DOI: https://doi.org/10.2298/SARH171114210K
UDC: 617.55-007.43-053.2-089

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Multifocal papillary thyroid microcarcinoma in the end stage of Hashimoto's thyroiditis

Božidar Kovačević[1], Snežana Kuzmić-Janković[2], Boško Milev[3], Vesna Škuletić[1]

[1]Military Medical Academy, Institute of Pathology and Forensic Medicine, Belgrade, Serbia;
[2]Military Medical Academy, Clinic of Endocrinology, Belgrade, Serbia;
[3]Military Medical Academy, Clinic of General Surgery, Belgrade, Serbia

SUMMARY

Introduction Frequent coexistence of papillary thyroid carcinoma (PTC) and Hashimoto's thyroiditis (HT) indicates their immunological connection, with no consensus on the cause and effect of this relationship. The aim of this report is to present an unusual case of occurrence of multifocal papillary thyroid microcarcinoma in severe thyroid atrophy as a result of the end stage of HT and to analyze its clinical significance.

Case outline A 59-year-old female patient with a 14-year-long history of HT was admitted for the surgical treatment of a cytologically suspected PTC. During disease evolution, ultrasound controls were performed once a year and the findings showed a progressive decrease in thyroid volume. The nodule in the right lobe was detected for the first time in 2014. After a one-year follow-up, the nodule size was 7 mm. Fine needle aspiration biopsy was performed and was reported as "suspicious for PTC." The patient underwent total thyroidectomy. Intraoperatively, thyroid gland was indistinguishable from the surrounding tissue and histopathological intraoperative consultation was performed in order to confirm malignancy and thyroid tissue. After gross examination, all surgical specimens weighed less than 3 g. A final diagnosis of multifocal papillary thyroid microcarcinoma with bilateral presentation and extrathyroidal extension was made. Seventeen months after total thyroidectomy was performed, the patient was well, with no evidence of metastasis or recurrence of papillary carcinoma.

Conclusion In the circumstances of severe thyroid atrophy, papillary microcarcinoma with infiltrative growth can lead to early extrathyroid extension, and even to the infiltration of surrounding structures.

Keywords: papillary microcarcinoma; Hashimoto's thyroiditis; end stage

INTRODUCTION

Papillary thyroid microcarcinoma (PTMC) is a size-defined variant of papillary thyroid carcinoma (PTC) measuring less than 10 mm [1]. It is the most common form of PTC and constitutes approximately half of PTC in patients older than 45 years and accounts for 39% of the cases of thyroid cancer in the USA [2, 3]. Most of PTMC show excellent behavior, but a small subset may recur or even metastasize, while mortality is less than 1% [4]. Treatment modalities of PTMC range from observation alone to an aggressive approach with total thyroidectomy, with or without lymph node dissection, and radioiodine ablation [5].

Hashimoto's thyroiditis (HT) is the most common thyroid-specific autoimmune disease (AD), with the annual incidence of 0.3–1.5 cases per 1,000 persons. The histological features of HT include diffuse lymphoid infiltration with formation of lymphoid follicles often with germinal centers, destruction, and atrophy of thyroid follicles frequently with oxyphilic metaplasia of thyrocytes, and different degrees of fibrosis. These histologic findings vary significantly among patients, so that HT represents a whole spectrum of clinicopathologic conditions. This spectrum now includes the classical, fibrous, fibrous atrophy, juvenile, hashitoxicosis, and IgG4-related variants [6, 7].

The fibrous atrophy variant of HT is characterized by severe thyroid gland (TG) atrophy, widespread destruction of the thyroid tissue with lymphoid infiltration and diffuse replacement by fibrous stroma. This variant of HT most likely represents the end-stage of this autoimmune process [6, 7].

The typical clinical presentation of HT is hypothyroidism with or without compression symptoms due to TG enlargement, and usually with high serum thyroid antibody [6]. The principal approach for medical treating of HT is substitution therapy with levothyroxine.

The indications for surgery in HT patients include the suspicion for malignancy, persistent symptoms associated with the disease, or a goiter that is increasing in size [6, 8].

