Matija Buzejic[1], Nikola Slijepcevic[1,2], Vlada Zivaljevic[1,2], Goran Zoric[1], Bozidar Odalovic[1,3], Katarina Tausanovic[1,2], Branislav Rovcanin[1], Milan Jovanovic[1], Duska Vucen[1], Boban Stepanovic[1], Ivan Paunovic[1,2]

# CASE REPORT OF PARATHYROID CARCINOMA IN AN END STAGE RENAL DISEASE PATIENT

**Introduction:** Parathyroid carcinoma is a rare endocrine tumor and among the rarest of all malignancies in human population. Especially rare entity is parathyroid carcinoma in patient with end stage renal disease who receive hemodialysis. Pathogenesis of parathyroid hyperplasia in patients who receive hemodialysis is well known but on the other side pathogenesis of parathyroid carcinoma in those patients is still unknown. We present a case of parathyroid carcinoma in patient with secondary hyperparathyroidism.

**Case outline** : A 67-year-old female on maintenance hemodialysis for 48 months was admitted to our hospital in April 2018 for the operation for a palpable neck mass**.** She developed end stage renal disease after two kidney operations due to Renal Cell Carcinoma. Level of parathyroid hormone was 1022 ng/L which is significantly higher above normal range, even do she was using vitamin D analogs**.** Ultrasonography revealed an isoechoic nodule in the left lobe of the thyroid gland measuring 27x29x29 mm. Lower left parathyroidectomy was performed along with ipsilateral lobectomy due to its infiltration. Histological analysis confirmed presence of parathyroid carcinoma. Plasma PTH level decreased on the second day to 56 ng/L

**Conclusion:** After surgical treatment patient was normocalcemic with significant reduce of PTH level. In patients with secondary hyperparathyroidism who develop parathyroid carcinoma parathyroidectomy represents only definitive kind of treatment.

**Key words** parathyroid carcinoma, hemodialysis, secondary hyperparathyroidism, parathyroidectomy, end-stage renal disease

[1] Center for Endocrine Surgery, Clinical Center of Serbia.

[2] School of Medicine, University of Belgrade.

[3] School of Medicine, University of Pristina-Kosovska Mitrovica.

## *Introduction*

Parathyroid hyperplasia and secondary hyperparathyroidism often accompany chronic renal failure. However, parathyroid carcinoma is a rare entity in end-stage renal disease (ESRD) patients. Until now about 1000 cases of parathyroid carcinoma have been reported until now [1]. Amongst these around 34 parathyroid carcinoma cases were diagnosed in patients with ESRD [2]. The diagnosis of parathyroid carcinoma is very difficult and it relies on the combination of preoperative, intraoperative and histopathological findings. Usually the signs and symptoms of highly elevated parathormone (PTH) level and hyperphosphatemia are present in those patients (bone pain, pruritus).

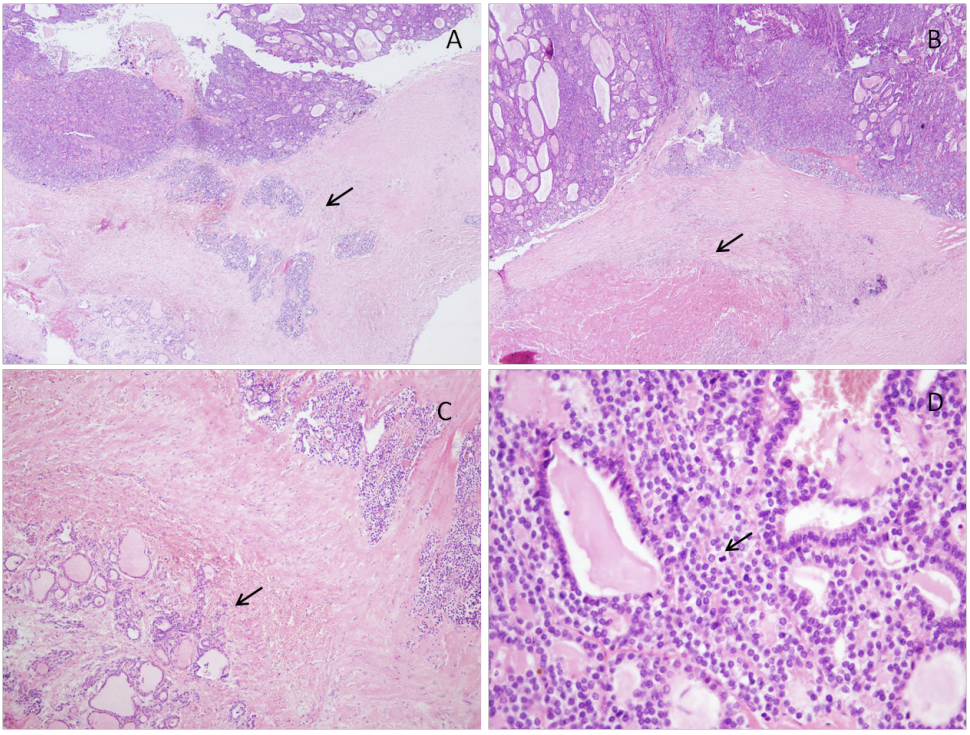
Seven patients with parathyroid carcinoma obscured in primary hyperparathyroidism were operated in our hospital in seven years period, and only three cases of parathyroid carcinoma in hemodialyzed patients in period of 19 years [3]. Three case series with two patients have already been reported [4-6]. In the present study we report a case of patient with ESRD and parathyroid carcinoma who underwent surgical treatment.

