

## *Concurrent ectopic mediastinal parathyroid carcinoma and neck parathyroid adenoma: a rare presentation*

### **Konkominan mediastinal paratiroid karsinom ve boyunda paratiroid adenoma: nadir tutulum**

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### **Abstract**

While mediastinal parathyroid carcinoma is a rare entity by itself, multiglandular coexistence of parathyroid carcinoma and parathyroid adenoma represents an extremely rare condition. Herein, we report such a rare presentation of multiglandular parathyroid neoplasm with an ectopic parathyroid carcinoma in the mediastinum and parathyroid adenoma on neck in a patient with persistent primary hyperparathyroidism (PHP). This 38-year-old female patient who initially presented with nephrolithiasis and osteopenia was subsequently diagnosed as having PHP. Following bilateral surgical neck exploration, existence of a parathyroid adenoma on the right side of neck was revealed. However, due to the persistence of hypercalcemia postoperatively, a single photon emission computed tomographic (SPECT/CT) examination was performed which showed a mass lesion in the anterior mediastinum. A surgical procedure was performed and the lesion, 10x10x3 mm in dimensions, confirmed to be a parathyroid carcinoma by histopathologic examination. At 1-year of follow-up there was no tumor recurrence or hypercalcemia. This is the first patient who had coexistent of ectopic mediastinal parathyroid carcinoma and parathyroid adenoma in the neck with persistent PHP. This case emphasises the difficulties in diagnosing and managing parathyroid disease. Multiple diagnostic studies are crucial for identification of multiple parathyroid glands in patients with persistent PHP.

**Keywords:** Parathyroid carcinoma, parathyroid adenoma, mediastinum, primary hyperparathyroidism

## Öz

Mediastinal paratiroid karsinom nadir görülmektedir, ancak multiglandüler paratiroid karsinom ile birlikte paratiroid adenomun görülmesi çok daha nadirdir. Persistan primer hiperparatiroidisi (PHP) olan bir hastada, mediastende ek-topik paratiroid karsinoma ile birlikte boyunda paratiroid adenoma birlikteliği olan nadir multiglandüler paratiroid neoplazi vakasını sunmaktayız. Nefrolitiazis ve osteopenia şikayeti olan 38 yaşında kadın hastaya PHP tanısı kondu. Bilateral boyun eksplorasyonu sonrası, boyunda sağ tarafta paratiroid adenoma saptandı. Postoperatif hiperkalsemi devam etmesi nedeniyle, tek proton emisyonlu tomografi (SPECT/CT) taramasında ön mediastende tutulum gösterildi. Lezyona cerrahi uygulandı, 10x10x3 mm boyutunda paratiroid karsinom histopatolojik olarak doğrulandı. 1-yıllık takip sonunda, tümör rekürrensi ve hiperkalsemi görülmedi. Persistan PHP'li hastada ektopik mediastende paratiroid karsinom ve boyunda paratiroid adenom birlikteliği olan ilk vakadır. Bu vaka paratiroid hastalığında tanı ve takipteki zorlukları göstermektedir. Persistan PHPT'li hastalarda multiple paratiroid bezleri gösterebilmek için multiple tanısal metodlar kullanılmalıdır.

**Anahtar Kelimeler:** Paratiroid karsinom, paratiroid adenoma, mediasten, primer hiperparatiroidi

## Introduction

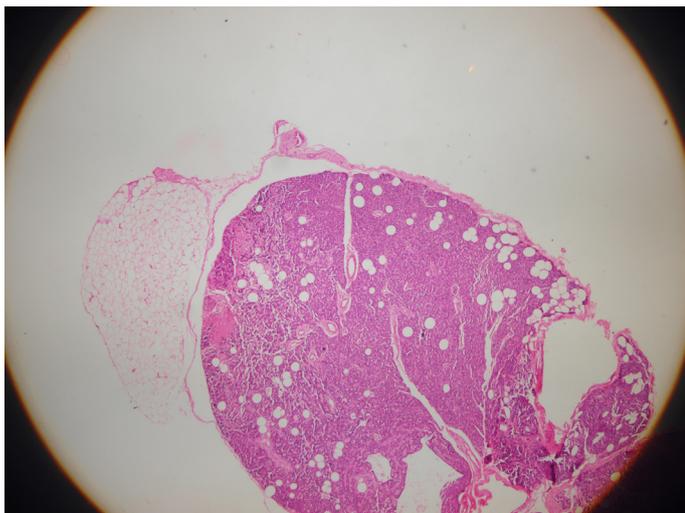
Carcinoma of the parathyroid gland is a very rare entity that is responsible for less than 1% of all cases with primary hyperparathyroidism (PHP) and that comprises only 0.005 % of all cancer patients [1]. Although approximately 30 to 70 % of the patients with parathyroid carcinoma present with a neck mass [2], 9 patients with parathyroid carcinoma presenting with ectopic mediastinal masses have been reported in the literature [3-8]. These patients with mediastinal mass generally tended to have severe PHP [2]. Despite the common view that parathyroid carcinoma occurs in only a single parathyroid gland, very rare cases of multiglandular parathyroid carcinoma have also been observed [9]. We present a patient with concurrent ectopic left mediastinal parathyroid carcinoma and parathyroid adenoma localized on the right side of neck.

