An uncommon association between parathyroid adenoma and Hodgkin disease

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The Authors refer their experience of a patient operated for adenoma of the inferior parathyroid of left lobe associated to a limphoadenopathy from HD. Diagnostic and therapeutical approach are described. The literature of these last decades reports a single case with similar characteristics, but not with the same association. Numerous neoplasias associated more frequently with parathyroid adenoma are mentioned and the probable causes of this association. Although the associations with other affections of the hemolymphopoietic system are relatively frequent, the causes of the rarity of the association between parathiroid adenoma and HD remain unkown.

KEY WORDS: Cyclin D1, Hodgkin disease, Primary hyperparathyroidism.

Introduction

Hyperparathyroidism is well known as a syndrome with an increased parathyroid hormone (PTH) that causes an increase of the serum level of calcium [1].
It is a common disease with an incidence level of 1 in 3000-4000 people [2].
Altough PHPT can occur with other neoplasms in the hereditary disease known as multiple endocrine neoplasia (MEN) of type 1 (95% of cases) or less commonly of type 2 [3], single or multiple adenoma of the parathyroid gland are responsible for primary hyerparathiroidism (PHPT) in 85% of patients [1].

Several studies report an association of parathyroid adenoma with other neoplasms, including haemathologic neoplasias. In particular, different studies report an association of PHPT with multiple myeloma [1, 4-7] and, less frequently, with cutaneous [8] and B cell lymphoma [9].
The association of Hodgkin's disease (HD) with hypercalcemia has been reported in the last 30 years by many authors [10-15] but its association with primary hyperparathyroidism is a very exceptional event [16].
We report a case of a 60 year old female patient with parathyroid adenoma and coexisting Hodgkin's disease. This exceptional finding brought us to review the literature concerning the association between parathyroid adenoma and haematologic neoplasias and evaluate a link on the basis of a genetic study.

Case Report

In June 2006 a 60 year old female patient was admitted to our hospital with a laterocervical swelling and hyperparathyroidism. The physical examination revealed

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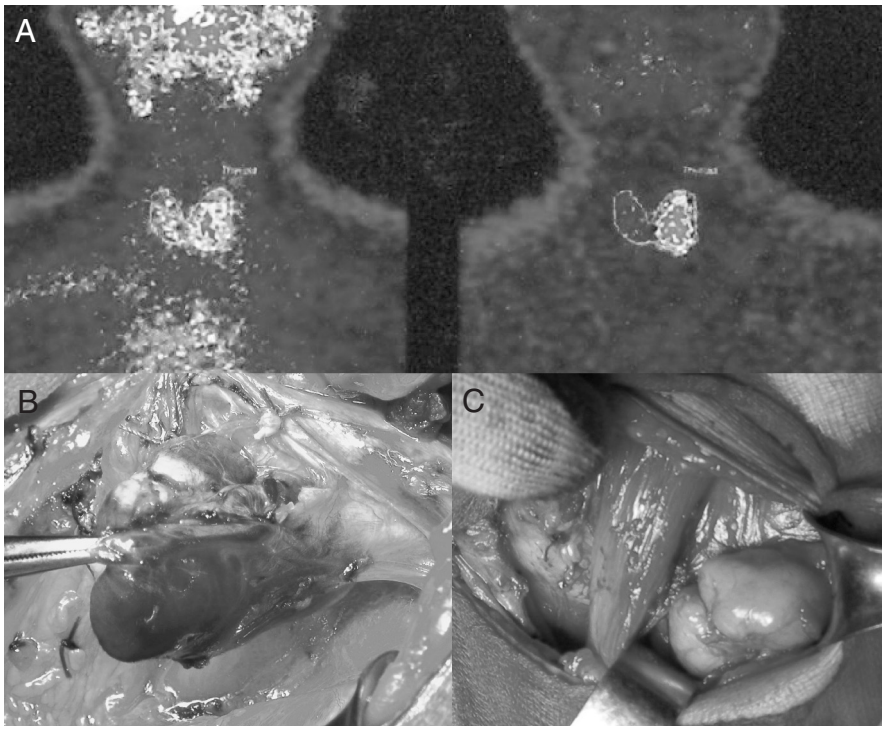

Fig. 1: **A-B**: Parathyroid ^{99m}-Tc e ^{99m}-Tc MIBI scintigraphy evidencing a hypercapting area on the left side after electronic subtraction of the radionuclides. **C**: Left parathyroid adenoma. **D**: On the left side of the sternocleidomastoid muscle insertion on sternum, left thyroid lobe where the parathyroid adenoma was resected and the lymphatic mass on the right side.

a 4 x 2 cm mass, in the sopraclavear left area. The patient had a neck scan that showed two masses: a nodular, solid and an hypoecogenic one (cm 4 x 1.6 x 2), positioned behind the distal third of thyroid left lobe, richly vascularizated, resembling a parathyroid with a volumetric growth, and a second one, located in the sopraclavear left area. This mass was referred to multiple limphoadenomegaly.