## *Case report*

A 67-year-old female on maintenance hemodialysis for 48 months was admitted to our hospital in April 2018 for the operation for a palpable neck mass. The patient had a stone surgically removed fourteen years before parathyroid surgery. Total nephrectomy of the right and partial nephrectomy of the left kidney were performed due to renal cell carcinoma ten years before she was admitted to our hospital. Four years after another partial nephrectomy of left kidney was performed because of the recurrence of renal cell carcinoma. Besides the urological procedures, the patient also had been diagnosed with chronic lymphocytic leukemia. In family history, her mother had been operated on thyroid gland for benign disease. She developed ESRD 2 years before surgery. At this time her calcium plasma level was 2,63 mmol/L, urea was 21 mmol/L and creatinine level was 416 μmol/L. At this moment the patient started to feel bone pain and pruritus. PTH level in plasma determined one year before operation was 1337 ng/L, and the day before surgery it was 1022 ng/L. On physical examination there was a palpable nodule in the region of the left lobe of the thyroid gland. $^{99m}$Tc-methoxyisobutylisonitrile (MIBI) was performed just few months before surgery and revealed a hyperfunctioning left inferior parathyroid gland located at the inferior pole of the left lobe of the thyroid gland. Whole-body Scintigraphy didn't reveal any deposits. Ultrasonography revealed an isoechoic nodule in the left lobe of the thyroid gland measuring 27x29x29 mm. The surgery was performed 24 hours after hemodialysis. The initial prepa-

ration of soft tissue was difficult, because the tumor was adherent to infrahyoid muscles. During preparation of the tumor, the internal jugular vein was injured and immediately sutured. After identification of the lower left parathyroid gland, measuring approximately 4 cm, it was removed along with infiltrated left lobe of the thyroid gland. The other glands seemed to be normal after neck exploration, so they were left in situ. The identified cervical lymph nodes were not enlarged. The tumor was divided into three fragments 40x30x30 mm, 15x10x10 mm and 10x5x5 mm in diameter and weighed 10 gr. Histological analysis confirmed presence of parathyroid cancer, based on the same criteria as in patient one (Figure 1). On the first postoperative day plasma PTH level decreased to 257 ng/L, and on the second day it was 56 ng/L. The serum level of calcium decreased from 2,81 mmol/L to 2,67 mmol/L and plasma phosphate increased from 1,7 mmol/L to 2,02 mmol/L. At first postoperative control, three months after the surgery, PTH level was 21 ng/L, calcium was 2,59 mmol/L, and phosphate was 1,1 mmol/L. Levothyroxine was prescribed due to lobectomy and at next follow-up the levels of serum TSH and FT4 remained within normal range.

*Figure 1. A – capsular invasion; B – necrosis; C – thyroid tissue; D – mitotic figures*



## *Discussion*

Parathyroid carcinoma is a rare type of endocrine tumor, with an approximate incidence of 0.005% among all cancers [1]. Preoperative diagnosis of PC is very hard to set, especially in patients with ESRD. In the absence of thyroid infiltration, locoregional or distant metastases, it is difficult for surgeons to make the diagnosis of parathyroid carcinoma. For pathologists the most challenging part is to differentiate between parathyroid carcinoma and atypical parathyroid adenoma [7]. The first parathyroid cancer in a patient receiving hemodialysis was reported by Berland et al. in 1982 and since then around 35 more cases are presented in the literature [4–6; 8–30].