In surgically treated patients, the occurrence rate of histologically proven HT in PTC is almost three times more often than in other thyroid diseases [9]. Frequent coexisting of PTC and HT indicates that these two diseases are immunologically linked with no consensus on the cause and effect of this relationship [7, 10].

The aim of this case report is to represent an unusual case of occurrence of multifocal PTMC

Received • Примљено: November 14, 2017
Revised • Ревизија: December 22, 2017
Accepted • Прихваћено: December 26, 2017
Online first: December 29, 2017

Correspondence to:
Božidar KOVAČEVIĆ
Insitute of Pathology and Forensic medicine, Military Medical Academy
Crnotravska 17
11000 Belgrade, Serbia
bozociti@yahoo.com

in the severe TG atrophy as a result of the end-stage of HT, and to analyze its clinical significance.

CASE REPORT

A 59-year-old female patient with a 14-year-long history of HT was admitted to our hospital for the surgical treatment (total thyroidectomy) of a cytologically suspected PTC. Initially, the diagnosis of HT was made according to TG hypofunction, increased serum level of thyroid-stimulating hormone (TSH) and detectable anti-thyroglobulin and anti-thyroid peroxidase antibodies (anti-TPO antibodies). During the disease evolution, the patient received substitution therapy with levothyroxine (100 μg/day). Ultrasound controls were performed once a year. Initially, TG was slightly enlarged, while the following findings showed a progressive decrease in TG volume. The presence of the nodule in the right lobe of the TG was detected for the first time in 2014. After a one-year follow-up (2015), due to increases in nodule size, a fine needle aspiration (FNA) biopsy was performed in another institution and was reported as "suspicious for PTC."

Preoperative laboratory examination revealed high serum anti-TPO antibodies concentration (> 1,500 IU/ml), while TSH measured 0.28 μmol/dl, and the level of free thyroxine (T4) was 21.2 pmol/l. Ultrasonographic examination revealed a reduced TG volume with diffuse low echogenicity. Dimensions of the right lobe were 16 × 10 × 9 mm, and of the left one 19 × 5 × 8 mm. The nodule with cytologically proven suspicion for PTC was in the right lobe, measured 7 × 4 mm and showed marked hypoechogenicity with spiculated margin.

Intraoperative findings

The patient underwent total thyroidectomy. Intraoperatively, the TG was inconspicuous and indistinguishable from the surrounding tissue while all four parathyroid glands were detected. In the anatomical space of the right lobe, a small nodule was noticeable to the surgeon. The nodule with surrounding tissue was extirpated and sent to the pathologist for an intraoperative consultation. Intraoperatively received tissue sample was examined as a frozen section and histopathological examination proved it to be PTC with small amount of thyroid tissue (histology described below). Using the position of the parathyroid glands and the recurrent laryngeal nerve (RLN) as a point of orientation, the remainder of the right, left lobe, and isthmus were removed, with the preservation of RLN. The left upper parathyroid gland was extirpated and implanted in the left sternocleidomastoid muscle.

Histopathology

Gross findings

The thyroid tissue sample received for intraoperative consultation measured 10 × 6 × 3 mm, it had pale red to tan color, and a firm to hard consistency. At the periphery, a small amount of adipose tissue was present. The rest of the right lobe, left lobe, and isthmus measured 13 × 8 × 3 mm, 16 × 6 × 3 mm, and 10 × 3 × 3 mm, respectively. Its consistency was firm and the color was pale red. These samples were processed for permanent section. The weight of the specimen was less than 3 g.

Microscopic findings

In histologically examined frozen section sample from the right lobe, a 6 mm PTMC was observed. The tumor had infiltrative growth, partially sclerotic stroma, and mixed follicular and papillary morphology. Minimal extrathyroidal extension of PTMC was examined in the present perithyroid tissue. At the periphery of the sample, part of the parathyroid gland was microscopically observed (Figure 1).

