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Concurrent papillary cancer of the thyroid gland and parathyroid carcinoma with paraplegia as the chief presenting complaint

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Summary. Association of primary hyperparathyroidism with various malignancies is a known phenomenon. However, hyperparathyroidism presenting as a result of parathyroid carcinoma in association with Nonmedullary thyroid carcinoma is quite rare. In this report a rare case of primary hyperparathyroidism is presented in which paraplegia and radicular pain of lower limbs were the presenting symptoms. The patient was histopathologically diagnosed with concurrent papillary cancer of the thyroid gland and parathyroid carcinoma. The characteristics of the patient's vertebral lesion were suggestive of Brown tumor. Ten days after parathyroidectomy, the patient exhibited delayed hungry bone syndrome.

Key words: parathyroid carcinoma, Brown tumor, thyroid cancer

«Concomitante cancro papillare della ghiandola tiroidea e carcinoma paratiroideo con paraplegia come manifestazione principale di malattia»

Riassunto. L'associazione di iperparatiroidismo primario con neoplasie di vario tipo è un fenomeno riconosciuto. Tuttavia, l'iperparatiroidismo derivante da un carcinoma della paratiroide in associazione con carcinoma tiroideo non midollare è piuttosto raro. In questo studio viene riportato il raro caso di un iperparatiroidismo primario in cui la paraplegia e il dolore radicolare degli arti inferiori sono stati i sintomi che si sono presentati. Al paziente è stata fatta una diagnosi istopatologica di cancro papillare della ghiandola tiroidea associato a carcinoma della paratiroide. Le caratteristiche delle lesioni vertebrali del paziente erano indicative del tumore di Brown. Dieci giorni dopo la paratiroidectomia, il paziente mostrava segni di sindrome "dell'osso affamato" ritardata.

Parole chiave: carcinoma paratiroideo, tumore di Brown, cancro della tiroide

Introduction

The prevalence of primary hyperparathyroidism is reported between 0.12% - 1% in the general population, mainly diagnosed during the work-up for hypercalcemia (1, 2).

This condition, frequently observed in women and the elderly, is strongly associated with radiation to the head and neck; (3) nonetheless, its underlying causes are almost always parathyroid adenomas rather than hyperplasias or carcinomas of the parathyroid gland (4).

Association of primary hyperparathyroidism with various malignancies is a known phenomenon (5). Nonmedullary thyroid carcinoma has been observed to coexist with primary hyperparathyroidism in slightly less than 4% of patients; however, concurrent papillary cancer of the thyroid gland and parathyroidal cancer is rare (6, 7).

Here we report a rare association of thyroid carcinoma with primary hyperthyroidism which manifested with spinal cord compression.

General case data

A 65 year-old Iranian man presented with a 3-month history of progressive fatigue and lower limb radicular pain, paraplegia and urinary retention. On neurologic examination, the muscular force in both lower limbs was 2/5 and a sensory level was detected around the T2-3 level. In the upper limbs, a 5/5 level of muscular force was found.

In view of the preliminary lab results which showed PTH=2297 pg/ml, VitD3=10.64 ng/ml, Ca=13.8 mg/dl and Ph=2.2 mg/dl, primary hyperparathyroidism was suspected. Ultrasound scan of the thyroid and parathyroid glands revealed multiple hypo echo nodules of less than 5 mm in diameter without calcification in both lobes and a mass in the left parathyroid gland which was further investigated with 99TC CT Spect. The resulting image was suggestive of Adenoma or Adenocarcinoma of the Parathyroid gland. Upon admission of the patient to hospital, preliminary treatment of hypercalcemia was initiated as follows.

On the first day of treatment the patient was put on IV Normal saline and Frusemide which lowered his plasma Ca level to 13.06 mg/dl. The lab and imaging results being ready, a verdict of left parathyroidectomy operation was reached. However, in view of his age and the hypo echo masses in the thyroid gland, on the following day he underwent total left thyroidectomy. The PTH level was checked during and following the operation, and showed a significant decline to 343 μg/dl. The Ca level also dropped to 9.77 mg/dl, which indicated a successful operation.

As part of the work-up for the patient's neurologic deficits (Paraplegia, Urinary retention etc.) which indicated a compressive myelopathy, he had a CT scan which showed an osteolytic lesion in T1 with involvement of the lamina and the spinous process. The MRI revealed a compressed fracture of T1 (Figure 1).

