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CASE REPORT

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SARCOID-LIKE GRANULOMATOUS MYOSITIS-ASSOCIATED HYPERCALCEMIA. AN INFREQUENT CASE TO CONSIDER

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Abstract PTH-independent hypercalcemia due to granulomatous disease is well-documented and sarcoidosis is the most characteristic disease, although there are others. We describe a case of sarcoid-like granulomatous myositis. An 87-year-old man was referred with tetraparesis and hypercalcemia (albumin-corrected calcium of 13.4 mg/dl) following a trip to the Caribbean. The evaluation showed a suppressed PTH, 25-hydroxy vitamin D of 7.5 ng/ml, ^{18}F-FDG PET/CT showed markedly increased uptake in intercostal, back, shoulder, buttock and thigh muscles and a deltoid biopsy confirmed extensive granulomatous myositis. He was prescribed glucocorticoids which resulted in normalized plasma calcium levels and complete recovery from tetraparesis. Sarcoid-like granulomatous myositis should be incorporated into the differential diagnosis of PTH-independent hypercalcemia, especially in the absence of clinical features of sarcoidosis and with special emphasis on the use of ^{18}F-FDG PET/CT to ensure a correct approach.

Key words: hypercalcemia, sarcoid-like granulomatous myositis, granulomatous disease

Resumen ***Hipercalcemia asociada a miositis granulomatosa sarcoidea simil- sarcoidea. Un caso infrecuente a considerar***. La hipercalcemia PTH-independiente asociada a enfermedades granulomatosas está bien documentada y la sarcoidosis es la enfermedad más característica, a pesar de que existen otras. Describimos un caso de miositis granulomatosa simil-sarcoidea. Un hombre de 87 años consultó por tetraparesia e hipercalcemia (calcio corregido por albúmina 13.4 mg/dl) luego de un viaje al Caribe. La evaluación mostró una PTH suprimida, 25-hidroxivitamina D 7.5 ng/ml, ^{18}F-FDG PET/CT mostró marcado aumento de captación a nivel de musculatura intercostal, dorsal, deltoidea, glúteos y muslos. Una biopsia deltoidea confirmó una miositis granulomatosa extensa. Se prescribieron glucocorticoides, resultando en normalización del calcio plasmático y completa recuperación de la tetraparesia. La miositis granulomatosa simil-sarcoidea debe ser incorporada dentro del diagnóstico diferencial de la hipercalcemia PTH-independiente, especialmente en ausencia de hallazgos clínicos de sarcoidosis y con especial énfasis en el uso de ^{18}F-FDG PET/CT para su correcta aproximación.

Palabras clave: hipercalcemia, miositis simil-sarcoidea, enfermedad granulomatosa

Granulomatous disease-associated hypercalcemia is well-documented and is caused by PTH-independent extrarenal expression of 1-α-hydroxylase (1α-OH) in macrophages, activated by unregulated production of 1-α,25-dihydroxycholecalciferol (1, 25$(OH)_2$D)[1]. Sarcoidosis is one of the most characteristic diseases of this hypercalcemia mechanism, although there are various others. Here, we present a case of granulomatous disease-associated hypercalcemia to describe a recently documented entity.

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Case report

An 87-year-old man consulted the Emergency Department with a 3-month history of progressive proximal tetraparesis, associated with weight-loss of 10 kg following a trip to the Caribbean. He had no fever or any other constitutional symptoms. The patient's medical record documented arterial hypertension, pacemaker use as a result of a complete AV block and family history of a daughter with systemic lupus erythematosus and Hashimoto's thyroiditis. Medications included amlodipine, valsartan and acetylsalicylic acid. There was no occupational, animal or drug exposures, nor any risk factors for tuberculosis. The physical examination revealed symmetrical proximal tetraparesis with preserved reflexes, without further relevant findings.

The blood tests showed albumin-corrected calcium of 13.4 mg/dl (normal, 8.5-10.5), phosphorous of 3.0 mg/dl (normal, 2.6-4.5), magnesium 1.2 mg/dl (normal, 1.6-2.4), creatinine 1.07 mg/dl and total creatine kinase (CK) levels of 64 U/l (normal, < 190). Additional tests revealed intact PTH of 12 pg/ml (normal 15-65; electrochemiluminescent immunoassay; Cobas/

Roche), 25OHD 7.5 ng/ml (normal, 20-50; chemiluminescent microparticle immunoassay; Architect i-Abbott), TSH 2.7 µIU/ml (normal, 0.3-4.2) (Table 1) A $1,25(OH)_2D$ level was not available. Serum and urinary protein electrophoresis did not reveal a paraprotein. Bone marrow aspiration and flow cytometry did not show any evidence of lymphoma or tuberculosis. Initial therapy with intravenous fluids and bisphosphonate (zolendronic acid, 4 mg iv) resulted in only modest improvement in his serum calcium.

