UDC 616.441-006.6-033.2:616.428:611.93

Tkachenko R.P., Kuryk O.G., Golovko A.S., Denisenko A.I.

MEDULLARY THYROID CARCINOMA WITH METASTASIS TO CERVICAL LYMPH NODES

State Research Institution "Research and Practical Centre of Preventive and Clinical Medicine"
State Administration of Affairs, Kyiv
Bogomolets National Medical University, Kyiv

Medullary thyroid carcinoma (MTC) is a rare disease, which makes up approximately 4-5% of all thyroid cancers and originates from the calcitonin-screening parafollicular C cells. MTC is a malignancy, which frequently spreads to cervical lymph nodes. The condition may be sporadic or hereditary, and the latter one constitutes 20-25% of all cases. We report a case of metastatic MTC manifested with cervical lymphadenopathy in a 67-year-old woman. Our patient underwent a total thyroidectomy. Final histopathology tests revealed medullary thyroid carcinoma. There were found two lymph nodes of 6 group and two lymph nodes of 2, 3, 4 groups in left side with MTC metastasis. In this article we also provided a general review of the classification, pathology, and clinical management of MTC. Our patient through 9 months after the operation was observed to have no MTC recurrence or residue. In 75-85% of cases the prognosis for patients with MTC is favourable with a 10-year survival rate. About 50% of the patients with MTC have the disease restricted with the thyroid gland only, and 95% of them have a 10-year survival rate. Approximately, one-third of the patients present locally invasive tumours or metastasis to the regional lymph nodes. The survival rate of patients with regional disease makes up 75%. Distant metastases may be detected in 13% of the patients at the initial diagnosis and can be regarded as signs of poor prognosis, when a 10-year survival rate in reached by only 40% of patients. Prognosis is better in patients with MEN 2A compared to sporadic MTC, because sporadic carcinoma is usually diagnosed later, when the disease is in its advanced stage. Thus, MTC is a rare thyroid malignant tumour, its management differs from that for differentiated thyroid cancers. Early diagnosis offers a higher likelihood of cure and long-term survival. Total thyroidectomy plus central compartment neck dissection is the modality of the treatment. All patients must pass through regular follow-up to avoid recurrence.

Key words: medullary thyroid carcinoma, metastasis, sporadic, total thyroidectomy, neck dissection, calcitonin.

Introduction

Medullary thyroid carcinoma (MTC) constitutes around 4-5% of all thyroid cancers [7]. MTC usually arises from parafollicular C-cells that normally secrete a number of peptide hormones such as calcitonin, serotonin, and vasoactive intestinal peptide; thus, it is widely accepted as a neuroendocrine tumour. As opposed to the more common papillary and follicular thyroid cancer subtypes, MTC represents a rare and under-characterized form of cancer, and may cause death if untreated [3, 20].

MTC can be sporadic, usually isolated to one thyroid lobe, or familial, the latter one is defined as part of the cancer syndrome known as Multiple Endocrine Neoplasia type 2 (MEN2) [17]. MEN2 is the result of an autosomal dominant, missense, gain-of-function mutation in the RET (Rearranged during Transfection) proto-oncogene [5]. Comparing the occurrence rate of sporadic and familial forms, we have found out the sporadic form make up 70% of the cases and familial form 10-20% of the cases [4]. In the majority of cases, the preoperative diagnosis is requires, based on the results of thyroid fine-needle aspiration cytology (FNAC), serum calcitonin level assessment, and RET proto-oncogene testing [12]. In approximately 10–15% of cases, diagnosis of MTC is made only after thyroidectomy. Histologically, tumours appear containing hyperplastic parafollicular C-cells, and predominantly present bilaterally. Sporadic MTC generally presents as a single tumour confined within one thyroid lobe [17].

The prognosis of MTC is worse compared with differentiated thyroid cancers, a 10-year survival rate is reached in 95.6% in cases restricted by the thyroid gland only; 40% for those present metastasis [20].In this article we describe the case report of a patient with sporadic MTC.