To rule out involvement of other areas in the spinal column, a whole body bone scan was performed which showed a general increase in radioactive uptake throughout the spinal-column suggestive of metabolic bone disorders. The patient promptly underwent decompression and fixation of T1. The excised bone which in appearance resembled metastasis, giant tumor or Brown tumor, was processed for histopathology. The histopathology reports for the thyroid, parathyroid and bone specimens were respectively as follows in Figures 2-4.

Oral Ca-Vit D supplement was started and, on the 8th day after the operation, he was discharged from hospital with a normal neurologic examination, including normal muscle force (5/5) and normal lab values (PTH=7.3 ng/ml, Ca=9.03 mg/dl).

Two days after discharge from the hospital the patient reported to the clinic with paresthesia and spasms in his limbs. In view of his lab values (PTH=23.8, Ca=7.06 mg/dl) he was diagnosed with hungry bone syndrome, was put on 1800 mg/day IV infusion of Calcium, Ca-D tablet BD, Effervescent Ca BD and Rocaltrol pearl BD for two weeks, and was discharged with Ca=8.6 mg/dl, PTH=23 μg/dl and Ph=2.79 mg/dl (Table 1).

Table 1. Chronicle of lab values for PTH, Ca and Ph over time.

	Upon admission to hospital	Following the operation	1 day after the operation	2 days after the operation	8 days after the operation	10 days after the operation	11days after the operation	14 days after the operation	18 days after the operation	Final discharge
Ca	13.80	9.77	9.23	9.05	9.03	7.06	7.11	7.78	8.30	8.6
Ph	2.20	1.45	1.46	1.50	2.40	2.51	2.60	2.70	2.70	2.79
PTH	2297	343	23.31	7.32	7.30	23.58	23.31	23.31	23.31	23

Table 2. Comparison of some parameters pertaining to the present case and two similar cases from the literature.

Case	Laboratory results	Time to diagnosis	Treatment	Outcome of treatment
The present case	PTH=2297 pg/ml, Ca=13.8 mg/dl, VitD3=10.64 ng/ml, Ph=2.2 mg/dl	3 months	Total left thyroidectomy, Fixation of T1	Normalization of lab values after 2 years' follow up
Lin SD, Tu ST, Hsu SR *et al*, 2005 (21)	PTH= 107 pmol/L; normal range, 1.8–7.3 pmol/L Ca= 4.05 mmol/L; normal range, 2.2–2.6 mmol/L	6 years	Total thyroidectomy and left parathyroidectomy. Bipolar arthroplasty 131I therapy	Serum levels of calcium and PTH remained normal during early follow-up for more than 6 years.
Mehmet Kiliç, *et al* (22)	Ca=9.92mg/dl (Normo-calcemic)	6 months	Total thyroidectomy parathyroidectomy, 131I therapy	No evidence of metastatic foci at one year, no recurrence of parathyroid cancer after 18 months
Carman R, *et al* (23)	PTH=925pg/ml, Ca=14mg/dl,	Without any complaints	Parathyroidectomy	Not included