## Case

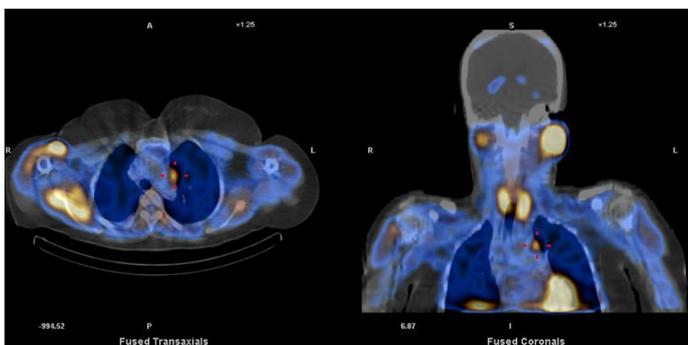
A 38 year-old women presented with fatigue, joint pain, constipation and renal calculi. Her medical history was unremarkable. The patient had negative family history of parathyroid conditions, kidney stones or other endocrine conditions. Her physical examination was unremarkable. At admission serum total calcium was 12.5 mg/dl (Normal range (NR): 8.8-10.6), phosphorus was 2.3 mg/dl (NR:2.5-4.5), intact parathyroid hormone (iPTH) was 198 pg/ml (NR:11.1-79.5), creatinine was 0.6 mg/dL (NR:0.66-1.09), creatinine clearance was 95.4, urinary 24h calcium excretion was 425 mg/day (NR: 100-400), albumin was 4.7 g/dl (NR:3.2-4.8), 25-OH vit D was 16.4 ng/mL (NR: Ad-

equat > 30). patient was diagnosed as having PHP on basis of hypercalcemia, hypophosphatemia, hypercalciuria, nephrolithiasis, osteopenia and elevated PTH levels. Tc-99m-Methoxybutylisonitrile (Tc-99m- MIBI) scintigraphy performed to visualize the hyperfunctioning parathyroid tissue preoperatively and showed no parathyroid lesions. Neck ultrasound (USG) determined the presence of a solid hypoechoic nodular lesion (4x4x8 mm) at the postero-inferior aspect of the right thyroid lobe adjacent to the thyroid capsule and carotid artery. This was followed by a bilateral neck exploration and parathyroid adenoma on right side neck region was confirmed by histopathologic examination (Figure 1). During subsequent postoperative one and three days, respectively, serum iPTH (190 and 188 pg/ml) and calcium (11.6 and 11.8 mg/dl) levels remain elevated. During first month follow-up, serum total Ca was 11.4 mg/dl and iPTH was 185 pg/ml. New imaging studies were performed to definitively localize the possible missed lesion. Sestamibi-Single Photon Emission Computed Tomography (SPECT/CT) identified a soft tissue lesion with increased uptake in the anterior mediastinum and no lesion in the neck region (Figure 2). Magnetic resonance (MRI) imaging of mediastinum and neck could not detect any suspicious neck or mediastinal nodes/mass. Due to the persistence of PHP and an ectopic mediastinal lesion seen on SPECT/CT, a second surgical intervention was recommended. A left-sided thoracotomy was performed which identified an ectopic mediastinal parathyroid gland (size 10x10x3 mm) in the anterior mediastinum. Histopathologic examination revealed the presence of a parathyroid car-

