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Malignant melanoma arising in melanin-producing medullary thyroid carcinoma



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ABSTRACT

INTRODUCTION: We report a case of malignant melanoma arising in medullary thyroid carcinoma that has not yet been described.

PRESENTATION OF CASE: A 66-year-old woman presented with a mass in her thyroid. The resected mass was black in color, and was composed of a mixture of classic medullary thyroid carcinoma and pleomorphic atypical cells containing melanin pigments. The pleomorphic atypical cells were morphologically consistent with malignant melanoma, and expressed Melan-A, HMB-45, and S-100 protein as determined by immunohistochemistry. Some of these cells were also positive for calcitonin and chromogranin A. Although the malignant melanoma metastasized to the lymph nodes, the patient remained free from local recurrence and distant metastasis and the primary malignant melanoma lesion was not identified for up to 11 years after the thyroidectomy.

DISCUSSION: 11 melanin-producing MTC cases have been reported to date. In the reported cases, the term “malignant melanoma” was not used, likely because the melanin-containing carcinoma cells were not morphologically consistent with malignant melanoma, but with medullary carcinoma.

CONCLUSION: Malignant melanoma arising in MTC may have a favorable prognosis.

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1. Introduction

Medullary thyroid carcinoma (MTC) is a malignant tumor of the thyroid that exhibits C-cell differentiation. Microscopically, MTC can exhibit divergent growth patterns and cytologic features, and several subtypes have been proposed, such as spindle cell, papillary, oncocytic, follicular, clear cell, giant cell, and paraganglioma-like variants [1]. MTC may produce melanin pigments, which is referred to as melanin-producing MTC [2–10]. The amount of melanin pigments ranges from microscopic foci to massive production. MTC that produces massive amounts of melanin is extremely rare.

We encountered a case of melanin-producing MTC that contained pleomorphic atypical cells expressing markers of both MTC (calcitonin) and melanoma. The pleomorphic atypical cells were morphologically and immunohistochemically consistent with malignant melanoma. To the best of our knowledge, such a case has

not yet been reported. Herein, we report the first case of malignant melanoma arising in MTC.

2. Presentation of case

A 66-year-old woman presented with an anterior neck mass that had persisted for one year. When the mass began to gradually increase in size, she visited Uchinomi Hospital for an evaluation. She had no hoarseness. She did not have a family history of MTC. On physical examination, the mass was located in the left lobe of the thyroid and was ovular, soft, and movable, with slightly irregular margins. Enlarged lymph nodes were not palpable in the neck region. Laboratory results, including those from a thyroid hormone test, were within normal limits. A chest radiograph revealed a deviation to the right of the trachea. No abnormal calcification was observed in the thyroid, and there was no evidence indicating metastatic lesions in the lung. Fine needle aspiration cytology and ultrasound examination were not performed, because it was not standard in 1984, when the patient was evaluated.

A partial thyroidectomy was planned and took place under general anesthesia. During the surgery, we noted many small black lymph nodes measuring 3–7 mm in the central and left lateral neck compartments. Metastatic melanoma was suspected based on the

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Fig. 1. Cut surface of the left thyroid mass (dorsal view). The mass is well demarcated and black in color.

intense black color of the cut surfaces of the thyroid tumor and lymph nodes. No dermal lesions suggesting malignant melanoma were observed on the patient's head, face, hands, or feet. The anatomical distribution of the black lymph nodes was consistent with that of metastatic nodes from thyroid cancer. We therefore suspected melanin-producing MTC, and performed total thyroidectomy with a left modified radical neck dissection. An extensive post-surgery examination, including the skin, nasopharynx, oral mucosa, upper gastrointestinal tract, and gynecologic organs, was performed by the specialists in the respective fields, but a primary site of the melanoma could not be identified. Serum calcitonin and carcinoembryonic antigen (CEA) levels at the time of surgery were 960 pg/mL (normal value: less than 100 pg/mL) and 6.1 ng/mL (normal value: less than 2.5 ng/mL), respectively. One month after the thyroidectomy, serum calcitonin levels had returned to normal (25 pg/mL). The patient remained free from local recurrence and distant metastasis and the primary malignant melanoma lesion was not identified for up to 11 years after the thyroidectomy. Additionally, serum calcitonin level remained within normal ranges.