Case Report

A 67-year-old woman found an anterior neck mass. She was referred to endocrinologist. An ultrasound examination of her neck showed a 1, 5 cm solid hypoechoic nodule of the left thyroid lobe and an additional nodule in the lower pole of the same lobe. A suspicious neck mass that appeared to be metastatic lymph nodes was noticed. The right thyroid lobe and the isthmus appeared to be normal. Serum levels of free triiodothyronine, free thyroxin, and thyrotrophin were within normal limits, and anti-thyroperoxidase / anti-thyroglobulin auto antibodies and anti-thyroglobulin antibody were negative. A preoperative calcitonin serum value was elevated, 240 ng/L. She had normal serum levels of calcium, phosphorus, and parathyroid hormone. FNA biopsy of the nodule was consistent with a diagnosis of medullary thyroid carcinoma. Our patient underwent a total thyroidectomy with neck exploration. An enlarged thyroid gland with a prominent left lobe were detected during the operation (Figure 1)

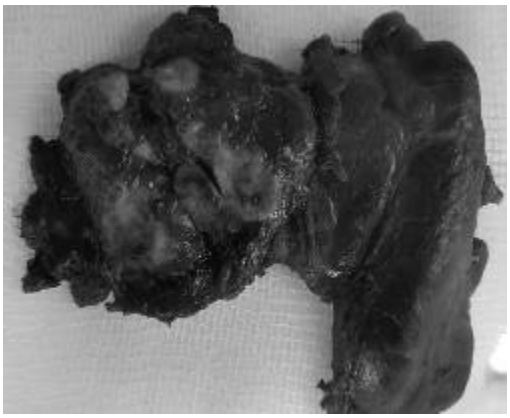

Figure 1. Specimen showing total thyroidectomy in the patient

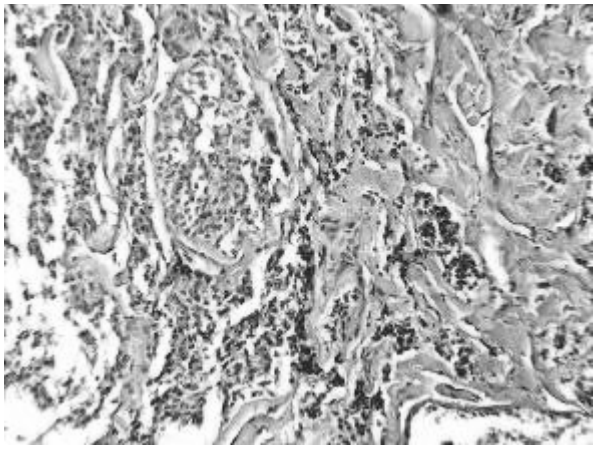

Figure 2. Medullary thyroid carcinoma with nesting proliferation of neoplastic parafollicular cells with stromal amorphous material deposition. Hematoxylin and eosin (H & E) staining. x200.

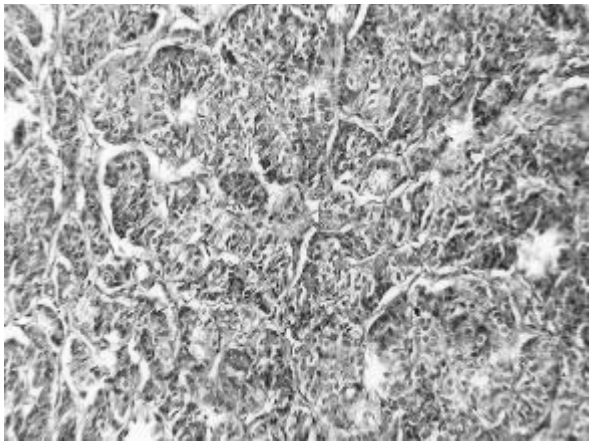

Figure 3. Medullary thyroid carcinoma. Polygonal cells with eosinophilic cytoplasm and little mitosis. Hematoxylin and eosin (H & E) staining. x200.

A neck dissection yielded six regional lymph nodes of 6 group, twenty lymph nodes of 2, 3.4 groups in left side and eighteen lymph nodes of 2,3.4 groups in right side. Surgical specimens were fixed in 10% buffered formalin, embedded in paraffin, and then stained with hematoxylin and eosin. For immunohistochemical studies, sections were incubated with the following primary monoclonal antibodies: chromogranin A, thyroglobulin, and calcitonin (Dako Corporation, Glostrup, Denmark). Appropriate positive and negative control sections were processed in parallel. The light microscopy identified two lesions. The tumour was limited by thyroid capsule. The nodules consisted of a sheet-like pattern of growing cells with round nuclei and clumped chromatin with scant amphophilic cytoplasm. Mitotic activity was low. The stroma contained a homogeneous and pink ground substance. Tumor cells were immunoreactive to calcitonin, chromogranin A, and were negative for thyroglobulin. There were found two lymph nodes of 6 group and two lymph nodes of 2,3.4 groups in left side with metastasis of medullary carcinoma. Pathologic findings in thyroid gland are shown in the figure 2 and figure 3 that demonstrate neoplastic proliferation of parafollicular cells in nesting pattern with amorphous eosinophilic material depositions in the stroma.