^{18}F-FDG PET/CT showed markedly increased uptake in intercostal, back, shoulder, buttock and thigh muscles, without mediastinal lymphadenopathy or other relevant tomographic findings (Fig. 1A, 1B). A deltoid biopsy was performed, which showed groups of non-caseating nor necrotising epithelioid granulomas and the presence of Langhans cells in association with atrophic, hypertrophic and necrotic muscle fibers with endomysial inflammatory infiltrate, indicative of a long-standing myositis (Fig. 1C). There was no evidence of vasculitis, no acid fast bacilli were identified on Ziehl-Neelsen stain and no fungal organisms. QuantiFERON-TB Gold essay, antinuclear antibody, antineutrophil cytoplasmic antibody and neoplastic disease tests were negative.

Thus, PTH-independent hypercalcemia-associated sarcoid-like granulomatous myositis was diagnosed. The applied treatment was high dose of glucocorticoids, resulting in normalized plasma calcium levels and complete recovery from tetraparesis. At the time of the follow-up 3 months after discharge, bioquemical parameters continued to be within the normal intervals, with tapering prednisone doses and no evidence of relapse.

Discussion

We present a case of sarcoid-like granulomatous myositis based on a PTH-independent hypercalcemia, muscle symptoms that drove us to ^{18}F-FDG PET/CT hallmarks and finally non-caseating granulomas certifying the diagnosis.

Sarcoid-like granulomatous myositis is an entity that has recently been described as a sarcoid muscular reaction without multisystemic symptoms, which would be concordant with sarcoidosis[2,3]. Unlike sarcoid myopathy, this entity presents with muscular weakness without pain or atrophy, normal levels of muscular enzymes, moderate to severe hypercalcemia, diffuse ^{18}F-FDG muscular uptake and no other sarcoidosis features. Data of 8 patients was compiled in a previously published series of cases. The symptoms included fatigue, proximal muscle weakness and weight loss, coupled with normal values of CK, severely elevated plasma calcium levels, with suppressed PTH and ^{18}F-FDG PET/CT showing diffuse and isolated muscle uptake, without perihilar or mediastinal lymph nodes in the cases where ^{18}F-FDG PET/CT was available. The biopsy showed diffuse non-necrotising granulomas in all of the cases, with positive immunohistochemistry for 1α-OH in those where it was carried out. Finally, all of them showed excellent clinical and calcaemic response to corticoids[2].