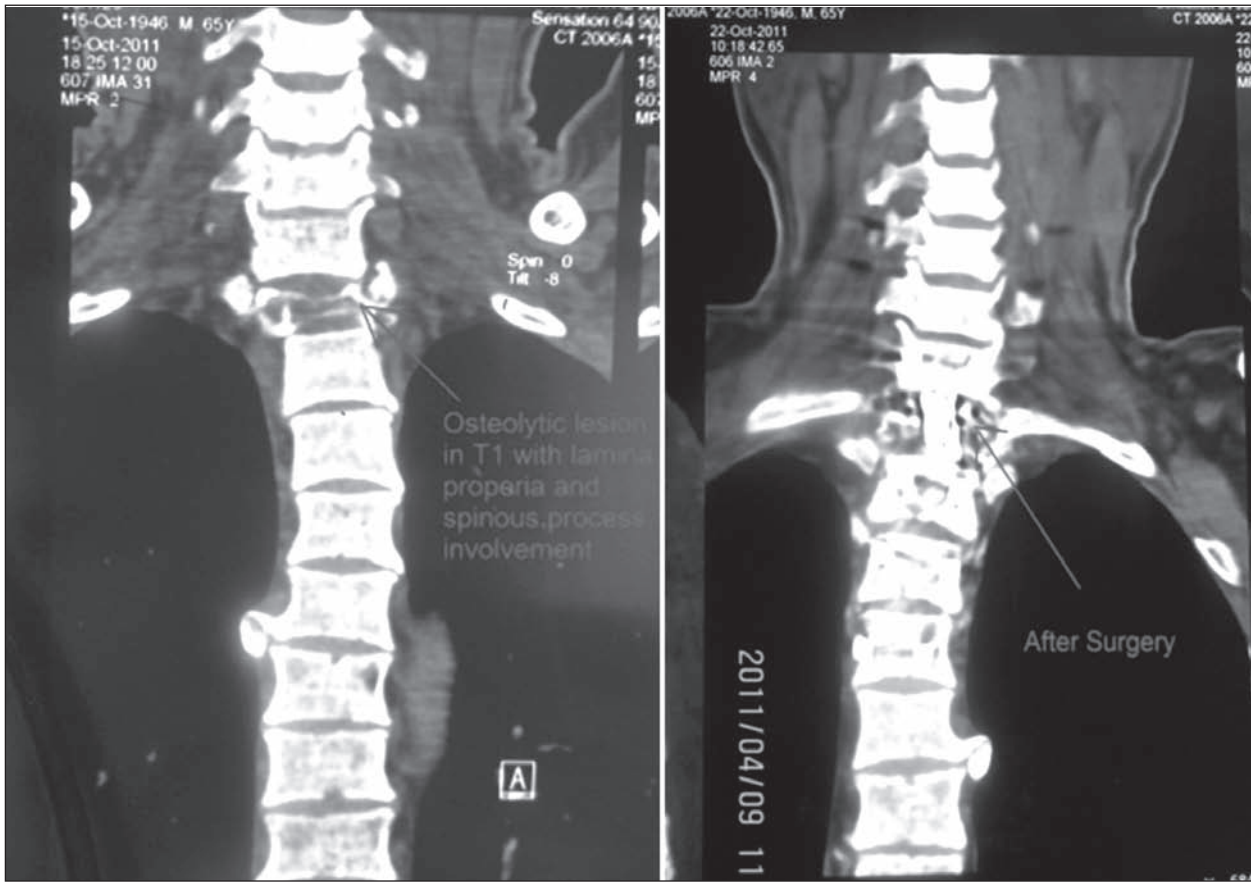

Figure 1. Compress fracture of T1 before and after surgery.

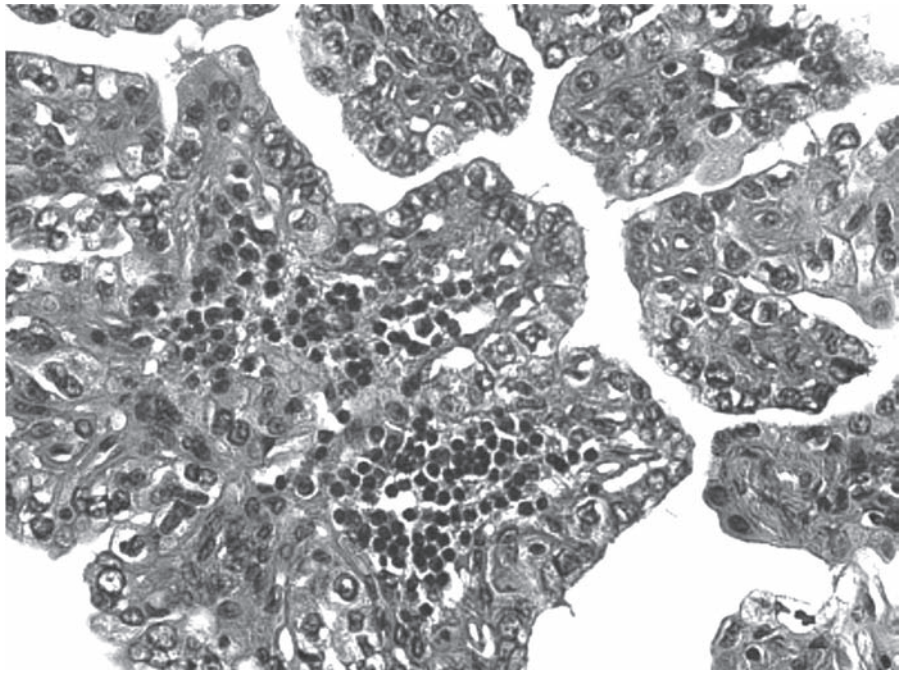

Figure 2. Tumor composed of papillary structure lined by crowded epithelial cells with overlapping nuclei having ground glass cytoplasm. HE stain, magnification 400x