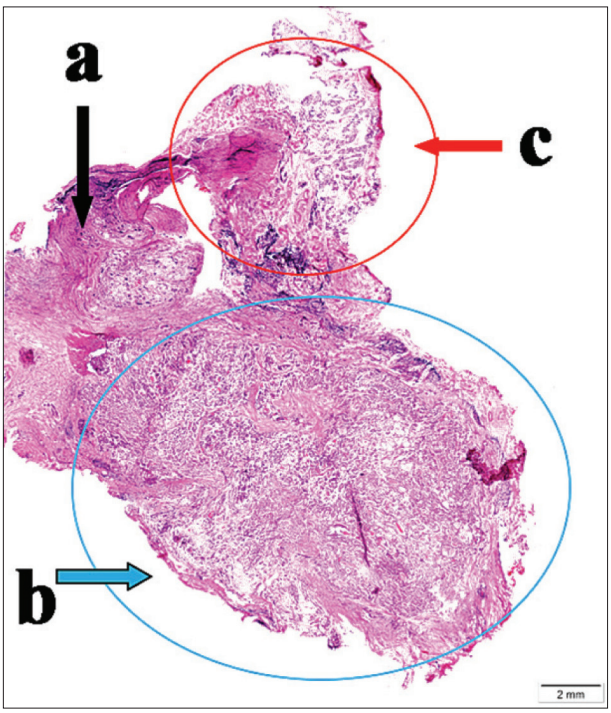

Figure 1. Frozen section; whole-mount section of thyroid tissue from the right lobe; a) atrophic thyroid with perithyroid tissue; b) 6 mm papillary thyroid carcinoma; c) part of the parathyroid gland (H&E, scanning magnification) whole-mount section of thyroid tissue from the right lobe; a 6 mm papillary thyroid microcarcinoma is partially surrounded with atrophic thyroid tissue and a part of the parathyroid gland at the top of the image (H&E, scanning magnification)

In the tissue sample from the left lobe, one more focus of PTMC was detected, measuring 3 mm in size. This focus had the classical morphology with typical nuclear features of PTC, sclerotic stroma, and infiltrative growth. Minimal extrathyroidal extension was also noted (Figure 2a).

The remainder of the TG was mostly replaced with fibrous tissue, which was confined to the gland. Thyroid follicles where atrophic, sporadically and lobulary distributed throughout several areas. Its diameter was very small, with the flattening of follicular epithelial cells, containing pale or thick colloid. In addition, there was evidence of lymphocyte

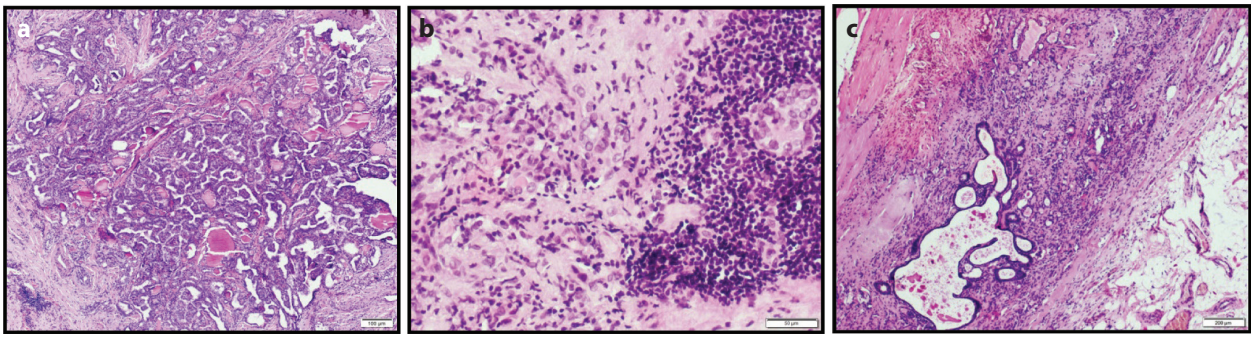

Figure 2. a) A 3 mm papillary thyroid microcarcinoma in the left lobe of the thyroid gland (H&E, ×100); b) lymphocytic inflammation with fibrosis, atrophy, and destruction of thyroid follicles (H&E, ×200); c) atrophic thyroid tissue, fibrosis, and a 1 mm thyroglossal duct remnant cysts in the isthmic region (H&E, ×40)

infiltration, with rare germinal center formation (Figure 2b). The blood vessels were small to medium size without occlusion and histological signs of inflammation. In the isthmic region, beside small atrophic follicles, an incidental 1-mm thyroglossal duct remnant cyst (TGDC) was also observed (Figure 2c).