In patients with end stage renal disease, parathyroid carcinoma may occur at any age, ranging from 20 years as Tseng et al. reported, up to 75 years as Jayawardene et al reported [18, 20]. Our patient was 67 years old. In primary hyperparathyroidism, the gender distribution of parathyroid carcinoma is approximately 1:1, and in ESRD patients there is a predominance female (1,57:1) without a known reason [31].

Parathyroidectomy is required in about 15% of patients after 10 years and 38% of patients after 20 years of ongoing dialysis therapy, and one of the strongest indication for operation is disease refractory to medical therapy (calcimimetics and vitamin D analogs) [32].

Although there is no hard evidence for it, we may agree with Berland et al. that sustained stimuli (hyperphosphatemia and high levels of PTH) to the parathyroid glands might cause parathyroid hyperplasia that eventually may become neoplastic [8]. Average levels of PTH in hemodialyzed patients range from 2 to 9 times more than the upper normal limit of the PTH assay and according to the National Kidney Foundation, PTH levels exceeding 800 ng/L is one of the indications for operation [33]. PTH levels in patients with ESRD are highly elevated, but they were measured with different assays. The highest level of PTH was in a case reported by Cabane et al and was measured 2287 ng/L [29]. Our patient had PTH level 1337 ng/L is 15 times more than the normal upper limit. Calcium level was elevated in 17 patients from literature, including our own. This indicates that patients who have hypercalcemia refractory to hemodialysis and have mildly to highly elevated PTH level might suffer from parathyroid carcinoma.

Several clinical and histological observations have shown that the size of the parathyroid gland, evaluated by ultrasonography, can be an indication for operation, with a critical size of 1 cm or more in diameter [34]. The size of carcinomatous gland in our patient was 2,9 cm measured by US, and macroscopic size was 4 cm. The weight of parathyroid glands in diffuse hyperplasia in ESRD patients is usually in the range of 1 to 3 gr [35, 36]. In our patient weight of the gland was 10 gr. This indicates that the size of the parathyroid gland along with the hypercalcemia, is one of the crucial

factors for setting the diagnosis of parathyroid carcinoma preoperatively. Macroscopic size and weight of parathyroid gland are two important factors for pathologist in making parathyroid carcinoma diagnosis.

In eleven cases metastasis of parathyroid carcinoma were described, 2 two of them were described in liver and nine in the lungs [10, 14, 15, 17, 18, 24, 27]. In one case patient had metastatic disease located in the lung and in the bones [24]. Tominaga et al. published a case series with 5 patients that had metastases in the lungs, and in 4 of them, parafibromin was positive [27]. Chromogranin was positive in patients with metastases to the lung, as reported by Khan et al. [24]. In 2002, germline HRPT2 (also known as CDC73 in literature) mutation was reported as the cause of hyperparathyroidism-jaw tumor (HPT-JT) syndrome, an autosomal dominant hereditary tumor syndrome, associated with a lifetime risk of parathyroid carcinoma, approaching 15 % [37]. Bi-allelic inactivation or mutation of HRPT2 has been reported in the majority of parathyroid carcinomas, but very rarely in sporadic benign parathyroid disease [29]. Furthermore, testing for HRPT2 mutation in patients presenting with parathyroid carcinoma often identifies occult HPT-JT syndrome, even in the absence of a family history or other manifestations of this syndrome [37]. Parafibromin as a product of mutation of HRPT2 gene, has a big importance in pathogenesis of parathyroid cancer, because it is rarely altered in benign parathyroid pathologies. Parafibromin is a predominantly nuclear protein, that acts as a tumor suppressor, and with its loss in immunostaining being characteristic for parathyroid carcinoma [27]. However, further studies on this topic are still required.

The acceptable surgical treatments for patients with secondary hyperparathyroidism are subtotal parathyroidectomy and total parathyroidectomy with parathyroid autotransplantation. In suspicious findings, an en-bloc resection of the tumor and the surrounding tissue, including paratracheal lymph nodes (level VI) and thyroid lobe at the same side, is an acceptable treatment as well [38].

