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Case Report / Приказ случаја

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

Мултифокални папиларни микрокарцином штитасте жлезде у завршној фази Хашимотовог тиреоидитиса

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SUMMARY

Introduction Common coexisting of papillary thyroid carcinoma (PTC) with Hashimoto's thyroiditis (HT) indicates its immunological link, with no consensus on a cause and effect of this relationship.

The aim of this report is to represent an unusual case of occurrence of multifocal papillary thyroid microcarcinoma in the severe thyroid atrophy as a result of the end stage of Hashimoto's thyroiditis and to analyze its clinical significance.

Case Outline A 59-year-old female patient with a fourteen years 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 one year follow up, the nodule size was 7mm. 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 specimen weighed less than 3g. 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 early lead to extrathyroid extension even to the infiltration of surrounding structures.

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

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 појаве мултифокалног папиларног микрокарцинома у атрофичној штитастој жлезди завршне фазе ХТ и анализа њен клинички значај.

Приказ болесника. Болесница, стара 59 година, са четрнастогодишњом историјом леченог ХТ, примљена је због оперативног лечења штитасте жлезде након 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 мм, када је учињена је аспирациона биопсија танком иглом. Цитолошки налаз је интерпретиран као „суспектан на ПТК". Након учињене тоталне тиреоидектомије укупна маса узорка била је мања од 3g. 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. После 17 месеци од 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

INTRODUCTION

Papillary thyroid microcarcinoma (PTMC) is a size-defined variant of papillary thyroid carcinoma (PTC) measuring less then 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 an annual incidence of 0.3 -1.5 cases per 1000 persons. The histological features of HT include diffuse lymphoid infiltration with formation of lymhoid follicules often with germinal centers, destruction and atrophy of thyroid follicules frequently with oxyphilic metaplasia of thyreocites, and different degree 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 variant [6,7].

The fibrous atrophy variant of HT is characterised 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 represent 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 suspicion for malignancy, persistent symptoms associated with the disease, or a goiter that is increasing in size [6,8].

In surgically treated patients occurrence rate of histologically proven HT in PTC is almost three times more often than in other thyroid diseases [9]. The common coexisting of PTC and HT indicates that these two diseases are immunologically linked with no consensus on a 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 in the severe TG atrophy as a result of the end stage of Hashimoto's thyroiditis and to analyze its clinical significance.

CASE REPORT

A 59-year-old female patient with a fourteen years 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 disease evolution patient received substitution therapy with levothyroxine (100 μg/day). Ultrasound controls were performed once a year. In the beginning 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 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 (>1500 IU/mL), while TSH measured 0.28 μmol/dl and level of free thyroxine (T4) was 21.2 pmol/l. Ultrasonographic examination revealed a reduced TG volume with diffuse low echogenicity. Dimension of the right and left lobe were 16x10x9 mm, and 19x5x8 mm, respectivly. The nodule with cytologically proven suspicion for PTC was in the right lobe, measured 7x4 mm and showed marked hypoechogenicity with spiculated margin.

Intraoperative findings

The patient underwent total thyroidectomy. Intraoperatively, the TG was incospicious and indistinguishable from the surrounding tissue while all four parathyroid glands were detected. In the anatomical space of the right lobe, small nodule was noticeable to the surgeon. The nodule with surrounding tissue was extirpated and sent to the pathologist for an intraoperative consultation (IOC). 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 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 is extirpated and implanted in the left sternocleidomastoid muscle.

Histopathology

Gross Findings. – The thyroid tissue sample received for IOC measured 10x6x3 mm, it had pale red to tan color, and a firm to hard consistency. At periphery, small amount of adipose tissue was present. The rest of a right lobe, left lobe and isthmus measured 13x8x3 mm, 16x6x3 mm and 10x3x3 mm, respectively. Its consistency was firm and a color was pale red. These samples were processed for permanent section. The weight of all specimen was less than 3 g.