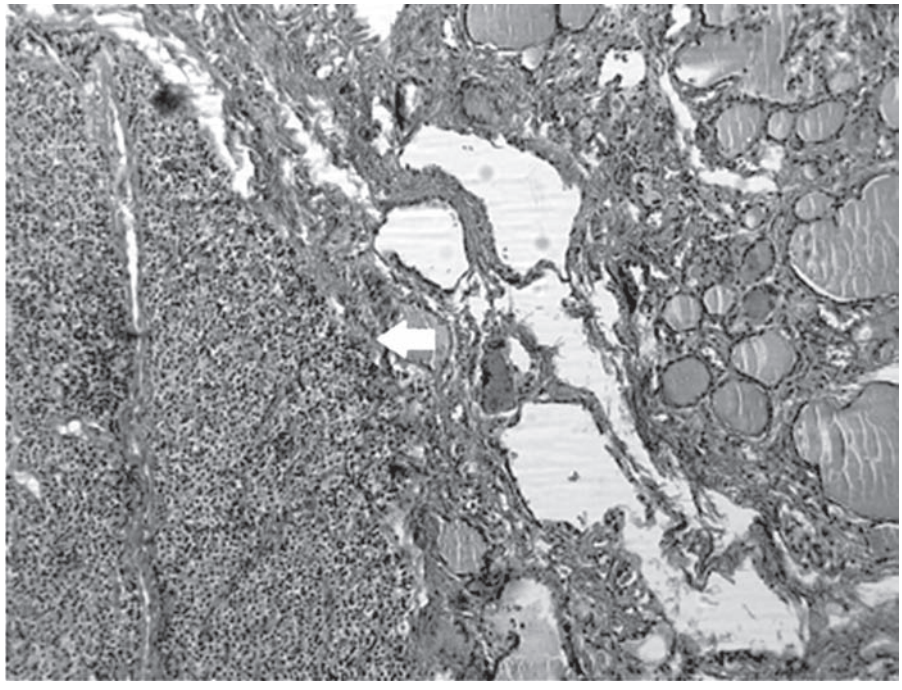

Figure 3. Parathyroid carcinoma, infiltration to the left lobe of thyroid, stage T3 NX MX (2 cm in diameter). HE stain, magnification 100x

Discussion and conclusions

Primary hyperparathyroidism is the third most common endocrine disorder after diabetes mellitus and thyroid dysfunction (8). Symptoms and signs are non-specific and include nausea, vomiting, fatigue, constipation, hypotonicity of muscles and ligaments myalgia and tenderness of muscles. Reports on the coincidence of primary hyperparathyroidism and myelopathy are anecdotal (9).

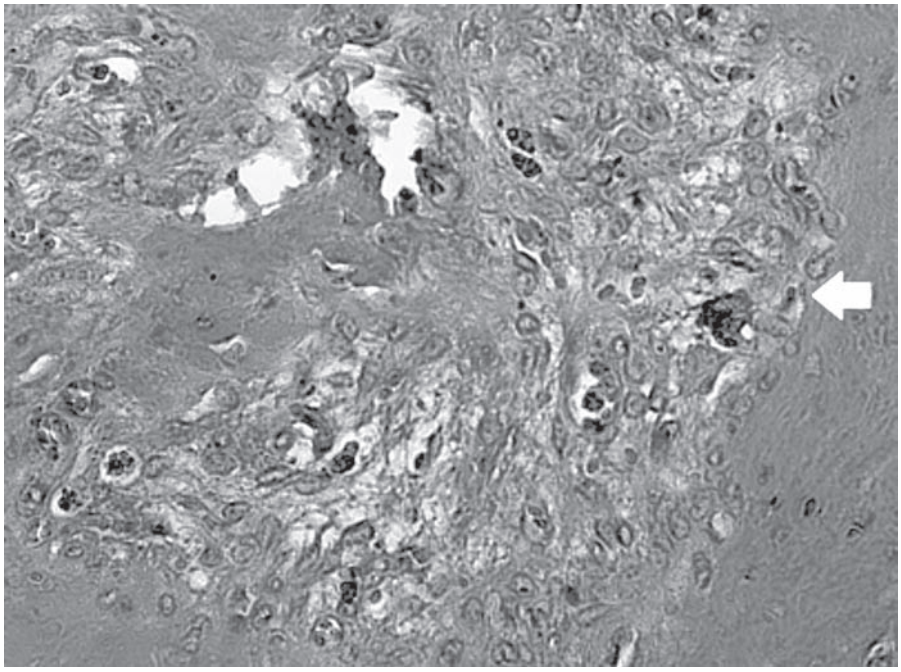

Figure 4. High bones turnover characterized by paratrabecular bone fibrosis and osteoclastic multi nucleated giant cells with hemosiderin depositions. HE stain, magnification 400x