2.1. Pathological findings

Grossly, a well-demarcated mass measuring $4.8 \times 3.0 \times 3.0$ cm was located in the left lobe of the thyroid. The cut surface was solid and intensely black in color (Fig. 1). Microscopically, the mass was well demarcated by a discontinuous fibrous capsule and composed of two distinct atypical cells. One cell type was large, round or pleomorphic, occupied a majority of the mass, and exhibited an alveolar or solid growth pattern (Fig. 2). The nests of cells were separated by a thin fibrovascular stroma. These atypical cells were discohesive and tended to be individually separated at the inner part of the nests. The cytoplasm was abundant as indicated by a low nucleus to cytoplasm (N/C) ratio, and the cell borders were distinct. Most of these atypical cells contained brown pigments, the quantity of which varied from scant to abundant. The brown pigments were positive by Fontana-Masson stain, negative by both Berlin blue and PAS stains, and perfectly bleached by 0.25% potassium permanganate and 2% oxalic acid, suggesting that they were composed of melanin. Despite the low N/C ratio, the nuclei were large, eccentrically located, and had prominent large nucleoli. Some of these cells exhibited rhabdoid features. Additionally, mitotic figures, multinucleated giant cells, and necrosis were detected. In all, the features of these atypical cells were microscopically consistent with malignant melanoma.

The second type of atypical cell found in the tumor was focally observed, especially in the subcapsular area (Fig. 3). These cells were small with a round or spindle shape. N/C was high, and the nuclei were bland and round or short spindle in shape. In contrast to the first type of atypical cell, their cell border was indistinct and they did not contain brown pigments. Amyloid materials that were

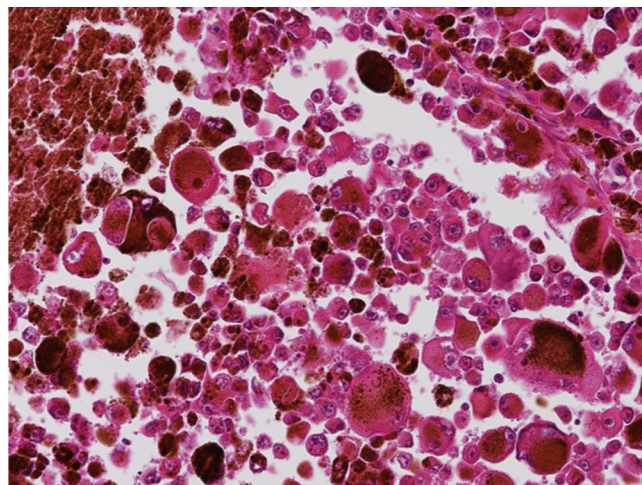


Fig. 2. H&E stain of the thyroid mass. Melanoma cells were considerably pleomorphic and contained various amounts of brown pigment.

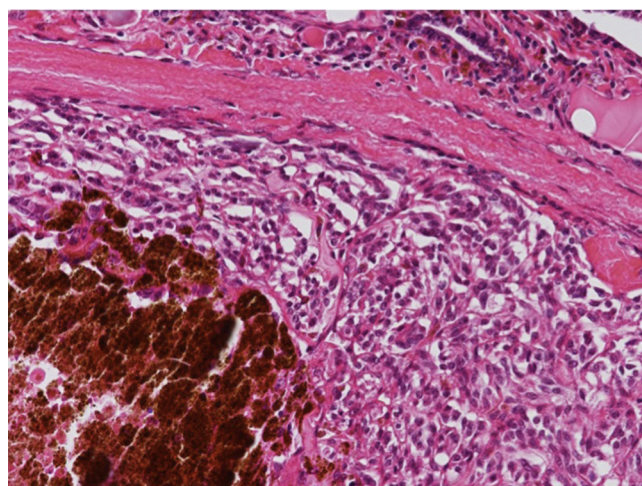


Fig. 3. H&E stain of the thyroid mass. Medullary carcinoma cells were visible in the subcapsular area.

confirmed by Congo-red stain were present in the stroma. The findings were consistent with classic MTC. Malignant melanoma and MTC were intimately intermingled without a front formation. The malignant melanoma had metastasized to 19 cervical lymph nodes (lt. III: 3/13, lt. IV: 10/25, lt. V: 1/6, and VI: 5/5), but metastasis of the MTC was not observed.

