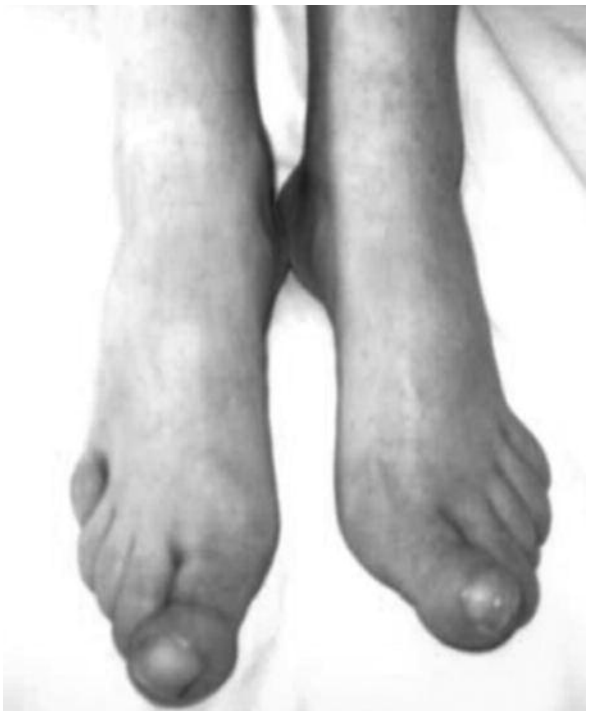

Figure 2. Photograph of the feet shows prominent clubbing of the toes.

Laboratory analysis showed the total serum calcium level of 2.08 mmol/L (normal range 2.20-2.65 mmol/L); serum phosphorus level of 0.93 mmol/L (normal range 0.87-1.45 mmol/L); vitamin D (25-OH) serum level of < 10.00 nmol/L (normal range 50-100 nmol/l); PTH level of 133 pg/mL (normal range 15-65 pg/mL); alkaline phosphatase level of 119 U/L (normal range 30-120 U/L), which confirmed the diagnosis of SHPT and vitamin D deficiency. Renal function was normal.

Ultrasonography didn't show the enlarged parathyroid glands. Dual-tracer (subtraction) parathyroid gland scintigraphy (Technetium-99m-MIBI) with SPECT imaging of the head, neck and thorax didn't show a photopenic focus.

Current radiographic findings of the hands (Figure 3) and feet (Figure 4) are actually uncommon, which is the consequence of long-time untreated SHPT. They show prominent soft-tissue expansion of the fingertips with massive osteolytic lesions of the distal phalanges, middle phalanges and even proximal phalanx, and parts with moderate changes – subperiostal resorption and osteoporosis.

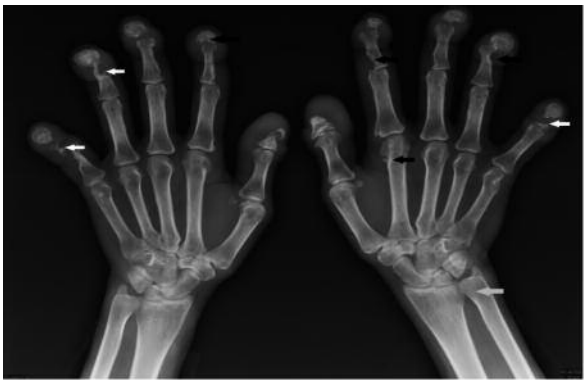

Figure 3. Radiograph of the hands: well-defined lytic lesions (*white arrow)*; subperiosteal resorption/erosion (*black arrow*); intracortical bone resorption small oval lucencies (*gray arrow*).

The additional radiography of thorax, skull, spine, pelvis and hips, and lower legs show osteoporosis and degenerative incipient gonarthrosis and coxarthrosis, as well as the degenerative changes of the spine and thoracic kyphoscoliosis, but without the changes within the primary disease.

Dual-energy X-ray absorptiometry study showed osteoporosis (lumbar spine T-score -2.7 Z-score -1.8; femur mean T-score -3.4 Z-score -2.6).