In conclusion, making the diagnosis of parathyroid carcinoma is hard, both in patients with normal renal function and also in those with ESRD. Parathyroid carcinoma may be suspected in the presence of a palpable neck mass, renal and skeletal symptoms, elevated serum calcium levels refractory to hemodialysis and extremely elevated plasma PTH levels. Nowadays, localization of parathyroid glands is easier thanks to ultrasonography, computer tomography (CT) and MIBI scan. CT can be used after surgery for the detection of possible local and distant metastases. MIBI scintigraphy is good for localizing ectopic or metastatic parathyroid tissue. Surgical treatment of patients suspicious for parathyroid carcinoma consist of subtotal parathyroidectomy with an ipsilateral lobectomy, and lymph node resection if necessary. The rarity of this disease requires treatment by experienced endocrine surgeons.

## *References*


1. Hundahl, SA, Fleming, ID, Fremgen, AM, Menck, HR. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985–1995: a National Cancer Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 1999; 86: 538– 44.
2. Bossola M, Tazza L, Ferrante A, Giungi S, Carbone A, Gui D, et al. Parathyroid carcinoma in a chronic hemodialysis patient: case report and review of the literature. *Tumori.* 2005; 91: 558–62.
3. Zivaljevic V, Zivic R, Diklic A, Bukvic B, Tatic S, Kazic M et al. Parathyroid carcinoma in primary hyperparathyroidism: single institution experience. Eur Surg. 2012; 44:394–399.
4. Iwamoto N, Yamazaki S, Fukuda T, Kondo M, Yamamoto N, Ono T et al. Two cases of parathyroid carcinoma in patients on long-term hemodialysis. Nephron,1990; 55: 429–431.
5. Rademaker P, Meijer S, Oosterhuis JW, Vermey A, Zwierstra R, Hem G, Geerlings W. Successful surgical treatment of parathyroid carcinoma in two haemodialysis patients. Nephrol Dial Transplant,1990; 5: 545–548.
6. Fuster D, Torregrosa JV, Esteve V, Ybarra J, Sabater L, Alós L, et al. Parathyroid carcinoma associated to secondary hyperparathyroidism in patients on dialysis: Two cases reports. Nefrologis. Vol. 27. Número 2. 2007. 27(2): 209–13.
7. Christakis I, Bussaidy N, Clarke C, et al., Differentiating atypical parathyroid neoplasm from parathyroid cancer, Ann. Surg. Oncol. 23. 2016; 2889–2897.
8. Berland Y, Olmer M, Lebreuil G, Grisoli J. Parathyroid carcinoma, adenoma and hyperplasia in a case of chronic renal insufficiency on dialysis. Clin Nephrol, 1982. 18: 154–158.
9. Anderson BJ, Samaan NA, Vassilopoulou-Sellin R, Ordonez NG, Hickey RC. Parathyroid carcinoma: features and difficulties in diagnosis and management. Surgery, 1983; 94: 906–915.
10. Ireland JP, Fleming SJ, Levison DA. Parathyroid carcinoma associated with chronic renal failure and previous radiotherapy to the neck. J Clin Pathol, 1985. 38: 1114–1118.
11. Sherlock DJ, Newman J, Holl-Allen RT. Parathyroid carcinoma presenting as tertiary hyperparathyroidism. Postgrad Med J, 1985; 6: 243–244.
12. Krishna GG, Mendez M, Levy B, Ritchie W, Marks A, Narins RG: Parathyroid carcinoma in a chronic hemodialysis patient. Nephron, 1985; 52: 194–195.
13. Kodama M, Ikegami M, Imanishi M, Uemura T, Takada M, Kohri K et al. Parathyroid carcinoma in a case of chronic renal failure on dialysis. Urol Int, 1989; 44: 110–112.
14. Tominaga Y, Numano M, Uchida K, Sato K, Asano H, Haba Tet al. Lung metastasis from parathyroid carcinoma causing recurrent renal hyperparathyroidism in a hemodialysis patients: report of a case. Surg Today, 1995; 25: 984–986.
15. Miki H, Sumitomo M, Inoue H, Kita S, Monden Y. Parathyroid carcinoma in patients with chronic failure on maintenance hemodialysis. Surgery, 1996; 120: 897–901.