Laboratory findings at the time of her admission revealed the following serum levels: parathyroid hormone 852 pg/ml (10-65pg/ml), calcium 14.3 mg/ml (8.8-10.5 mg/ml), phosphorus 2,1 mg/dl (2.7-4.5mg/dl), alkaline phosphatase 668 U/L (98-279 U/L) .

Parathyroid scintigrafy, using different enhancements in two following steps (^{99m}Tc and ^{99}Tc - ^{6}MIBI scintigraphy), and then elaborated with a subtraction technique, detected a round area with an increased captation, located on the lower portion of the left thyroid lobe.

The patient was treated by surgical therapy. Through a cervical incision the mass located on the left thyroid lobe was successfully removed according to surgical guidelines that indicate adenomectomy as the treatment of choice in symptomatic and asymptomatic patients with documented increased level of PTH, and calcemia [17,18].

During the surgical treatment was relieved a PTH levels of 930 pg/ml before adenoma excision and, after the excision, a level of 191 pg/ml at 10' and a level of 98 pg/ml at 20'.

Using the same cervical incision was also removed the mass located in the sopraclavear area in order to allow an histological diagnosis.

Pathology findings revealed a parathyroid adenoma and in the supraclavear node a HD with limphocitic-nodulaire prevalence (WHO) classified, with immunohistochemical reaction, as immunophenotipe CD20+;CD 30.

The postoperative period was uneventful and the patient was discharged from the hospital three days after surgery. No late complications were reported in the follow up.

The patient was sent to the Oncology Division where she had further investigations in order to establish an appropriate therapy.

Discussion

Altough association between the increase rate of incidence of malignant tumors in PHPT patient are not fully understood, we can made some Hypothesis.

Hypercalcemia in the adenomas of parathyroids must be well differentiated by the hypercalcemia as a common metabolic complication frequently associated with malignancies [19,20].

In a minority of neoplastic patients hypercalcemia can be related to the bone metastasis. In the majority of cases it can be caused by PTH related proteins (PTHrP) produced by the neoplasm [21-25].

Rarely the hypercalcaemia is related to an ectopic production of PTH or calcitriol, or still, of prostaglandins from the tumour [8,15].

Hypercalcemia from localized osteolysis is caused on the contrary by a heterogenous group of mediators, assets in the processes of bone resorption, locally produced by

neoplastic cells. The transforming growth factor-E (TGF-E), interleukine 1 (IL-1), interleukine 6 (IL-6), prostaglandins, tumours necrosis factor - α (TNF-α) and other citokines can have a role in the hypercalcaemia from localized osteolysis. In particular it is unclear the action of these mediators in hypercalcemia associated to multiple myeloma [4,6,26]. Some authors have postulated a role of the PTH that stimulates stromal-osteoblastic cells to produce IL -6: this IL, in fact, is responsible for the development of plasmacell's dyscrasias [4-6,27].
In the patients affected by lymphoma, in addiction to PTHrP, the biochemical mediator responsible for an increased level of calcemia is often represented by calcitriol (1,25 [OH]2 D3) [15,25]. It has been demonstrated that the lymphomatous tissue is able to convert 25-hydroxyvitamin D to calcitriol in vitro and some Authors, verifying that the macrophagic cells can produce calcitriol if stimulated from specific citokines, assess that macrophagic cells normally infiltrating the neoplastic tissue could be responsible for the hypercalcaemia mediated from calcitriol in the patients affected by lymphoma [28-30]. Finally it is interesting to observe that some citokines and growth factors produced by neoplastic cells, also like various constituents of the extracellular matrix, can modulate the production of PTHrP and its effect on renal tubules and bone tissue [24].
The association of hyperparathyroidism and HD in the same patient is an exceptional event and we have found a single case reported in the literature in the past few years [16]. On the contrary we have found in the literature more cases about the association of hyperparathyroidism with lymphoproliferative affections like: lymphoma to cells B [9] lymphoma not Hodgkin of extranodal localization [20], and primitive cutaneous lymphoma [8]. During the last few years, however, the studies of molecular genetics have allowed to clear the fine mechanisms implied in the cellular cycle, characterizing many of the genes that regulate it.