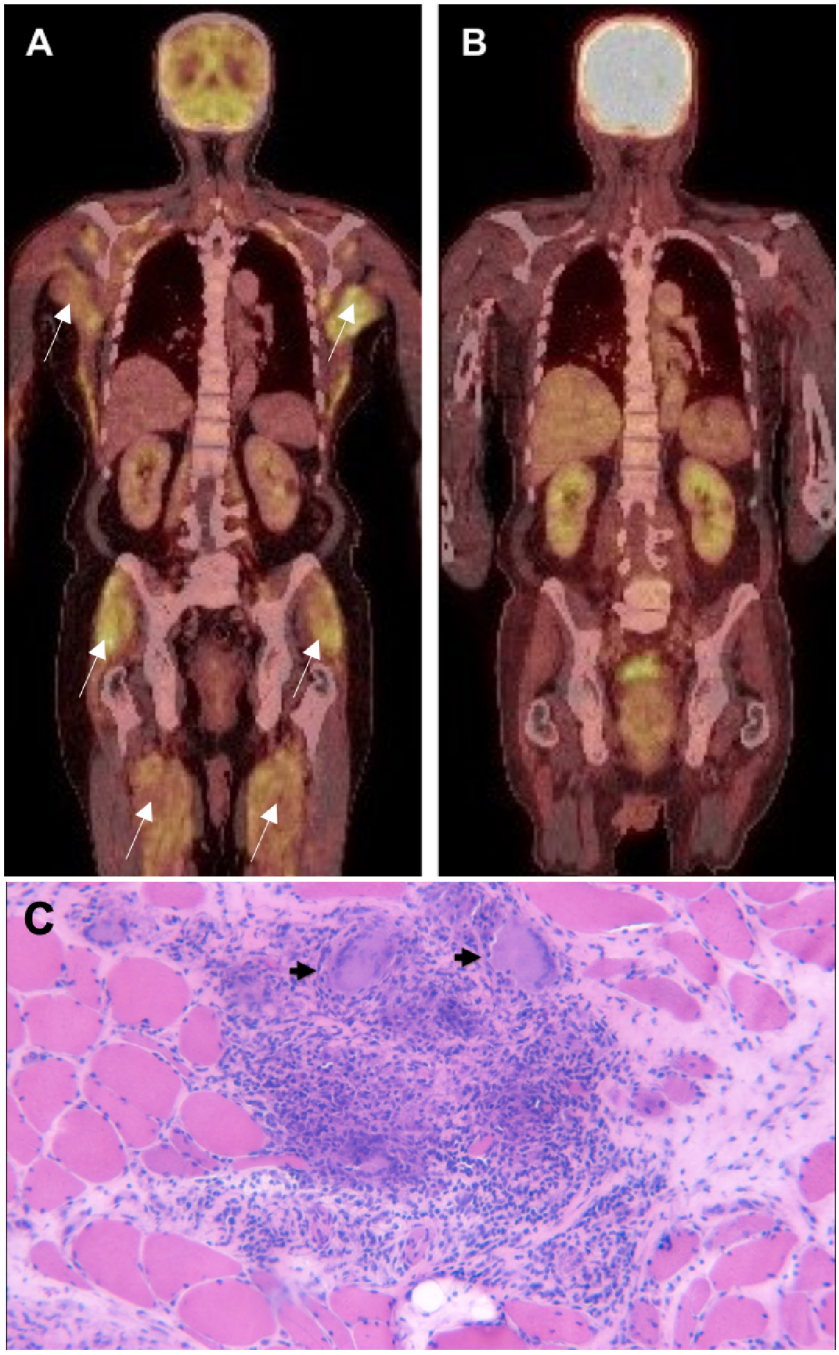
The differential diagnosis must be established based on other causes of muscular granulomas and PTH- independent hypercalcemia. In a series of 2985 samples of muscle biopsies, granulomatous myositis was found in 0.5% of the cases. The most frequent cause was sarcoidosis in 50%; followed by vasculitis in 16% of the cases[4]. Sarcoidosis is a multisystemic inflammatory disease characterised by non-caseating granuloma formation in multiple organs[5]. The diagnosis requires compatible medical history, radiological and histological profile, as well as the exclusion of other diseases that could show the same symptoms. Given that the diagnosis is one of exclusion, it cannot be confirmed with absolute certainty. The histological muscle compromise related to this disease has been reported in up to half of the patients, but only in less than 3% of the cases with clinical repercussions[5]. Three

TABLE 1.– *Parameters during the hospital stay*

Parameter	Day 01	Day 03	Day 07	Day 10	Day 16	Normal values
Calcium (mg/dl)	13	12.6	11.8	9.8	9.4	8.5-10.5
Phosphorous (mg/dl)	3.3	4.3			3.0	2.6-4.5
Albumin (gr/dl)	3.7		3.3	3.2		3.5-5.0
PTH (pg/ml)	12					15-65
CK total (U/l)	64					
25OHD (ng/ml)	7.5					20-100
VHS	10				2	1-19
Creatinine (mg/dl)	1.07			1.31		0.7-1.2
Urine calcium 24 hours (mg/24 h)			470			25-300
Treatment	Zoledronate 4 mg e/v		Methyl-prednisolone 1.5 g			

PTH: parathyroid hormone; CK: total creatine kinase; 25OHD: 25-hydroxy vitamin D

Fig. 1.– ^{18}F-FDG PET/CT. A): Coronal images revealing multiple intense ^{18}F-FDG uptakes in intercostal, back, shoulder, buttock and thigh muscles (white arrows). B: Complete regression of aforementioned pathologic ^{18}F-FDG uptakes after 3 months of steroid treatment. C: Deltoid muscle histopathology. Non-caseating nor necrotising epithelioid granulomas and the presence of Langhans cells in association with muscle fiber with increase variability of their diameters given by the presence of isolated atrophic, hypertrophic and necrotic fibers with endomysial inflammatory infiltrate, indicative of a long-standing myositis (black arrows). Hematoxylin and eosin.