Based on the above findings, a diagnosis of multifocal PTMC with bilateral presentation and minimal extrathyroid extension was made (p(m)T3NxMx), in the setting of severe TG atrophy as a result of long-standing HT.

Patient follow-up and outcomes

The patient's postoperative recovery was uneventful. Six weeks after surgery, the patient underwent radioiodine ablation therapy. The patient was well, with no evidence of metastasis or recurrence of PTC 17 months after total thyroidectomy was performed.

DISCUSSION

Most of PTMC show favorable outcome with practically benign clinical course. Although the American Thyroid Association recommended that patients with PTMC should undergo hemithyroidectomy for small, unifocal, intrathyroidal carcinomas in the absence of prior head and neck irradiation, familial thyroid carcinoma, or clinical detectable cervical lymph node metastasis, there is still no consensus in the management of PTMC, resulting in a wide spectrum treatment modalities, ranging from observation without treatment to total thyroidectomy with or without lymph node dissection, and radioiodine ablation [5, 11, 12, 13]. The importance of recognizing the subset of PTMC, with its potential for more aggressive behavior, had influence on further treatment. The most commonly reported morphological characteristics of PTMC related to its aggressive behavior are as follows: extrathyroid extension, multifocality, lymph node and distant metastasis, vascular invasion, tumor size, total tumor diameter, histological form of PTMC and its peripheral localization [4, 5, 13, 14]. Peripheral/subcapsular localized PTMC can lead to early extrathyroid extension and in a case of posterior localization it can infiltrate trachea and RLN [12, 14].

The presence of PTMC in atrophic TG can also be a risk for early extrathyroid extension and infiltration of perithyroid structures. In our case, TG atrophy is caused by long-standing AD clinically diagnosed as HT. Over time, progressive thyroid cell damage and destruction of parenchyma can lead to marked gland atrophy. In these cases, TG is very small, usually weighing 1–6 g and is barely identifiable on gross examination. This form of the disease is also referred to as a fibrous atrophy variant of HT, and in case when extreme atrophy of the TG follows goitrous disease, like in our case, it most likely represents the end-stage of this autoimmune process [5, 6, 7].

Patients with HT are usually treated conservatively with levothyroxine therapy in an attempt to decrease thyroid volume and supplement thyroid hormone [6]. The most common reason for surgical treatment of HT is the presence of a thyroid nodule with cytology suspicious for malignancy or compressive symptoms due to TG. The most common surgical complications are hypoparathyroidism due to parathyroid gland injury, and symptoms caused by RLN damage [6, 8]. In our case, removed part of the parathyroid gland did not cause clinical signs of hypoparathyroidism. According to McManus et al. [8], surgical complications after thyroidectomy was performed in patients with HT, are more often compared to patients without HT because inflammatory process in TG and perithyroid tissue makes TG more adhere to the surrounding structure. On the other hand, postoperative complications after thyroidectomy was performed are reduced if surgeons perform a larger number of surgeries per year [15]. The surgery of atrophic TG is even more at risk of surgical complications since the entire TG is in close vicinity to RLN. The TG can be inconspicuous from the surrounding anatomical structure and intraoperative consultation with the pathologist may sometimes be necessary to ensure that the removed tissue belongs to the TG.

Intrathyroidal TGDC are rare. In recently published clinicopathologic series of TGDC, intrathyroidal localization is reported in 1.6% of cases. The presence of TGDC in our case represents an incidental microscopic finding without clinical importance and influence on surgical treatment and operative approach. Its presence in the tissue sample clinically marked as an isthmus can suggest that at least part of it represents the atrophic pyramidal

lobe as the most common form of the inferior thyroglossal duct remnant [16].