Discussion

Medullary thyroid cancer (MTC) is a neuroendocrine tumour of the parafollicular C-cells of the thyroid gland and makes for approximately 4-5% of thyroid carcinomas [7]. Sporadic MTC is usually diagnosed in aged patients over 50 and is somewhat prevalent among women. Hereditary MTC is, however, more common in the younger age group, of which multiple endocrine neoplastic type 2A (MEN 2A) and familial thyroid cancer usually arise when patients are in their 30s, and MEN 2B is typically detected in those who are over 20. Hereditary forms are transmitted as an autosomal dominant trait either alone as familial MTC (FMTC) or as part of MEN 2A or 2B [12]. Germline mutations of the RET proto-oncogene (RET) found on chromosome 10q11 are responsible for FMTC s and may be present in more than 95% of the hereditary MTCs and in about 25% of the sporadic MTCs [5].

The prognosis of MTC is better compared with the prognosis of poorly-differentiated, malignant, anaplastic thyroid cancer, but is worse than the more well-differentiated and benign papillary and follicular thyroid tumors [9]. Therefore, early diagnosis is necessary prevent recurrence and enhance survival rates of these patients [20].

The most common presentation of sporadic MTC is a painless solitary thyroid nodule, and multi-

focality and bilaterality are the features of the hereditary forms. Cervical lymph node metastasis is approximately found in 50% of the cases at the time of diagnosis, whereas distant metastases are present in 10% of the cases; higher incidence being those with large tumour size or multifocal tumours [18]. The literature states that MTC included the encapsulated type, follicular type, oncocytic type, squamous type, cribriform type, rosette formation, osteogenic sarcoma type, and pseudopapillary types [22]. The histology did not seem to influence the course of the disease. In our study, the female patient presented with multiple nodules, and cervical metastases were found out.

Calcitonin is the most sensitive and specific tumour marker at the preoperative diagnosis and during the post-operative follow up. Calcitonin values lower to the normal limits after the resection of the tumour and regional involvement is regarded as complete tumor regression. Thus, according to the American Thyroid Association, it is not routinely recommended and hence preoperative normal calcitonin value can not exclude the diagnosis of MTC [19]. Another biomarker, CEA, is also produced by the neoplastic C-cells, and it has been useful in predicting the prognosis for MTC patients, more importantly when preoperative serum calcitonin values are negative [16]. CEA may be found in over 50% of the MTC patients, and levels above 30 ng/ml strongly indicate a poor prognosis. It is also seen that CEA values higher then 100 ng/mL are found to be associated with extensive lymph node involvement and distant metastasis [25]. Here, our patient had significantly raised levels of serum calcitonin which regressed to baseline following the surgery, but CEA did not.

Neck ultrasound should be performed as the conventional approach in thyroid examining. Although MTC has no classical ultrasound specifics, this technique can be helpful in visualizing the nodule characteristics, enlarged lymph nodes, if any, and to guide FNAC from the suspicious nodules. FNAC is usually the first line of investigation for diagnosing thyroid nodules [8]. In our case, classical features of MTC in FNAC were seen including plasmacytoid appearance of cells and multiple spindle-shaped cells with the presence of amyloid.

Total thyroidectomy along with central compartment neck dissection is the treatment of choice for the patients with medullary thyroid carcinoma. The incidence of central neck metastasis can be as high as 81% in patients with palpable tumours and thus, central compartment neck dissection provides a better survival and cure rate than total thyroidectomy alone [23]. Since there is a huge risk of neck metastasis, even in tumours <1 cm, few surgeons do recommend bilateral lateral neck dissection in all patients with MTC [24].

