



Hypercalcemia and multiple osteolytic lesions in a child with disseminated paracoccidioidomycosis and pulmonary tuberculosis

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Abstract

Objective: To describe the case of a child with paracoccidioidomycosis who presented hypercalcemia with multiple osteolytic lesions.

Description: A 6-year-old boy was admitted with a one-month history of fever and hepatosplenomegaly. On admission, he looked sick, pale, and had disseminated lymphadenopathy and hepatosplenomegaly. The laboratory findings included anemia (hemoglobin = 6.8 g/dl), eosinophilia (1,222/mm³), thrombocytopenia (102,000/mm³), and hypoalbuminemia (serum albumin = 2.2 g/dl). *Paracoccidioides brasiliensis* was identified in bone marrow examination. In the second week after admission, the patient presented joint pain, poor activity and difficulty in walking. He presented hypercalcemia (maximum value = 14.9 mg%) and reduction in renal function, which lasted for two weeks. On the 42nd day after admission, his chest X-ray showed lytic lesions in clavicle, scapula, ribs, and humerus, with bilateral slipped capital humeral epiphysis. The patient presented nephrocalcinosis and nephrolithiasis, reduction in creatinine clearance and evidence of tubular lesions. At the end of the second month after admission, *Mycobacterium tuberculosis* was isolated in gastric lavage. The child received treatment for paracoccidioidomycosis and tuberculosis and has not had any sequelae for 3 years.

Comments: The development of symptomatic hypercalcemia leading to renal lesion, associated with multiple osteolytic lesions, had never been described in paracoccidioidomycosis. Although pulmonary tuberculosis was diagnosed and could be related to hypercalcemia, the sudden onset of hypercalcemia and its normalization without specific treatment for tuberculosis suggests that bone lysis was the most important factor in the genesis of hypercalcemia.

J Pediatr (Rio J). 2005;81(4):349-52: Paracoccidioidomycosis, tuberculosis, hypercalcemia, osteolytic lesions, children.

Paracoccidioidomycosis (PCM) is a fungal disease caused by *Paracoccidioides brasiliensis*. There are two forms of the disease: subacute juvenile or the chronic adult form. The chronic form predominantly affects the lungs. In the subacute form, which affects children and young adults, the febrile lymphoproliferative syndrome is the major clinical manifestation.¹⁻⁵ In this clinical form, osteoarticular

involvement occurs in up to 20% of the cases, with lytic lesions in any bone; however, these lesions are more frequent on the chest and on the shoulder girdle.^{6,7}

Hypercalcemia has already been described in granulomatous diseases such as sarcoidosis and tuberculosis⁸⁻¹⁰ and also in fungal diseases,¹¹ but has been rarely associated with PCM.¹² Thus, the aim of the present study is to describe the case of a child with PCM who presented with hypercalcemia and diffuse osteolytic lesions.

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Case report

A 6-year-old white boy was admitted with a one-month history of high-grade fever. Three days after admission, the patient presented with an increase in abdominal volume and with skin lesions. He was referred from the basic health care unit because his fever had not subsided and also because hepatosplenomegaly had been noted.

The patient was in good general health, pale, and had small (1.0 to 1.5 cm) and movable lymph nodes, which were

palpable in all cervical and axillary lymph node chains. Skin lesions (varicella-like) were observed on the face and trunk. His abdomen was distended and tense on palpation, and the liver was nontender and palpable 8 cm below the right costal margin, whereas the spleen was nontender and palpable 10 cm below the left costal margin. On admission, his lab tests showed the following results: hemoglobin 6.8 g/dl; hematocrit 19.8%; leukocyte count 6,060/mm³ (56% segs and 20% eosinophils); platelet count 102,000/mm³; aspartate aminotransferase 7 U/l; alanine aminotransferase 27 U/l; urea 27 mg/dl; creatinine 0.48 mg/dl; alkaline phosphatase 429 U/l (up to 269 U/l); gamma-glutamyl transferase 116 U/l (9-40 U/l); serum albumin 2.2 g/dl (3.5-5 g/dl) and serum gammaglobulin 2.72 g/dl (0.8-1.6 g/dl). A myelogram was performed due to a suspected diagnosis of leukosis. It revealed a large number of oval-shaped structures with a refractile cell wall and with multiple budding, suggesting *Paracoccidioides brasiliensis*. The abdominal ultrasound showed an enlarged liver with a homogeneous echotexture, reaching the iliac fossa and the cluster of lymph nodes in the hepatic hilum; and also an enlarged spleen (16 cm). The chest x-ray showed perihilar infiltration and normal skeletal development. Due to a suspected diagnosis of PCM, intravenous administration of sulfamethoxazole-trimethoprim was initiated (8 mg/kg/day of trimethoprim). The HIV test was negative. No serological test for PCM was carried out.