The connection between HT and PTC has a long history of debate with no consensus on the link between these two thyroid diseases. In a meta-analysis, Lee et al. [9] showed that the occurrence rate of HT in PTC patients, after thyroidectomy was performed, was 2.8 times higher than in HT patients with benign thyroid diseases. Contrary to this report, a statistically significant correlation between HT and PTC was not found in biopsy samples in population-based studies after FNA was performed [17]. In a recent meta-analysis, which included 27 studies of different type (thyroidectomy, selective FNA, and FNA studies) with 76,281 patients, results confirmed that HT predisposed patients to the development of PTC [18]. On the other hand, most studies showed that HT is associated with a better prognosis of PTC and more limited disease, with a significantly lower frequency of extrathyroidal extension, nodal and distant metastases compared to those without HT [9, 19, 20].

In addition to different results about frequency and prognosis of PTC in patients with HT, there is still an open question whether the development of PTC is induced by chronic autoimmune inflammation ("inflammation-induced carcinoma"), or whether HT develops because of cross-reacting antitumor immunity ("tumor defense-induced autoimmunity"), and how PTC develops despite (auto)immunity [7, 10, 21].

In our case, the presence of PTMC in almost completely destroyed TG due to long duration of HT suggests its ability to escape the host's immune response and to survive despite the (auto)immune response. According to different studies, this tumor ability might occur because of immune tolerance or it can be explained by various immune-escape mechanisms, including secretion of specific immune-regulatory cytokines (e.g. Il-4, Il-10), changed number and function of immune cells (e.g. tumor-infiltrating lymphocytes), and expression of specific proteins on tumor cells (HLA-G, FasL, PD-L1) [10].

In conclusion, in the circumstances of severe TG atrophy, PTMC with infiltrative growth can lead to early extrathyroid extension and even to the infiltration of surrounding structures. The treatment of choice, even in cases of a small lesion with cytologically proven suspicion for malignancy should be a total thyroidectomy and it should be performed by an experienced surgeon.

REFERENCES

1. Lloyd RV, Osamura RY, Klöpel G, Rosai J. World Health Organization Classification of Tumors of Endocrine Organs. Pathology and genetics of tumors of endocrine organs. IARC: Lyon; 2017.
2. Hughes DT, Haymart MR, Miller BS, Gauger PG, Doherty GM. The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years. Thyroid. 2011; 21(3):231–6.
3. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg. 2014; 140(4):317–22.
4. Bradley NL, Wiseman SM. Papillary thyroid microcarcinoma: the significance of high risk features. BMC Cancer. 2017; 17(1):142.
5. Lee YD. Surgical Strategy for Papillary Thyroid Microcarcinoma. J Korean Thyroid Assoc. 2014; 7(1):48–56.
6. Akamizu T, Amino N, DeGroot LJ. Hashimoto's Thyroiditis. [Updated 2013 Dec 20]. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK285557/
7. Ahmed R, Al-Shaikh S, Akhtar M. Hashimoto thyroiditis: a century later. Adv Anat Pathol. 2012; 19(3):181–6.
8. McManus C, Luo J, Sippel R, Chen H. Is thyroidectomy in patients with Hashimoto thyroiditis more risky? J Surg Res. 2012; 178(2):529–32.
9. Lee JH, Kim Y, Choi JW, Kim YS. The association between papillary thyroid carcinoma and histologically proven Hashimoto's thyroiditis: a meta-analysis. Eur J Endocrinol. 2013; 168(3):343–9.
10. Ehlers M, Schott M. Hashimoto's thyroiditis and papillary thyroid cancer: are they immunologically linked? Trends Endocrinol Metab. 2014; 25(12):656–64.
11. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016; 26(1):1–133.
12. Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, et al. An observation trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg. 2010; 34(1):28–35.
13. Xue S, Wang P, Liu J, Chen G. Total thyroidectomy may be more reasonable as initial surgery in unilateral multifocal papillary thyroid microcarcinoma: a single-center experience. World J Surg Oncol. 2017; 15:62.
14. Moghaddam PA, Virk R, Sakhdari A, Prasad ML, Cosar EF, Khan A. Five Top Stories in Thyroid Pathology. Arch Pathol Lab Med. 2016; 140(2):158–70.
15. Adam MA, Thomas S, Youngwirth L, Hyslop T, Reed SD, Scheri RP, et al. Is there a minimum number of thyroidectomies a surgeon should perform to optimize patient outcomes? Ann Surg. 2017; 265(2):402–7.
16. Thompson LD, Herrera HB, Lau SK. A Clinicopathologic Series of 685 Thyroglossal Duct Remnant Cysts. Head Neck Pathol. 2016; 10(4):465–74.
17. Jankovic B, Le KT, Hershman JM. Clinical Review: Hashimoto's thyroiditis and papillary thyroid carcinoma: is there a correlation? J Clin Endocrinol Metab. 2013; 98(2):474–82.
18. Lai X, Xia Y, Zhang B, Li J, Jiang Y. A meta-analysis of Hashimoto's thyroiditis and papillary thyroid carcinoma risk. Oncotarget. 2017; 8(37):62414–24.
19. Anand A, Singh KR, Kushwaha JK, Hussain N, Sonkar AA. Papillary Thyroid Cancer and Hashimoto's Thyroiditis: An Association Less Understood. Indian J Surg Oncol. 2014; 5(3):199–204.
20. Lai V, Yen TW, Rose BT, Fareau GG, Misustin SM, Evans DB, et al. The Effect of Thyroiditis on the Yield of Central Compartment Lymph Nodes in Patients with Papillary Thyroid Cancer. Ann Surg Oncol. 2015; 22(13):4181–6.
21. Sáez JMG. Hashimoto's Thyroiditis and Thyroid Cancer. J Hum Endocrinol. 2016; 1:003.