In the 2009 American Thyroid Association (ATA) guidelines for the surgical management of MTC, the extent of calcitonin preoperative elevation guides the selection of preoperative imaging studies, which in turn influence the extent of the surgery [10]. A majority of guideline authors agreed to a consensus view that sporadic MTC in adults should be treated, at a minimum, with total thyroidectomy and central node dissection. In the consensus ATA view, ipselateral level II–V dissection is best justified by suspicious lymph nodes on examination, ultrasound, or other imaging or intraoperative findings [11]. A prophylactic approach to ipselateral neck dissection is favoured by some authors because the incidence of lateral node metastases in macroscopic MTC is roughly 80% [6].

All those patients who present the disease limited to the thyroid gland without neck node involvement tend to have a low recurrence rate and rarely die of their disease [13]. However, since a lot of patients with MTC have nodal disease at the time of presentation, they are at a greater risk for developing recurrent or persistent disease. Thus, they must adhere to a strict postoperative follow-up and monitoring. The postoperative follow-up should begin 2-3 months after operation and it is based on serum calcitonin and CEA levels. For localization of the recurrence or residue of the MTC, various scintigraphic methods are applied with using the radiolabelled molecules [14]. Our patient through 9 months after operation was observed to have no recurrence or residue of the MTC.

The prognosis for patients with MTC is favourable when a 10-year survival rate is achieved by 75-85% [20]. About 50% of the patients with MTC have disease restricted to the thyroid gland, and have a 10-year survival rate is achieved by 95% of the patients. Approximately, one-third of the patients present local invasive tumours or metastasis to the regional lymph nodes. The survival rate of patients with regional disease made up 75%. Distant metastases may be seen in 13% of the patients at the initial diagnosis and is of a poor sign for prognosis, when a 10-year survival rate is achieved by only 40% of patients. Prognosis is better in patients with MEN 2A compared with sporadic MTC, because sporadic carcinoma is usually diagnosed later when the disease is far gone.

Radio-active iodine therapy seems to have no role in MTC as the tumour originates from parafollicular C-cells, which do not accumulate iodine [21]. Both radiation therapy and conventional chemotherapy have limited effect in the treatment of patients with MTC [15].

Conclusion and perspectives

MTC is a rare thyroid malignancy; its management differs from that for differentiated thyroid cancers. Early diagnosis offers a higher likelihood of cure and long-term survival. Total thyroidectomy plus central compartment neck dissection is the modality of treatment. All patients must adhere to regular follow-up to avoid recurrence of the condition.