At the end of the first week in hospital, the patient had leukopenia (2,950 leukocytes/mm³) and thrombocytopenia (48,000/mm³); therefore, amphotericin B deoxycholate (1 mg/kg/day) was added to the initial drug regimen. On the 14th day after admission, the patient presented with arthralgia, hypoactivity and difficulty in walking. Leukopenia improved (6,140 leukocytes/mm³), whereas albuminemia and hypercalcemia decreased substantially (1.52 g/dl and 11.2 mg%, respectively). On the 20th day after admission, the electrolytic disorder worsened, and calcium, potassium and magnesium levels of 12.9 mg%, 2.2 mEq/l and 1.8 mEq/l, respectively, were observed. The physical examination showed improvement of hepatosplenomegaly, and amphotericin B therapy was discontinued to prevent the deterioration of the electrolytic disorder. On the 25th day after admission, hypercalcemia (14.9 mg%) and hypokalemia (2.2 mEq/l) persisted despite IV hyperhydration with saline solution, potassium replacement, and administration of furosemide (2 mg/kg/day). There was also an increase in urea (62 mg/dl) and creatinine (0.7 mg/dl) levels, with a creatinine clearance of 58 ml/min/1.72m². The parathyroid hormone concentration amounted to less than 1 pg/ml (normal value = 12-72); serum phosphorus reached 6.1 mg/l (normal value = 3.5-5); the maximum tubular reabsorption rate for phosphorus (TmP) was 5 mg/ml/RFG (normal value = 2.5-4); calciuria reached 13 mg/kg/day (normal value up to 4); and urinary calcium/urinary creatinine ratio was 0.7 (normal value below 0.21). Limb pain and hypercalcemia persisted up to the 32nd day after admission. At this time, the abdominal ultrasound showed acute parenchymatous nephropathy with bilateral nephrocalcinosis and urolithiasis in the left kidney. As apathy and hypoactivity

persisted and since the chest x-ray revealed perihilar condensation, suggesting lymph node enlargement, gastric lavage was performed for the investigation of tuberculosis, and a liver biopsy was used to investigate other diseases that could be related to the poor outcome. Another myelogram was performed, showing severe hypoplasia and absence of parasites.

On the 42nd day after admission, the chest x-ray showed, for the first time, lytic lesions in clavicle, scapula, ribs and humerus; bilateral slipped capital humeral epiphysis, and left humerus fracture (Figures 1, 2 and 3).

^{99m}Tc-MDP bone scintigraphy showed diffusely decreased uptake in the skull cap, anterior and posterior costal arches, humerus, proximal third of the radius, hip bone, and femur. Since the liver biopsy still showed a large amount of fungi, amphotericin B therapy was reestablished for 20 days. At this time, creatinine clearance improved (86 ml/min/1.72m²), but the alpha-1-microglobulin/urinary creatinine level reached 10.64 (normal value below 0.17), suggesting tubular lesion. At hospital discharge, this ratio amounted to 0.44.

At the end of the second month after admission, *Mycobacterium tuberculosis* was identified in the gastric lavage, and a drug regimen with isoniazid, rifampicin and pyrazinamide was initiated. Bone involvement was treated in a conservative manner, that is, only with immobilization of the fractured humerus.

The patient was discharged after three months, with restricted arm abduction, and with the prescription of oral sulfamethoxazole-trimethoprim and the three-drug regimen (isoniazid, rifampicin and pyrazinamide) for tuberculosis. The patient has been in outpatient follow-up for three years, having completed the recommended treatment, with total normalization of laboratory parameters and with normal mobility of shoulder joints.

A written informed consent was signed by the patient's legal representative.



Figure 1 - Chest x-ray showing perihilar infiltration and lytic lesions in clavicle, scapula and humerus; bilateral slipped capital humeral epiphysis, and left humerus fracture

Comments

PCM in children predominantly affects the reticuloendothelial system, often causing febrile lymphoproliferative syndrome. Some authors suggest that children older than 10 years tend to show more severe osteoarticular and skin involvement than younger ones, in whom the liver and spleen are more commonly involved.^{1,2,4,5} The case presented here was characterized by a febrile lymphoproliferative syndrome with bone involvement.