Мултифокални папиларни микрокарцином штитасте жлезде у завршној фази Хашимотовог тиреоидитиса

Божидар Ковачевић[1], Снежана Кузмић Јанковић[2], Бошко Милев[3], Весна Шкулетић[1]

[1]Војномедицинска академија, Институт за патологију и судску медицину, Београд, Србија;
[2]Војномедицинска академија, Клиника за ендокринологију, Београд, Србија;
[3]Војномедицинска академија, Клиника за општу хирургију, Београд, Србија

САЖЕТАК

Увод Честа удруженост папиларног тиреоидног карцинома (ПТК) и Хашимотовог тиреоидитиса (ХТ) упућује на њихову имунолошку повезаност, иако њихове узрочно-последичне везе нису разјашњене.

Циљ овог рада је био да прикаже неуобичајену појаву мултифокалног папиларног микрокарцинома у атрофичној штитастој жлезди завршне фазе ХТ и анализира њен клинички значај.

Приказ болесника Болесница стара 59 година, са четрнаестогодишњом историјом леченог ХТ, примљена је због оперативног лечења штитасте жлезде после цитолошки утврђене сумње на постојање папиларног карцинома. У току лечења ХТ и ултразвучних контрола праћено је прогресивно смањење величине штитасте жлезде. Чвор у десном режњу штитасте жлезде први пут је дијагностикован 2014. године. После годину дана величина чвора износила је око 7 *mm*, када је учињена аспирациона биопсија танком иглом. Цитолошки налаз је интерпретиран као „суспектан на ПТК". После учињене тоталне тиреоидектомије укупна маса узорка била је мања од 3 *g*. Интраоперативно, штитаста жлезда је била неупадљива и тешко препознатљива од околног ткива. Интреоперативно је потврђен малигнитет. Патохистолошки је дијагностикован мултифокални, билатерални папиларни микрокарцином штитасте жлезде са обостраним, минималним екстратиреоидним ширењем. Седамнаест месеци после оперативног лечења болесница је добро, без постоперативних компликација, рецидива и метастаза папиларног карцинома.

Закључак У околностима тешке атрофије штитасте жлезде папиларни микрокарциноми инфилтративног раста могу рано да покажу екстратиреоидно ширење и инфилтрацију околних структура.

Кључне речи: папиларни микрокарцином, Хашимотов тиреоидитис, завршна фаза