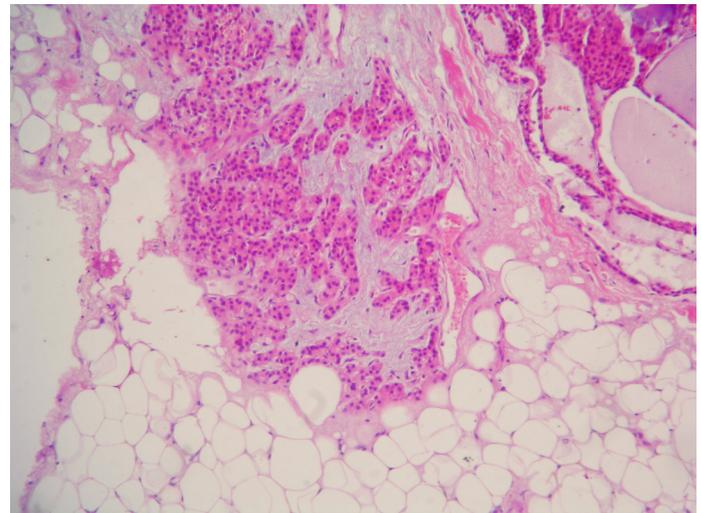
cinoma with evidence of invasion in the capsule and surrounding adipose tissue, without metastatic lymph nodes. Ki67 index was 3 %, mitotic count 2 (Figure 3). This was reevaluated by an endocrine pathologist. The final statement was parathyroid carcinoma as initially reported. Subsequent postoperative first and three days, serum calcium (8.5 and 8.7 mg/dl) and iPTH (65 and 68 pg/dl) levels were decreased at normal range, respectively. Patient achieved a normocalcemic status on the first postoperative days and remained normocalcemic status during postoperative 3, 6 and 12 months. One year after second operation, the patient continues to remain asymptomatic with normal calcium and iPTH levels. The most recent chest computed tomography (CT) failed to demonstrate any lesions in the mediastinum and neck region.



**Figure 1.** Parathyroid adenoma at right neck region was confirmed by histopathologic examination during bilateral neck exploration



**Figure 2.** Sestamibi-Single Photon Emission Computed Tomography (SPECT/CT) showed a soft tissue lesion with increased uptake in the anterior mediastinum and no lesion in the neck region. Red arrows are shown increased uptake in anterior mediastinum.



**Figure 3.** Histopathologic examination showed a parathyroid carcinoma with invasion in capsule and surrounding adipose tissue without metastatic lymph nodes. Ki67 index was 3 %, mitotic count 2.

## Discussion

Most of patients with parathyroid carcinoma present with a neck mass and these patients generally tended to have severe PHP [2] and absence of this findings result in significant diagnostic challenge for the clinician [9]. To our knowledge, until now only 9 PHP patients with large mediastinal ectopic parathyroid carcinoma have been reported in the literature [3-8] and four cases of concurrent parathyroid adenoma and carcinoma in the neck have been reported [9-12]. In this paper, a patient with concurrent ectopic mediastinal parathyroid carcinoma and neck parathyroid adenoma is presented. This is the first patient with PHP accompanied by coexistent ectopic mediastinal parathyroid carcinoma and neck parathyroid adenoma. Cure is possible in more than 95 % of the patients with PHP following initial surgery. Potential causes of persistent PHP following surgery may include inadequate surgical skills, inadequate parathyroid resection, or ectopic or multiglandular parathyroid neoplasms. Methods that have been proposed to increase surgical success rates in patients with persistent PHP are generally aimed at better lesion localization using several approaches including <sup>99m</sup>Tc-MIBI scintigraphy, high-resolution USG, CT or MRI scan of the neck and mediastinum, SPECT/CT, selective venous sampling and USG-guided fine needle aspiration with iPTH determination in the aspirate in the suspected parathyroid lesion, intraoperative iPTH assay

and intraoperative gamma probe application [13]. In our patient, initially a surgical neck exploration was performed due to the presence of the clinical signs/symptoms of hyperparathyroidism. The histopathologic examination confirmed a diagnosis of right parathyroid adenoma. Due to the failure of the initial surgery to normalize PHP, imaging studies were performed with Sestamibi-SPECT before the second surgical intervention, revealing an ectopic mediastinal parathyroid carcinoma. Because the serum calcium level decreased and iPTH level increased after first parathyroidectomy it can be assumed that the parathyroid adenoma was not clinically silent. iPTH rise after operation may be due to disappearance of inhibitory effect of adenoma on serum iPTH. Tc-99m-Methoxybutylisonitrile (Tc-99m-MIBI) scintigraphy performed to visualize the hyperfunctioning parathyroid tissue preoperatively showed no parathyroid lesions, while a neck ultrasound determined the presence of a solid hypoechoic nodular lesion (4x4x8 mm). Sestamibi-technetium-99m is taken up by the large number of mitochondria in parathyroid tissue, and it accumulates in parathyroid adenomas [14]. Scintigraphy with 99mTc-sestamibi has a sensitivity of 85–100 % and specificity close to 100% in parathyroid adenomas [15]. The sensitivity of 99mTc-sestamibi scan in parathyroid carcinoma seems to be similar to that obtained for the evaluation of the adenoma but no specific characteristics exist for distinguishing benign disease from parathyroid carcinoma [16-17]. The sensitivity of sestamibi-SPECT is limited in multiglandular disease and in adenomas smaller than 500 mg [18-19]. Double adenomas or parathyroid hyperplasia (true-negative cases) can cause false negative MIBI scan [20]. Variability of radiotracer uptake in parathyroid adenomas is another reported factor and is attributable to differences in perfusion and metabolic activity, oxyphil cell content, P-glycoprotein expression, and multidrug resistance-related protein expression and cell cycle [21]. The negative scan result seen in our case may be due to the small size of parathyroid adenoma. SPECT/CT imaging systems provide a major benefit for precise anatomic localization of ectopic mediastinal parathyroid adenomas [21]. This could explain the absence of detection of the parathyroid cancer in the sestamibi scan and later appearance in the SPECT/CT.