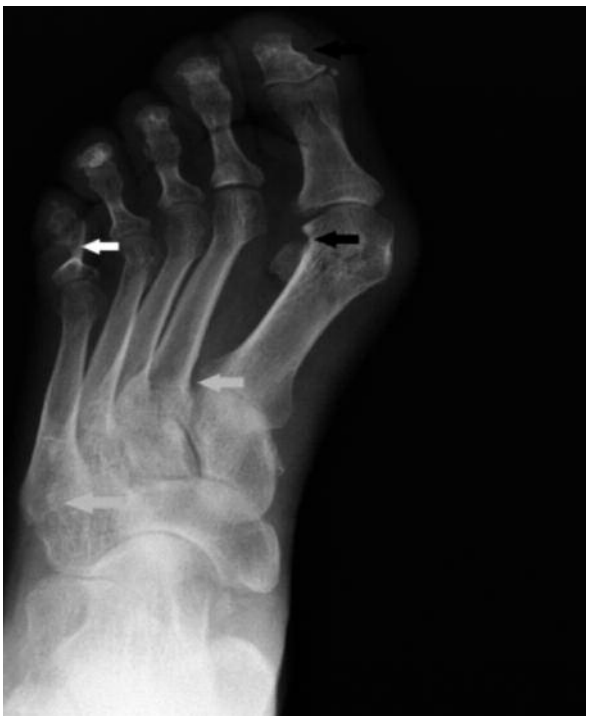

Figure 4. Radiograph of the feet: well-defined lytic lesions (*white arrow*); subperiosteal resorption/erosion (*black arrow*); intracortical bone resorption small oval lucencies (gray arrow).

The patient is given the therapy consisting of calcium and vitamin D supplement and bisphosphonates.

The additional laboratory analyses showed IgA level of 0.5 g/L (normal 0.7-4 g/L), IgM level of 0.2 g/L (normal 0.4-2.3 g/L) and normal levels of IgG, C3, C4 and serum albumin; WBC 6.800/mm^3 with normal white blood cell count.

Peripheral blood smear test confirmed the presence of about 70% neutrophils with hyposegmented of mainly bilobed nuclei (Figure 5) and about 30% neutrophils with the regular segmentation of nuclei, and other white blood cells, erythrocytes and platelets are normal. Electron microscopy showed neutrophils with significantly lowered number of primary and secondary granules compared to granules in a healthy person; there was also absence of primary granules in some neutrophils (Figure 6).

The additional diagnostic tests were done with the aim to exclude the diseases which can be associated with digital clubbing. Laboratory analysis showed that CRP, RF and ANA were within the regular range. They also showed a regular thyroid function, regular range of pituitary hormones, cortisol, aldosterone and sexual steroids.

No diseases of the heart, lungs, liver or kidneys were diagnosed. The abdominal and pelvis ultrasound showed small gallstone with the other findings being regular. The finding of esophagogastroduodenoscopy showed the subacute gas-

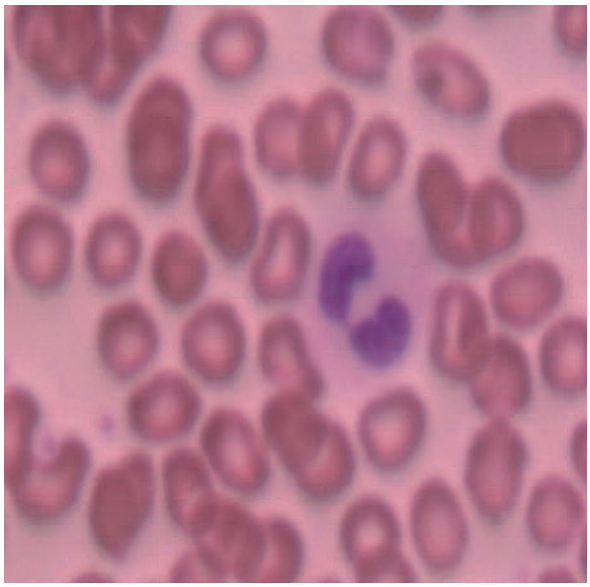

Figure 5. Peripheral blood smear. (MayGrunwald Giemsa staining, ×100 magnification): neutrophil with a bilobed nucleus.