Laboratory results are nonspecific, including, for instance, anemia, eosinophilia, hypoalbuminemia, hypergammaglobulinemia, high alkaline phosphatase levels and a high erythrocyte sedimentation rate.^{4,7} In



Figure 2 - Right shoulder x-ray



Figure 3 - Left shoulder x-ray

this case, the initial laboratory findings did not show hepatic or renal involvement. Although the liver biopsy showed a large amount of fungi, no laboratory evidence of hepatocellular lesion was found; only an increase in gamma glutamyl transferase was observed, which may be due to the compression of bile ducts by lymph nodes of the hepatic hilum. Other authors have already described this situation, which is often associated with hyperbilirubinemia.¹³⁻¹⁵

Bone marrow hypoplasia, which persisted for over one month after treatment initiation, was probably caused by fungal infection, as revealed in the first myelogram, and was not related to the use of amphotericin B or sulfonamide, since the bone marrow recovered despite the continued use of these drugs.

The diagnosis of tuberculosis was not exclusive to the case described herein. The association of these granulomatous diseases has been described in approximately 10% of PCM cases.¹⁶

Hypercalcemia is when the serum calcium level exceeds 11 mg% or when the ionic calcium level is greater than 5.6 mg% (or > 1.4 mmol/l).¹⁷ On the 14th day after admission, the patient complained of arthralgia and difficulty in walking, which was accompanied by hypercalcemia (11.2 mg%) and hypoalbuminemia (1.5 g%). Since each gram% of the reduction in albumin levels decreases 0.8 mg% of calcium levels, the highest calcium level value to be expected in this case is 8 mg%,¹⁷ which shows that calcium levels were already quite elevated. Based on the chest x-ray taken on the 42nd day after admission, which revealed multiple and extensive osteolytic lesions that could not be seen in the previous radiological examinations, the main hypothesis of hypercalcemia is that of bone destruction by the fungus. Hypercalciuria, expressed as mg/day or as the calcium/urinary creatinine ratio; parathyroid hormone (PTH) suppression; hyperphosphatemia associated with elevated maximum tubular reabsorption of phosphate;¹⁸ the development of nephrocalcinosis and nephrolithiasis and the deterioration of the glomerular filtration rate, occurring simultaneously with hypercalcemia, are all compatible with the increase in the availability of calcium and phosphorus in the extracellular fluid.¹⁷⁻¹⁹ The fact that no previous history of vitamin D supplementation existed rules out the possibility of vitamin D intoxication, which could mimic the same laboratory results.

In this case, though, it should be underscored that the well-known effect of poor adaptation of the kidneys to hypercalcemia might have occurred. In other words, the increase in calciuria levels occurs less often than the increase in the filtered load of calcium, thus keeping calcium levels elevated.^{18,19} Although this effect relatively protects the kidneys from the intratubular deposition of calcium, it acts to maintain hypercalcemia.¹⁹

Other effects of hypercalcemia on the kidneys include the impaired action of vasopressin, arteriolar vasoconstriction, and decrease in the glomerular capillary ultrafiltration coefficient.¹⁹ Although polyuria was not detected, renal function was reduced, reaching a clearance

of 58 ml/min/1.72m². Hyperhydration and the use of furosemide were enough to normalize calcium levels, and in the medium run, renal function as well. The detection of an increase and normalization of alpha-1-microglobulin/urinary creatinine indicates that the effect of the tubular lesion was transient and reversible.

The medical literature describes cases of hypercalcemia associated with granulomatous diseases, such as tuberculosis,⁹ sarcoidosis,¹⁰ histoplasmosis,¹¹ and cryptococcosis,²⁰ with only one case including PCM.¹² These reports show no association with osteolytic lesions, and hypercalcemia is poorly defined. This might occur due to an increase in the synthesis of 1.25(OH)₂D₃ in macrophages;^{9,10,21} however, this mechanism has already been contested in coccidioidomycosis.²² In this case report, the possibility that hypercalcemia could, in part, result from a similar mechanism should not be ruled out, because of its association with tuberculosis. Nevertheless, the sudden onset and later normalization of the disease, in addition to all correlations described above, suggest that bone lysis was the key element in the development of hypercalcemia.

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