Results of the immunohistochemical analysis are summarized in Table 1. The large pleomorphic atypical cells (melanoma cells) expressed Melan-A (Fig. 4A), HMB-45 (Fig. 4B), and S-100 protein as determined by immunohistochemistry, and were focally positive for calcitonin (Fig. 5A), chromogranin A, CEA and cytokeratin 7. Specifically, the melanoma cells that contained scant melanin pigments or were located near the stroma tended to react with the antibodies. The melanoma cells were negative for PAX8, TTF-1, cytokeratin MNF116, cytokeratin 20, and EMA. The small atypical cells (MTC cells) were diffusely positive for calcitonin (Fig. 5B), chromogranin A, and CEA, and negative for Melan-A, HMB-45, S-100 protein, calcitonin, chromogranin A, CEA, and cytokeratin 7. Ki-67 labeling indices of the malignant melanoma and MTC components were more than 40% and less than 1%, respectively.

Table 1
Results of the immunohistochemical analysis.

Antibody (Vendor, Clone, Dilution)	Medullary carcinoma	Malignant melanoma
Calcitonin (Dako, polyclonal, 1:10)	+	+ (Focal)
Chromogranin A (Dako, DAK-A3, 1:400)	+	+ (Focal)
CEA (Histofine, COL-1, 1:4)	+	+ (Focal)
Thyroglobulin (Dako, polyclonal, 1:5)	–	–
PAX 8 (Protein Tech Group, polyclonal, 1:200)	+ (Focal)	–
TTF-1 (Dako Cytomation, 8G7G3/1, 1:100)	+ (Focal)	–
Cytokeratin MNF116 (Abcam, MNF116, 1:100)	+	–
Cytokeratin 7 (Dako, OV-TL 12/30, 1:50)	+	+ (Focal)
Cytokeratin 20 (Dako, Ks20, 1:50)	–	–
EMA (Dako, E29, 1:50)	–	–
Melan-A (Novocastra A103, 1:25)	–	+
HMB-45 (Dako, HMB45, 1:50)	–	+
S-100 protein (Dako Cytomation, polyclonal, 1:2)	–	+
Vimentin (Nichirei, V9, predilution)	+	+
Ki-67 (Dako, MIB-1, 1:200)	Less than 1%	More than 60%