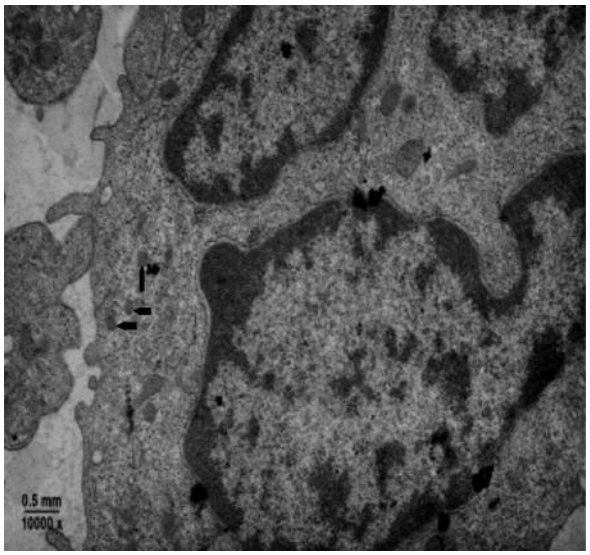

Figure 6. Electron microscopy (ultrathin section, ×10.000 magnification): neutrophil with significantly lowered number of secondary granules (red arrows, secondary granules) and absence of primary granules.

tritis. Colonoscopy was normal. There was no presence of fecal fat in the stool.

She had no apparent focal neurological deficits.

Psychiatric and psychological test showed that the patient is depressive with the border-line intelligence with the significant reduction of the mental efficiency.

Discussion

Digital clubbing is a rare clinical finding and usually represents a sign of underlying disease. If the primary process is identified and treated successfully, clubbing is usually reversed completely[1,3].

There are only few cases of digital clubbing in patiens with primary hyperparathyroidism and severe SHPT in dialysis patients. Davis et al[6] reported that patients with digital clubbing represented only 0.6% of their dialysis population, while Grekas et al[8] reported two patients with digital clubbing associated with severe SHPT in a chronic kidney disease represented 0.3% of their dialysis population. We haven't come across papers dealing with the relation of digital clubbing and SHPT caused by vitamin D deficiency.

Digital clubbing is explained as a specific soft-tissue reaction to the disease in this area, that is, reaction on an augmented digital bone resorption and loss of skeletal support. Clubbing is most marked where the shortening of the terminal phalanges is greatest[6,9]. Clubbing usually develops over years, and occurs first in the thumb and forefinger, and in the other fingers later[2,3].

It is unknown which growth factors lead to stromal and vascular changes in clubbing in patients with SHPT caused by vitamin D deficiency.

The pathogenesis of digital clubbing is explained in hypertrophic osteoarthropathy; the most accepted is the megakaryocyte/platelet theory which points out the importance of platelet-derived growth factor VEGF (vascular endothelial growth factor)[3,10].

Vitamin D deficiency in adults can precipitate or exacerbate osteopenia and osteoporosis[5]. Early deficiencies are linked with schizophrenia, and adult deficiencies with depression and cognitive decline[11]. Low vitamin D levels are also associated with tendencies to high infection rates (especially respiratory infections caused by Mycobacterium tuberculosis and Gram-negative bacteria)[5,12].

Our patient has SHPT and osteoporosis, she is depressed and of borderline intelligence with a significant reduction of mental efficience. Tendency to different infections appeared in her childhood (recurrent respiratory infections, conjunctivitis, otitis media, and diarrhea) when hypogammaglobulinemia and bilobed neutrophils nuclei were found. Examinations of a peripheral blood smears were done several times in her adulthood, when the patient was without any signs of infections. Each time these tests confirmed a high percentage of neutrophils with atypical bilobed nuclei. This nuclear morphology with decreased cytoplasmic granularity points towards Neutrophil-specific granule deficiency (SGD). SGD is an extremely rare congenital disease characterized by neutrophils with atypical bilobed nuclei and lack of primary, specific, and tertiary granule proteins, resulting in frequent and severe bacterial infections. Acquired specific granule deficiency has been reported in neonates and thermal injury[13,14].

In adulthood, our patient has had recurrent respiratory tract infections. Complete previous medical documentation shows that she has never had severe complications of infectious, septicaemia or skin infections, which is common in individuals with SGD.

This paper for the first time describes digital clubbing as an unusual complication of the SHPT caused by vitamin D deficiency associated with atypical neutrophils.

The only recognized treatment for clubbing is treatment of the primary lesion, and its prognosis is completely dependent on the underlying process[3].

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