Література

1. Almeida M.Q. Recent advances in the molecular pathogenesis and targeted therapies of medullary thyroid carcinoma / M.Q. Almeida, A.O. Hoff // Curr. Opin. Oncol. - 2012. – Vol. 24. – P. 229-234.
2. Alagarsamy J. Cytological diagnosis of metastatic medullary thyroid carcinoma: a case report / J. Alagarsamy, S. Satish, S. Nirmala // Int. J. Adv. Med. - 2015. – Vol. 2. – P. 51-53.
3. Balakrishnan V. A Rare Presentation of Medullary Carcinoma Thyroid / V. Balakrishnan, K.K. Saroshkumar, S.M. Sarin [et al.] // J. Med. Case Reports. - 2016. - Vol. 4, No. 1. – P. 8-11.
4. Barbieri R.B. Evidence that polymorphisms in detoxification genes modulate the susceptibility for sporadic medullary thyroid carcinoma / R.B. Barbieri, N.E. Bufalo, R. Secolin [et al.] // Eur. J. Endocrinol. - 2012. – Vol. 166(2). – P. 241–245.
5. Cakir M. Medullary thyroid cancer: Molecular biology and novel molecular therapies / M. Cakir, A.B. Grossman // Neuroendocrinology. - 2009. – Vol. 90. – P. 323-348
6. Greenblatt D.Y. Initial lymph node dissection increases cure rates in patients with medullary thyroid cancer / D.Y. Greenblatt, D. Elson, E. Mack, H. Chen // Asian J. Surg. - 2007 - Vol. 30. – P. 108-112.
7. Grozinsky-Glasberg S. Medullary thyroid cancer: A retrospective analysis of a cohort treated at a single tertiary care center between 1970 and 2005 / S. Grozinsky-Glasberg, C.A. Benbassat, G. Tsvetov [et al.] // Thyroid. - 2007. – Vol. 17. – P. 549-556.
8. Hsieh M.H. Fine needle aspiration cytology stained with Rius method in quicker diagnosis of medullary thyroid carcinoma / M.H. Hsieh, Y.L. Hsiao, T.C. Chang // J. Formos Med. Assoc. - 2007. – Vol. 106. – P. 728-735
9. Hung W.W. Medullary thyroid carcinoma with poor differentiation and atypical radiographic pattern of metastasis / W.W. Hung, C.S. Wang, K.B. Tsai [et al.] // Pathol. Int. - 2009. – Vol. 59. – P. 660-663.
10. Kloos R.T. Medullary thyroid cancer: management guidelines of the American Thyroid Association / R.T. Kloos, C. Eng, D.B. Evans [et al.] // Thyroid. – 2009. – Vol.19. – P. 565–612.
11. Links T.P. Endocrine tumours: Progressive metastatic medullary thyroid carcinoma: First- and second-line strategies / T.P. Links, H.H. Verbeek, R.M. Hofstra, J.T. Plukker // Eur. J. Endocrinol. - 2015. – Vol. 172. – P. 241-51.
12. Machens A. Increased risk of lymph node metastasis in multifocal hereditary and sporadic medullary thyroid cancer / A. Machens, S. Hauptmann, H. Dralle // World J. Surg. – 2007. – Vol. 31. – P.1960-1965.
13. Machens A. Locoregional recurrence and death from medullary thyroid carcinoma in a contemporaneous series: 5-year results / A. Machens, S. Hauptmann, H. Dralle // Eur. J. Endocrinol. - 2007. – Vol. 157. – P. 85-93.
14. Maia A.L. Diagnosis, treatment, and follow-up of medullary thyroid carcinoma: Recommendations by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism / A.L. Maia, D.R. Siqueira, M.A. Kulcsar [et al.] // Arq. Bras. Endocrinol. Metabol. - 2014. – Vol.58. – P. 667-700.
15. Meijer J.A. Radioactive iodine in the treatment of medullary thyroid carcinoma: A controlled multicenter study / J.A. Meijer, L.E. Bakker, G.D. Valk [et al.] // Eur. J. Endocrinol. - 2013. – Vol. 168. – P. 779-786.
16. Meijer J.A. Calcitonin and carcinoembryonic antigen doubling times as prognostic factors in medullary thyroid carcinoma: a structured meta-analysis / J.A. Meijer, S. le Cessie, W.B. van den Hout [et al.] // Clin.Endocrinol. - 2010. - Vol.72, No.4. – P. 534-542.
17. Moo-Young T.A. Sporadic and familial medullary thyroid carcinoma: State of the art / T.A. Moo-Young, A.L. Traugott, J.F. Moley // Surg. Clin. North Am. - 2009. – Vol. 89. – P. 1193-1204.
18. Mozafar M. Cervical Lymph Node Involvement by Medullary Carcinoma of Unknown Origin; a Rare Presentation / M. Mozafar, M.R. Sobhiyeh, N. Tadayon, N. Bolouri // Int. J. Endocrinol. Metab. - 2010. – Vol. 1. – P. 51—54.
19. Panagiotakou A. “Atypical” Non-Secretory Medullary Thyroid Carcinoma: Case Report and Review of the Literature / A. Panagiotakou, D. Ioannidis, D. Lilis, G. Karageorgos // Endocrinol. Metab. Int. J. - 2017. - Vol. 4(3). – P. 85-89.
20. Roman S. Prognosis of medullary thyroid carcinoma: Demographic, clinical, and pathologic predictors of survival in 1252 cases / S. Roman, R. Lin, J.A. Sosa // Cancer. - 2006. – Vol. 107. – P. 2134-2142.
21. Roy M. Current understanding and management of medullary thyroid cancer / M. Roy, H. Chen, R.S. Sippel // Oncologist. - 2013. – Vol 18. – P. 1093-1100.
22. Priya R. Medullary carcinoma of thyroid: Case report and a review of literature / R. Priya, N. Virmani, J.P. Dabholkar // J. Head Neck Physicians Surg. - 2016. Vol .4. - 80-84.
23. Scollo C. Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer / C. Scollo, E. Baudin, J.P. Travagli [et al.] // J. Clin. Endocrinol. Metab. – 2003. – Vol. 88. – P. 2070-2075.
24. Sippel R.S. Current management of medullary thyroid cancer / R.S. Sippel, M. Kunnimalaiyaan, H. Chen // Oncologist. - 2008. – Vol. 13. – P. 539-547.
25. vanVeelen W. Medullary thyroid carcinoma and biomarkers: past, present and future / W. vanVeelen, J.W. de Groo, D.S. Acton // J. Internal Med. - 2009. - Vol.266, No.1. – P. 26-140.

