An uncommon association between parathyroid adenoma and Hodgkin disease

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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. Although 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 hyperparathyroidism (PHPT) in 85% of patients 1.

Several studies report an association of parathyroid adenoma with other neoplasms, including haematologic 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...
A 4 x 2 cm mass, in the supraclavicular 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 vascularized, resembling a parathyroid with a volumetric growth, and a second one, located in the supraclavicular left area. This mass was referred to multiple lymphadenomegaly.

Laboratory findings at the time of her admission revealed the following serum levels: parathyroid hormone 852 pg/ml (10-65 pg/ml), calcium 14.3 mg/ml (8.8-10.5 mg/ml), phosphorus 2.1 mg/dl (2.7-4.5 mg/dl), alkaline phosphatase 668 U/L (98-279 U/L).

Parathyroid scintigraphy, using different enhancements in two following steps (99mTc and 99Tc - 9MIBI 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.

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 supraclavicular area in order to allow an histological diagnosis.

Pathology findings revealed a parathyroid adenoma and in the supraclavicular node a HD with lymphocitic-nodulaire prevalence (WHO) classified, with immunohistochemical reaction, as immunophenotipe CD20+;CD30.

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

Although 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.

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.

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

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, tumors 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. Some authors have postulated a role of the PTH that stimulates ostomal-osteoblastic cells to produce IL -6: this IL, in fact, is responsible for the development of plasmacell's dyscrasias. Finally it is interesting to observe that some macrophagic cells normally infiltrating the neoplastic tissue, 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. 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.

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. On the contrary we have found in the literature more cases about the association of hyperparathyroidism with lymphoproliferative affections like: lymphoma and Hodgkin disease. The association of hyperparathyroidism and HD is very uncommon. From our knowledge only one other case, has been reported regarding association between HD and parathyroid adenoma. 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. Although 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 chromosomal break point rearrangement on 11q13, related to PRAD1 gene (responsible for Cyclin D1 synthesis) and mutation of menin gene too. 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 affected by PHPT. The menin 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 malignacies. Its relationship with cyclin D1 function was postulated for the first time by Arnold et Coll. 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.

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 possible to postulate a link between menin 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. Although 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 chromosomal break point rearrangement on 11q13, related to PRAD1 gene (responsible for Cyclin D1 synthesis) and mutation of menin gene too.

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.

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 perché affetta da iper-paratiroïdismo conseguente ad un adenoma paratiroideo associato a linfonodopatia sopravclavare dimostrato 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 presente lavoro.

References


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