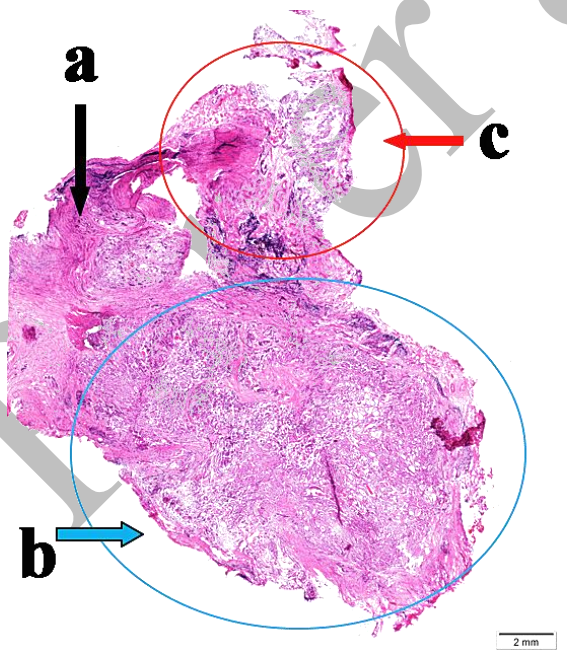
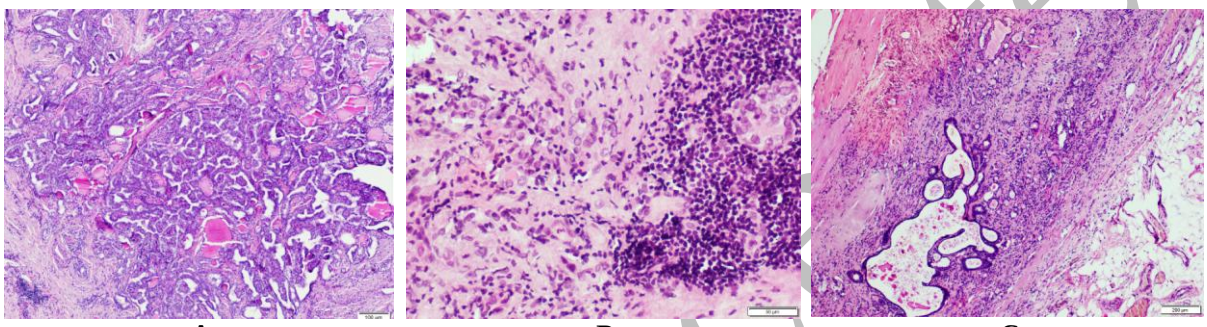


Figure 1. Frozen section, H&E scanning magnification. Whole-mount section of thyroid tissue from the right lobe: a) atrophic thyroid with perithyroid tissue; b) 6 mm size of PTC; c) part of the parathyroid gland.

Microscopic Findings. – In histologically examined frozen section sample from right lobe a 6 mm PTMC was observed. 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).

In the tissue sample from left lobe one more focus of PTMC was detected, measuring 3 mm in size. This focus had a 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 through several areas. Its diameter was very small with flattening of follicular epithelial cells, containing pale or thick colloid. In addition, there was evidence of lymphocyte infiltration with rare germinal center formation (Figure 2B). The blood vessels were small to medium size without occlusion and histological sign of inflammation. In the isthmic region, beside small atrophic follicles, an incidental one millimeter thyroglossal duct remnant cyst (TGDC) was also observed (Figure 2C).



A **B** **C**

Figure 2. A – A 3 mm size PTMC in the left lobe of the TG (H&E, x100). B – Lymphocytic inflammation with fibrosis, atrophy and destruction of thyroid follicles (H&E, x). C – Atrophic thyroid tissue, fibrosis and a 1 mm thyroglossal duct remnant cysts in the isthmic region (H&E, x40).

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 had no complications during the postoperative period. Six weeks after surgery, the patient underwent treatment with 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 shows 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 [11], there are still no consensus in the management of PTMC, resulting in a wide spectrum treatment modalities range from observation without treatment [12] to total thyroidectomy with or without lymph node dissection, and radioiodine ablation [5,13]. Importance of recognition subset of PTMC with potential to more aggressive behavior had influence to further treatment. The most commonly

reported morphological characteristics of PTMC related to its aggressive behavior are: extrathyroid extension, multifocality, lymph node and distant metastasis, vascular invasion, tumore 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 localisation 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 between 1 to 6 g and is barely identifiable on gross examination. This form of 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 represent the end-stage of this autoimmune process [5,6].

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 presence of a thyroid nodule with a 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. 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 [8]. On the other hand, postoperative complications after thyroidectomy was performed are reduced if surgeons perform a larger number of the surgeries per year [15]. The surgery of atrophic TG is even more at risk of surgical complication because the whole TG is in a close vicinity of RLN. The TG can be inconspicuous from surrounding anatomical structure and sometimes, to in prove that removed tissue belong to the thyroid, intraoperative consultation of pathologist may be necessary.

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

The relationship 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 JH et al. showed that the occurrence rate of HT in PTC patients, after thyroidectomy was performed, was 2.8 times higher than HT patients in 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 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 a still open question whether is development of PTC 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 suggest its ability to escape host immune response and to survive despite an (auto)immune response. According to the different studies, this tumor ability might occure 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, PDL-1) [9].

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

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