Реферат

МЕДУЛЯРНА КАРЦИНОМА ЩИТОПОДІБНОЇ ЗАЛОЗИ З МЕТАСТАЗАМИ В ШИЙНІ ЛІМФАТИЧНІ ВУЗЛИ

Ткаченко Р.П., Курик О.Г., Головко А.С., Денисенко А.І.

Ключові слова: медулярна карцинома щитоподібної залози, метастази, спорадичні форми, тиреоїдектомія, шийна лімфодисекція, кальцитонін.

Медулярна карцинома щитоподібної залози є рідкісним захворюванням, яке становить приблизно 4-5% всіх випадків раку щитовидної залози і походить з кальцитонін-секретуючих парафолікулярних С-клітин. МКЩЗ часто поширюється на шийні лімфатичні вузли. Зустрічається у спорадичних (75-80%) і сімейних (20-25%) формах. Представлений випадок медулярної карцином щитоподібної залози з метастазами в шийні лімфатичні вузли у 67-річної жінки. Пацієнтці була проведена тотальна тиреоїдектомія з шийною лімфодисекцією. Заключний патогістологічний діагноз підтвердив медулярну карциному щитоподібної залози. Були виявлені метастази у двох лімфатичних вузлах 6 групи і у двох лімфатичних вузлах 2,3.4 груп зліва. В обговоренні представлений огляд класифікацій, патогенезу, діагностики та лікування медулярної карциноми щитоподібної залози. Зазначено, що у нашої пацієнтки через 9 місяців після операції не виявлено рецидиву або метастазів медулярної карциноми щитоподібної залози. Отже, медулярна карцинома щитоподібної залози - це рідкісне новоутворення щитовидної залози, характеризується частим метастазуванням и поганим прогнозом за відсутністю лікування. Рання діагностика забезпечує більш високу вірогідність успішного лікування і довгострокового виживання. Тотальна тиреоїдектомія з лімфодисекцією шиї є основою лікування. Всі пацієнти повинні проходити регулярне обстеження з метою можливого виявлення рецидиву або метастазів медулярної карциноми щитоподібної залози.

Реферат

МЕДУЛЛЯРНАЯ КАРЦИНОМА ЩИТОВИДНОЙ ЖЕЛЕЗЫ С МЕТАСТАЗАМИ В ШЕЙНЫЕ ЛИМФАТИЧЕСКИЕ УЗЛЫ

Ткаченко Р.П., Курик Е.Г. , Головко А.С., Денисенко А.И.

Ключевые слова: медуллярная карцинома щитовидной железы, метастазы, спорадическая форма, тотальная тиреоидэктомия, лимфодиссекция шеи, кальцитонин.

Медуллярная карцинома щитовидной железы является редким заболеванием, которое составляет приблизительно 4-5% от всех видов рака щитовидной железы и происходит из кальцитонин-секретирующих парафолликулярных С-клеток. Медуллярная карцинома щитовидной железы - редкая злокачественная опухоль, которая часто метастазирует в шейные лимфатические узлы. Встречается в спорадических (75-80%) и семейных (20-25%) формах. Представлен случай медуллярной карциномы щитовидной железы с метастазами в щейные лимфатические узлы у 67-летней женщины. Пациентке была проведена тотальная тиреоидэктомия с шейной лимфодиссекцией. Заключительный патогистологический диагноз подтвердил медуллярную карциному щитовидной железы. Были обнаружены метастазы в двух лимфатических узлах 6 групп и двух лимфатических узлах 2,3,4 групп слева. В обсуждении представлен обзор классификаций, патогенеза, морфологической картины, диагностики и лечения медуллярной карциномы щитовидной железы. Отмечено, что у нашей пациентки через 9 месяцев после операции не выявлено рецидива или метастазов медуллярной карциномы щитовидной железы. Таким образом, медуллярная карцинома щитовидной железы является редким злокачественным новообразованием щитовидной железы, характеризуется частым метастазированием и плохим прогнозом при отсутствии лечения. Ранняя диагностика дает более высокую вероятность успешного излечения и долгосрочного выживания. Тотальная тиреоидэктомия с лимфодиссекцией шеи являются основой лечения. Все пациенты должны проходить регулярное обследование с целью возможного выявления рецидива или метастазов медуллярной карциномы щитовидной железы.