In contrast with relative asymptomatic clinical picture in benign parathyroid conditions, patients with parathyroid cancer generally present with signs of severe hyperparathyroidism such as bone disease (pathological fractures, Brown's tumor), renal disease (nephrolithiasis) or hypercalcemic crisis [1]. Thirty to 70 % of cases with parathyroid cancer have palpable neck mass, while fewer than 5 % of patients with adenomas have a palpable mass in the neck. In contrast with previous reports, our patient did not have severe PHP and do not present with a large mediastinal mass, probably related to the establishment of an early diagnosis due to concurrent parathyroid adenoma. Most of the patients with parathyroid carcinoma have already undergone surgery due to a suspicion of parathyroid adenoma, and a definitive diagnosis requires postoperative histopathologic examination [4]. Criteria for definitive diagnosis of the parathyroid carcinoma include capsular and vascular invasion, invasion of the adjacent tissues, and regional lymph node and distant metastasis [1,12]. In our patient, the diagnosis of mediastinal parathyroid carcinoma was established on the basis of capsular and adjacent adipose tissue invasion. CDC73 gene mutations cause hyperparathyroidism-jaw tumor syndrome by reducing produced functional parafibromin that is produced. Hyperparathyroidism-jaw tumor syndrome was not exactly diagnosed in this case while CDC73 mutation was not investigated in our country. This was limitations of our management.

Parathyroid carcinoma represents a rare entity by itself, and concurrent occurrence of other parathyroid pathologies in the other parathyroid gland is even more uncommon [22]. Generally parathyroid carcinomas are thought to arise in only one parathyroid gland, while multiglandular parathyroid neoplasms have also been observed [9]. To our knowledge, only four patients with multiglandular concurrent parathyroid adenoma and carcinoma have been reported until now [9-12]. Chatterjee et al. [9] have reported a case of multiglandular parathyroid neoplasm with carcinoma on one side and adenoma on the contralateral side of the neck. Goldfarb et al. [12] have reported a patient with synchronous parathyroid carcinoma, parathyroid adenoma, and papillary thyroid carcinoma. Pai et al. [11] have described a case of multiglandular parathyroid

neoplasm with carcinoma on left side and adenoma on the left side of the neck. Similarly, Ashkenazi et al. [10] have reported a subject with concurrent nonfunctional carcinoma of the left parathyroid gland and a functioning parathyroid adenoma in the neck. In our patient, persistence of serum calcium and iPTH levels postoperatively led to search for a missed parathyroid gland tissue including the mediastinum and parathyroid area. Postoperative serum calcium and iPTH assays are not only useful in the detection of remnant or metastatic parathyroid lesions only [22], but also for the diagnosis of coexistent parathyroid carcinoma or adenoma. Because localizing studies for parathyroid disease do not detect all tumor foci, Pai et al. [11] advocate the use of routine localizing studies in combination with an intraoperative parathyroid hormone assay to help identify all diseased glands. Intraoperative PTH measurement or intraoperative frozen sections were not used in our case. Intraoperative PTH measurement is helpful if concurrent lesions are in the neck as shown by Pai et al. [11] If intraoperative PTH was used in first operation it could cause unnecessary 4-gland exploration but if it was used in 2nd operation it would be of benefit. This case emphasises the difficulties in diagnosing and managing parathyroid disease. Multiple diagnostic studies are crucial for identification of multiple parathyroid glands in patients with persistent PHP. The functional and anatomic information obtained by SPECT/CT makes it the favored method for preoperative detection and localization of the cause of PHP and avoiding reoperation.

### Abbreviations

PHP, primary hyperparathyroidism; iPTH, intact parathyroid hormone; SPECT/CT, Sestamibi-Single Photon Emission Computed Tomography; MRI, Magnetic resonance; CT, computed tomography; USG, ultrasound.

### Declarations of conflicting interests

Consent to participate: A consent to publish was obtained from patient.

Availability of data and materials: All data are freely available for scientific purpose.

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**Authors' Contributions:** MC, SB, contributions to conception and design, or acquisition of data, or analysis and interpretation of data, involved in drafting the manuscript, MK, contributions to conception and design, or acquisition of data, or analysis and interpretation of data; GS, acquisition of data, or analysis and interpretation of data; EC, revising it critically for important intellectual content; and have given final approval of the version to be published.

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