^{18}F-FDG PET/CT = fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography

forms of presentation have been described: nodular sarcoid myopathy, characterised by multiple painful nodules in proximal muscles; acute sarcoid myopathy, which is infrequent and characterised by CK elevation-related proximal weakness with fast development; and chronic sarcoid myopathy, which is characterised by progressive symmetrical proximal muscle weakness, pain, atrophy and normal levels of muscle enzymes, the latter being the most frequently described manifestation[6]. Isolated extrapulmonary manifestation of sarcoidosis is seen in 2% of the cases, and only 1.5-5.5% of these present calcium related disorders. Finally, the presence of non-caseating granulomas in a single organ is insufficient for diagnosing sarcoidosis because, by definition, sarcoidosis is a systemic disease that should involve multiple organs. Pulmonary compromise is the only symptom that allows to form the diagnosis, even by itself[7, 8].

Other granulomatous disorders described as rare causes of PTH-independent hypercalcemia include granulomatosis with polyangiitis, Crohn's disease, rheumatoid arthritis, Langerhans cell granulomatosis, foreign substance reactions, such as to talc in former mold makers and to silicone in cosmetic injections, infectious diseases such as tuberculosis, non-tubercular mycobacteria, leprosy, *Cryptococcus neoformans* and *Pneumocystis jirovecci* infections[9]. In Chile, it is particularly relevant to rule out tubercular granulomas as a possible cause, which are typically caseating. In our case, the absence of this features in the biopsy, added to the negative QuantiFERON, makes this diagnosis highly unlikely. Additionally, sarcoid reactions have been described in the context of solid tumours such as seminoma, leiomyoblastoma, squamous cell bronchogenic carcinoma and lymphomas[1, 11]. This is why it is essential to rule out these conditions before establishing the diagnosis of isolated muscular sarcoid reaction. A directed examination of these conditions was carried out, which allowed us to discard them.

Even though it is unknown how frequent the occurrence of hypercalcemia as a symptom is among all the granulomatous diseases, in sarcoidosis it is described in 10% of the patients[5] and its mechanism involves the unregulated conversion of 25OHD into its active form, $1,25(OH)_2D$, through the extrarenal expression of 1α-OH in activated macrophages[1]. The link between $1,25(OH)_2D$ -related hypercalcemia and granulomatous diseases was first described in 1939 in sarcoidosis patients with hypercalcemia and/or hypercalciuria[12]. In 1981 an increase of $1,25(OH)_2D$ was observed in anephric patients and with end-stage renal disease (ESRD), thus establishing that the kidney was not the source of the elevated serum concentrations of $1,25(OH)_2D$ (13). In 1985, it was demonstrated that pulmonary macrophages convert 25OHD to $1,25(OH)_2D$ in sarcoidosis[14]. It has been suggested that gamma-interferon secreted by these cells plays an essential role in the process. Under standard conditions, increased concentration of $1,25(OH)_2D$ acts as a source of negative autocrine feedback, decreasing the expression of 1α-OH and increasing mRNA concentrations of 24-hydroxilase in reticuloendothelial cells, thus producing lower synthesis and higher catabolism of the active hormone[15]. However, in *in vitro* models it has been observed that said regulation is lost when both gamma-interferon and $1,25(OH)_2D$ are present, which would explain the excessive production of the active hormone in granulomatous diseases[15]. Unfortunately, it was not possible to measure $1,25(OH)_2D$ in our patient because of the unavailability of the test in our laboratory. It is worth pointing out that he started showing symptoms after a trip to the Caribbean, with sustained exposure to the sun. The association of sunlight exposure with hypercalcemia raised the possibility that abnormal vitamin D metabolism might play a role in the pathogenesis of hypercalcemia. In fact, there are well-established cases where Vitamin D_3 supplementation precipitate hypercalcemia in granulomatous disorders[10], as well as in rheumatoid arthritis and candidiasis[9].

Vitamin D-mediated hypercalcemia treatment includes a reduction in dietary calcium uptake, avoidance of sun exposure and treatment of the underlying cause. The unregulated 1α-OH production of granulomatous tissue is usually adequately corrected with glucocorticoids in moderate doses within 3 to 5 days of initiating treatment[1]. The reported prognosis based on studies of case series of hypercalcemia secondary to sarcoid-like granulomatous myopathy is encouraging, with rapid and complete recovery within 18.5 months of monitoring. Relapse was only observed in a single case[2].

In conclusion, we present a case of a very uncommon entity characterised by muscular sarcoid reaction with severe PTH-independent hypercalcemia. Our view is that this new entity must be incorporated into the differential diagnosis of PTH-independent hypercalcemia, especially in the absence of clinical features of sarcoidosis and with special emphasis on the use of ^{18}F-FDG PET/CT to ensure a correct approach.

Conflict of interest: None to declare

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