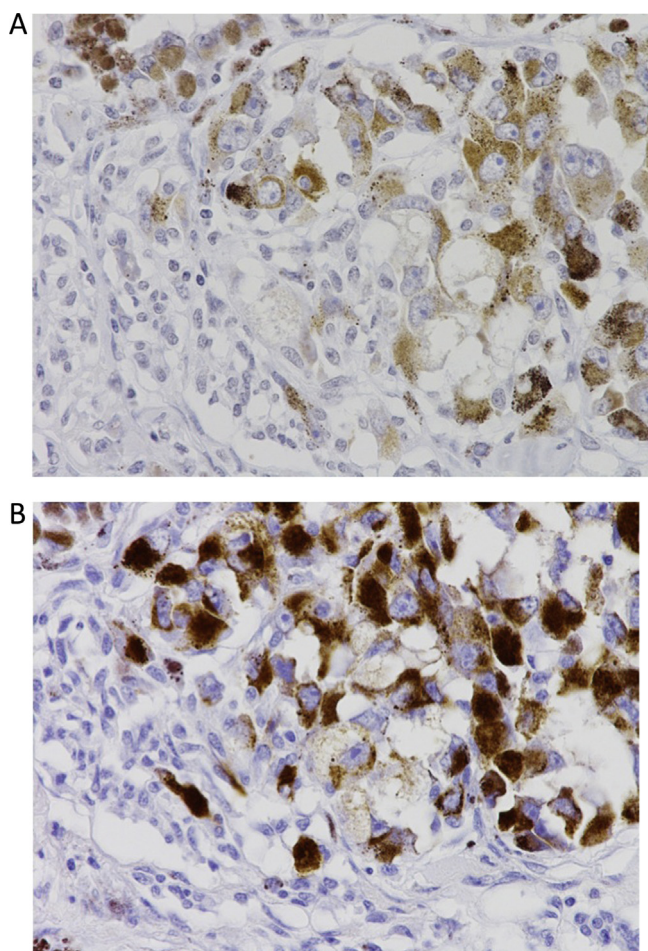


Fig. 4. Immunohistochemical detection of Melan A (A) and HMB-45 (B). Melanoma cells were positive for Melan A (A) and HMB-45 (B).

3. Discussion

MTC is a malignant tumor that exhibits C-cell differentiation [1], a phenotype typically determined by immunohistochemical staining using an antibody against calcitonin. Additionally, MTC expresses CEA and neuroendocrine markers including chromogranin A. The small-sized atypical cells observed in the current case morphologically resembled classic MTC, and this diagnosis was confirmed using immunohistochemistry to detect calcitonin, CEA, and chromogranin A expression.

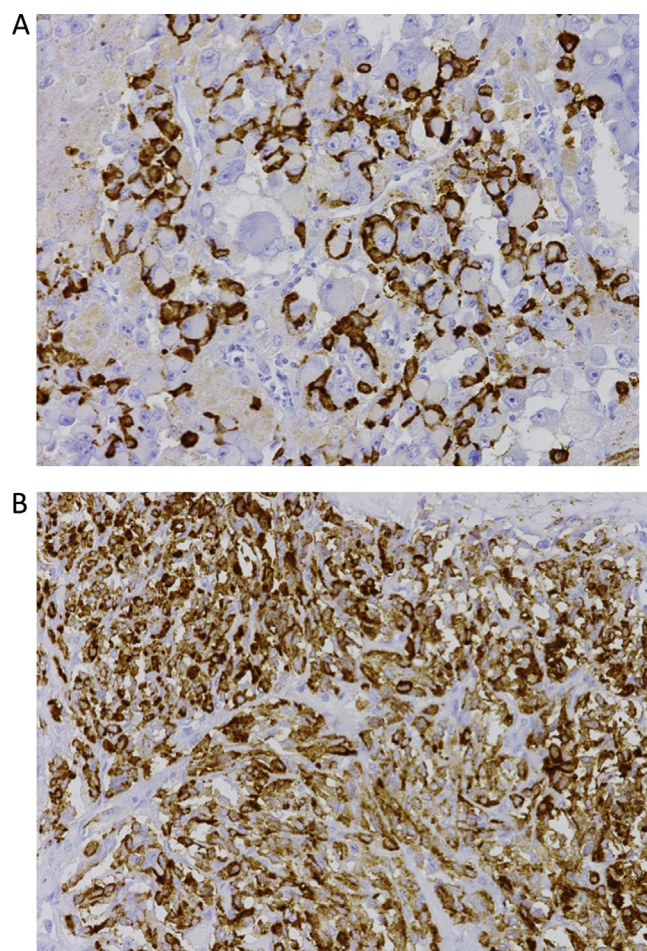


Fig. 5. Immunohistochemical detection of calcitonin. Melanoma cells were only focally positive for calcitonin (A), whereas, medullary carcinoma cells were diffusely positive (B).

MTC can show multidirectional differentiation, resulting in a number of subtypes, such as mucin-producing MTC, MTC with squamous differentiation, and melanin-producing MTC [1], the latter of which is extremely rare. In the current case, the large pleomorphic atypical cells contained melanin pigments, as confirmed by Fontana-Masson staining and bleaching method. Additionally, some of these cells were immunohistochemically positive for calcitonin, CEA, and chromogranin A expression. Therefore, the current case was consistent with melanin-producing MTC.