Only 1-3% of primary hyperparathyroidism cases prove to be parathyroid carcinoma (9). With the increasing number of primary hyperparathyroidism cases being diagnosed, the prevalence of parathyroid carcinoma has also risen (10-12). This being so, and in view of the importance of timely diagnosis of cancer associated with grave morbidities, any case of PTH-dependent primary hyperparathyroidism must raise the suspicion of carcinoma.

The diagnosis between parathyroid adenoma and carcinoma is not simple for the pathologist, however, the histopathologic features of parathyroid cancer include thick fibrotic bands, high mitotic activity, a trabecular growth pattern, a specific capsular and vascular pattern and invasion of adjacent tissues (13, 14). Parathyroidal adenoma is more prevalent in women and peaks in the sixth decade of life, however, parathyroidal cancer has no gender preponderance and mostly afflicts patients in their fifth decade of life (3). Due to skeletal involvement and sky-high levels of Ca and PTH, the case presented was viewed from the beginning with the probability of cancer in mind - a diagnosis which was later on confirmed by histopathology.

Concurrence of thyroidal and parathyroidal maladies was first described in 1947 (15). The incidence of thyroidal conditions in patients who had undergone parathyroidectomy was reported to vary between 2.5% and 17.65%, while the incidence of primary hyperparathyroidism in patients who had thyroid diseases was reported to be between 0.3 to 8.7% (16). However, the co-existence of papillary thyroidal cancer and parathyroidal cancer (as in the present case) is absolutely anecdotal, with only few such cases being reported to this day (17). Our case represents the only confirmed concurrence of non-medullary thyroidal cancer and parathyroidal cancer in Iran.

Brown tumors are essentially a kind of osteolytic cystic lesion with vascular elements which may be a complication of primary or secondary hyperparathyroidism (18). Their prevalence is slightly higher in primary hyperparathyroidism (0.3 *vs* 0.2), however, the higher prevalence of secondary hyperparathyroidism making them more likely to be caused by it (18). The prevalence of Brown tumor is declining as hypercalcemias are readily detected by routine laboratory tests and consequently hyperparathyroidism tends to be diagnosed at early stages. Common sites of involvement for Brown tumors include the metacarpi, phalanxes, mandible, pelvis and femur (8). Involvement of the spinal column by Brown tumors is quite rare as only 9 such cases associated with primary hyperparathyroidism and 14 associated with secondary hyper-

parathyroidism were found during a review of the literature. Of all of these cases, 15 (65%) had symptoms of spinal cord compression (19). In the present case, paraplegia and radicular pain in the lower limbs had ensued following a compressed fracture of T1 due to the destruction caused by Brown tumor.

Another complication of the parathyroidectomy operation is hungry bone syndrome which is more common in patients with radiological evidence of PTH-related osteolysis. Other risk factors for development of this condition include age, higher levels of tumor resection and vitamin D deficiency. With cessation of extra PTH production, not only does resorption of Ca from bones fail to continue as abundantly as before, but the bones begin to take up Ca from the blood which may result in hypocalcemia within a few hours of the operation and may last up to 1 week (19). Hypocalcemia in hungry bone syndrome is associated with hypophosphatemia and hypomagnesemia. Only one case of hungry bone syndrome has been reported in which the condition lasted for 1 year after the operation. However, the hyperparathyroid state in this case was secondary to chronic renal failure.

Delayed hungry bone syndrome mostly starts before day 8 following the operation (20). In the present case, hungry bone syndrome occurred 10 days after the operation while the patient was being treated with oral Ca supplement.

The rarity of the clinical manifestations in the present case of parathyroid carcinoma (radicular pain, paraplegia and urinary retention) as well as its associations (late-onset hungry bone syndrome, concurrence of non-medullary thyroid cancer and parathyroid carcinoma, spinal column involvement of Brown tumor with compressive myelopathy) makes it an interesting case to include in the medical literature as shown in Table 2 (21-23). Moreover, reviewing this case must alert physicians to the possibility of Brown tumor as the underlying cause of aggressive metastasis-looking involvement of the spinal column.

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