16. Liou MJ, Lin JD, Huang MJ, Huang JY, Hsueh C, Jeng LB. Parathyroid carcinoma with postoperative prolonged hypocalcemia in a patient with chronic renal failure. J Formos Med Assoc, 1996; 95: 337–341.
17. Djema AI, Mahmoud MD, Collin P, Heymann MF. Tertiary hyperparathyroidism: parathyroid cancer with liver metastases in a hemodialyzed patient. Nephrologie, 1998; 19: 121–123.
18. Tseng CC, Huang JJ, Wang MC, Lan RR, Sung JM, Chen FF. Parathyroid carcinoma with multiple lung metastases. Nephrol Dial Transplant, 1999; 14: 449–451.
19. Takami H, Kameyama K, Nagakubo I: Parathyroid carcinoma in a patient receiving long-term hemodialysis. Surgery, 1999; 125: 239–240.
20. Jayawardene S, Owen WJ, Goldsmith: Parathyroid carcinoma in a dialysis patient. Am J Kidney Dis, 2000; 36: 26–30.
21. Kuji T, Kitamura H, Yasuda G, Umemura S, Kimura T, Shimizu S et al. Different pathological findings in each of four parathyroid glands in a long-standing hemodialysis patient. Clin Nephrol, 2000; 54: 413–417.
22. Zivaljevic V, Krgovic K, Tatic S, Havelka M, Dimitrijevic Z, Diklic A, et al. Parathyroid cancer in a hemodialysis patient: a case report. Tumori. 2002; 88(5): 430–2.
23. Srouji IA, Resouly IA, Path FR. Case of thymic parathyroid carcinoma in a hemodialysis patient: application of tumor chemosensitivity testing. J Laryngol Otol, 2004. 118: 162–164, 2004.
24. Khan MW, Worcetser EM, Straus FH, Khan S, Staszak V, Kaplan E. Parathyroid carcinoma in secondary and tertiary hyperparathyroidism. J Am Coll Surg, 2004; 199: 312–319.
25. Falvo L, Catania A, Palermo S, Sorrenti S, Bonifazi AP, De Stefano M et al. Bilateral synchronous parathyroid carcinoma in a patient on long-term hemodialysis: presentation of a rare clinical case and review literature. Int Surg. 2005 Jan-Mar; 90(1): 18–22.
26. Diaconescu MR, Glod M, Costea I, Grigorovici M, Covic A. Parathyroid carcinoma in a patient on hemodialysis for renal failure. Rev Med Chir Soc Med Nat Iasi. 2006;110(1):152-6.
27. Tominaga Y, Tsuzuki T, Matsuoka S, Uno N, Sato Tet al. Expression of parafibromin in distant metastatic parathyroid tumors in patients with advanced secondary hyperparathyroidism due to chronic kidney disease. World J Surg. 2008 May; 32(5): 815–21.
28. Ardalan MR Parathyroid carcinoma in hemodialysis patients; it should not be diagnosed as a thyroid nodule. Journal of Parathyroid Disease 2013; 1(2): 25–26.
29 Cabané P, Gac P, Alvo A, Rodriguez F, Eugenia M, et al. Mediastinal Paratthyroid Carcinoma in A Patient with Chronic Kidney Disease in Hemodialysis. Endocrinol Metab Int J. 2016; 3(3): 00047.
30 Pappa A, Hackaman T, Simultaneous Incidental Parathyroid Carcinoma and Intrathyroid Parathyroid Gland in Suspected Renal Failure Induced Hyperparathyroidism. Surg J 2017; 3: e23–e24.
31. Hundahl, SA, Fleming, ID, Fremgen, AM, Menck, HR. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985–1995: a National Cancer

Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 1999; 86: 538– 44.

32. Schneider R, Slater EP, Karakas E, Bartsch DK, Schlosser K. Initial parathyroid surgery in 606 patients with renal hyperparathyroidism. World J Surg, 2012; 36: 318–326.
33. Yuen NK, Ananthakrishnan S, Campbell MJ. Hyperparathyroidism of Renal Disease. Perm J. 2016; 20(3): 15–127.
34. Goto S, Komaba H, Fukagawa M. Pathophysiology of parathyroid hyperplasia in chronic kidney disease: preclinical and clinical basis for parathyroid intervention. NDT Plus. 2008; 1(Suppl 3.): iii2-iii8.
35. Roychowdhury M. Anatomy and histology. Pathology Outlines. com website. https://www.pathologyoutlines.com/topic/parathyroidanatomy.html.
36. Grimelius L, Akerstrom G, Johansson H, Bergstrom R. Anatomy and histopathology of human parathyroid glands. Pathol Annu 1981; 16: 1–24.
37. Gill AJ. Understanding the genetic basis of parathyroid carcinoma. Endocr Pathol. 2014 Mar; 25(1): 30–4.
38. Schulte K-M, Talat N. Diagnosis and management of parathyroid cancer. Nat Rev Endocrinol. 2012; 8: 612–22.