To the best of our knowledge, 11 melanin-producing MTC cases have been reported to date [2–10], with variable microscopic findings. In the published reports, carcinoma cells were described as classic, spindled, or pleomorphic. Melanin production also varied from scant to abundant. In some cases, melanin-producing cells were localized to dendritic or sustentacular cells [5,6]. The melanocytic differentiation was confirmed by the presence of melanin pigments or by the expression of HMB-45 or S-100 protein. In the reported cases, the term “malignant melanoma” was not used, likely because the melanin-containing carcinoma cells were not morphologically consistent with malignant melanoma, but with medullary carcinoma.

In the current case, the majority of the tumor was occupied by large pleomorphic cells with massive melanin pigments. These atypical cells were considerably pleomorphic and were similar to anaplastic thyroid carcinoma (ATC) or the anaplastic variant of MTC, with the exception of the presence of melanin pigments. In 1980, Mendelsohn et al. first proposed an anaplastic variant of MTC [11]. According to the report, most of the carcinoma cells retained C-cell properties as determined by immunohistochemistry. However, most of the large pleomorphic cells observed in the current case were negative for the C-cell markers, including calcitonin, chromogranin A, and CEA, and were positive for melanoma markers including Melan-A, HMB-45, and S-100 protein. In addition, the cells were negative for PAX8, which is known to be expressed in MTC and ATC [12]. In all, these data strongly suggest that the large pleomorphic cells are malignant melanoma. Malignant melanoma metastasizing to the thyroid is not rare, but the presence of large pleomorphic carcinoma cells expressing both MTC and melanoma markers suggests that this is not the case. Additionally, we could not locate the primary malignant melanoma lesion despite extensive examination of the other organs. Consequently, we concluded that the current case is one of malignant melanoma arising in melanin-producing MTC, which has not yet been reported.

MTC is a type of neuroendocrine carcinoma that produces hormones or regulatory proteins. Malignant melanoma is a malignant tumor arising from melanocytes derived from a structure in the human embryo called the neural crest. Although neuroendocrine carcinoma and malignant melanoma have different embryological origins, carcinomas with both neuroendocrine and melanocytic differentiations have been reported in the retroperitoneum [13], adrenal gland [14], thymus [15], skin [16], nasal mucosa [16], and lung [17]. Similarly, in the current case, there were three types of carcinoma cells: classic MTC cells, carcinoma cells having both C-cell and melanocytic characteristics (melanin-producing MTC cells), and malignant melanoma cells without C-cell characteristics. It is postulated that the tumor arose from polyclonal evolution of common precursor cells with the ability to produce both hormones and melanin, or that MTC transformed into a more aggressive cancer with the ability to produce melanin.

The long-term prognosis of the current case is very interesting. Considering the extensive pleomorphism, high Ki-67 labeling index, presence of extensive nodal metastasis, and known outcome of malignant melanoma, the tumor described in the current case should be highly malignant. Nevertheless, no detectable recurrence or distant metastasis occurred up to 11 years post-surgery. The prognosis of the anaplastic variant of MTC composed of large pleomorphic cells resembling ATC is significantly better than that of ATC [11]. Similarly, malignant melanoma arising in MTC may have a favorable prognosis.

4. Conclusion

We report a case of malignant melanoma arising in melanin-producing MTC that has not previously been described. The

diagnosis of malignant melanoma was confirmed by classic histologic findings and immunohistochemical results. Contrary to expectation, malignant melanoma arising in MTC may have a favorable prognosis.

Conflicts of interest

All authors have nothing to declare.

Sources of funding

All authors have nothing to declare.

Ethical Approval

In this study, ethical approval has been given in ethics committee in Kuma Hospital.

Consent

In this study, consent approval has been given by the patient and her family.

Authors contribution

Mitsuyoshi Hirokawa and Tsutomu Daa contributed on immunohistochemical study. Akira Miyauchi and Minoru Otsuru were surgeon who operated this case.

Guarantor

The Guarantor of this report is Dr. Akira Miyauchi.

Disclosure

All authors have nothing to declare.

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