Genetic overview

Among these, at the beginning of the 1990s, was cloned, beginning from a localized chromosomic rearrangement on 11q13, the PRAD1 gene, that is responsible for cyclin D1 [31,32]. This protein acts as a receiver and an integrator of marks coming from the outside of the cell like, for example, growth factors (IGF I and IGF II), hormones androgens and estrogens, lysophosphatidic and retinoic acid, TGF-β, and PTHrP. Moreover it exercises its action on proteins responsible for the histone acetylation and deacetylation, and on the kinase cicline dependent (CDK). In this way it stimulates cells from the G1 phase to S phase [32]. Moreover on the cellular cycle it acts indirectly inactivating the protein pRB and thus favoring the evolution towards the neoplastic transformation [32, 33].
Oncogenes like Ras, Src, ErbB2, β-catenina induce the synthesis of cyclin D1, which, in its turn, interacts with several trascrictional factors [32].
Gene PRAD-1 was characterized the first time in a patient affected from parathyroid adenoma near the promoter of the gene for PTH after rearrangement [32,34].
Different studies have demonstrated its increased expression, and therefore a role, in the genesis of other neoplasms: melanoma, breast and colon cancer or prostatic neoplastic pathologies and lymphomas too [32].
A recent study has considered the role of mutation in another protein, *the menin*, to explain the elevated potential for tumorigenesis in other organs in patients coaffected by PHPT [9]. The menine gene is located on the same human chromosome 11q13 and it is responsible for autosomal dominant form of the disease MEN type 1. It is a nuclear protein that acts as a tumor suppressor inactivating the AP1 positive regulator factor of cell proliferation JunD: when there is a menin loss or disabling of menin's ability to bind to JunD or missense mutation of JunD that disables JunD binding to menin, it is possibly a major incidence of malignancies [9].
Its relationship with cyclin D 1 fuction was postulated for the first time by Arnold et Coll. [36], but recently other studies have demonstrated the effects of Jun D and menin on cyclin D1 expression. The AP1 site in the cyclin D1 promoter can bind several AP1 proteins, including Jun D, and could even be the critical site for the direct action of Jun D with menin. However the current data do not address whether cyclin D1 is a mediator or a bystander in the Jun D-menin actions on growth. Similarly, even an indirect effect of Jun D on the cyclin D1 promoter, does not affect considerations here about JunD-menin downstream expressions [35].
Thus it is necessary to begin further studies to evaluate, in the HD, the precise mechanism of cyclin D1 action, and its relationship with the menin function and if it is possibile to postulate a link beetween menine gene mutation and HD related to parathyroid adenoma.

Conclusions

We report a case of parathyroid adenoma associated with HD. The association between parathyroid adenoma and HD is very uncommon. From our knowledge only one other case, has been reported regarding association between HD and parathyroid gland hyperplasia [16].
Altough an association between parathyroid adenoma and other malignant tumors is a common finding, we single out some neoplasms in which the association seems to be a consequence of a cromosomic break point rearrangement on 11q13, related to PRAD1 gene (responsible for Cyclin D1 synthesis) and mutation of menin gene too. [9, 31, 32]
In fact both mutated genes were identified at the beginning in a patient affected by PHPT. In our opinion this

evidence could explain the higher incidence of particular neoplasias in those patients affected by parathyroid adenoma. In those neoplastic pathologies related to lymphomatoid tissues, multiple myeloma is the most frequent [1,4-7].

In our experience the patient has been successfully treated with surgical resection of the neoplasms resulting in an improvement of patient's serum calcium and oncological integrated therapy. The follow up of our patient shows no relapse of disease at the present time.

Riassunto

Gli Autori fa riferiscono la loro esperienza relativa a una paziente operata perchè affetta da iper-paratiroidismo conseguente ad un adenoma paratiroideo associato a linfonodopatia sopraclaveare dimostratasi poi essere linfoma di Hodgkin (HD). Numerose malattie neoplastiche del sistema emopoietico sono state associate agli adenomi delle paratiroidi e in particolare i linfomi non Hodgkin, in letteratura però abbiamo trovato un solo caso con parametri simili al nostro. L'eccezionalità di questa associazione ha fornito alcuni spunti oggetto del presenta lavoro.

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