—Case Reports—

The Reality of Multiple Endocrine Neoplasia Type 2B Diagnosis: Awareness of Unique Physical Appearance Is Important

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Background: Multiple endocrine neoplasia type 2B (MEN2B) is an extremely rare syndrome mainly caused by *RET*918 germline mutations. MEN2B typically causes medullary thyroid carcinoma (MTC), pheochromocytoma, and unique physical characteristics including mucosal neuroma, distinctive facial appearance, and Marfanoid habitus. Most patients have abdominal symptoms such as bloating, intermittent constipation, and diarrhea. MTC is the most important determinant of mortality in patients with MEN2B. Establishing the diagnosis of MEN2B at a curative stage of MTC is crucial.

Case Presentation: We have encountered four patients with MEN2B. Two were hereditary cases from the same family, and two were considered *de novo* cases with phenotypically normal parents. Mean age at diagnosis was 25.5 years (range, 13–39 years). Although all patients had shown mucosal neuroma on the lips and tongue, in addition to gastrointestinal symptoms from infancy, diagnoses were made from symptomatic MTC even for the hereditary patients (our index case was a 14-year-old girl, whose mother was subsequently diagnosed with advanced MTC). Genetic tests for *RET* mutations revealed the M918T mutation in all patients. Two patients developed pheochromocytoma, two died from distant metastases of MTC, and two received treatment for multiple metastases of MTC (one with vandetanib).

Conclusions: In our patients with MEN2B, prophylactic or early thyroidectomy could not be performed. The characteristic phenotype associated with MEN2B is almost always seen prior to detection of MTC or pheochromocytoma. Knowledge about the non-endocrine manifestations of MEN2B needs to be shared among pediatricians and gastroenterologists. (J Nippon Med Sch 2018; 85: 178–182)

Key words: multiple endocrine neoplasia, medullary thyroid carcinoma, mucosal neuroma, prophylactic thyroidectomy, megacolon

Introduction

Multiple endocrine neoplasia type 2B (MEN2B) is a rare syndrome mainly due to the *RET*918 germline mutation. The incidence is approximately one per million births in Japan. MEN2B typically causes medullary thyroid carcinoma (MTC), pheochromocytoma, and unique physical characteristics including mucosal neuroma, distinctive facial appearance, and Marfanoid habitus. Most patients have abdominal symptoms such as bloating, intermittent constipation, and diarrhea. MTC is the most important determinant of mortality in patients with MEN2B. Establishing the diagnosis of MEN2B at a curative stage of MTC is crucial. We encountered four patients with MEN2B between 1996 and 2017 (**Table 1**).

Case Presentation

Case 1: A 14-year-old girl was referred to our department with a palpable neck mass. She had a medical history of intestinal malrotation. She presented with mucosal neuromas on her lips and tongue. She was diagnosed with MEN2B with MTC and distant metastasis to the lung, and showed no sign of pheochromocytoma. Serum CEA and calcitonin at diagnosis were 36 ng/mL and 26,000 pg/mL, respectively. She underwent total thyroidectomy with bilateral neck dissection. The tumor was 22 mm in the maximum diameter and it invaded the

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Table 1

Case	Age	Sex	Family history	Initial symptom	MTC at diagnosis		Pheochromocytoma (years)	Mucosal neuroma	Gastro-intestinal manifestations	Marfanoid habitus	*RET* mutation	CEA*7	Calcitonin*8	Outcome (present age)	Recurrence of MTC	Postoperative follow-up (year)
					Lymph node metastasis	Distant metastasis						(at diagnosis) / (at last examination)				
1	14	F	+	MTC*1	+	Lung	-	+	Megacolon	-	M918T	36	26,000	Died	Lung	9
												97	63,000	(at 23 years old)		
2	39	F	+	MTC*2	+	-	Unilateral*5	+	Bloating	-	M918T	27	2,300	Alive	Lung, Bone	20
							(Lt: 39)					35	12,100	(58 years old)	Liver	
3	36	F	-	MTC*3	+	-	Bilateral*6	+	-	-	M918T	46	4,603	Died	Liver	Unknown
							(Lt: 37, Rt: 42)					38	9,900	(age unknown)		
4	13	M	-	MTC*4	+	Lung	-	+	Megacolon	-	M918T	837	9,865	Alive	Lung	1
									Constipation			18	300	(15 years old)		

*1: pT4am (Ex2: jugular vein, ¢22 mm) N1b (6/15) M1
*2: pT4am (Ex2: trachea, ¢26 mm) N1b (6/29) M0
*3: pT3 m (Ex1: anterior cervical muscle, ¢30 mm) N1b (24/65) M0
*4: pT4a (Ex2: recurrent laryngeal nerve, ¢41 mm) N1b (16/30) M1
*5: Laparotomy, Retroperitoneal approach, ¢50 mm
*6: Lt: Laparotomy, Retroperitoneal approach, ¢40 mm, Rt: Laparotomy, Transperitoneal approach, ¢39 mm
*7: Normal: 0–5 ng/mL
*8: Normal: 15–86 pg/mL

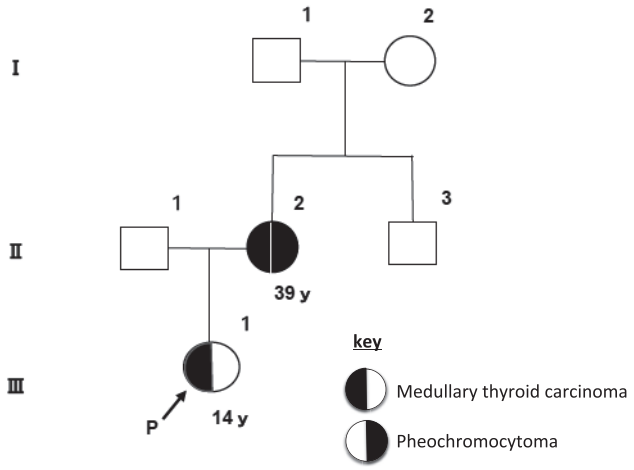

Fig. 1

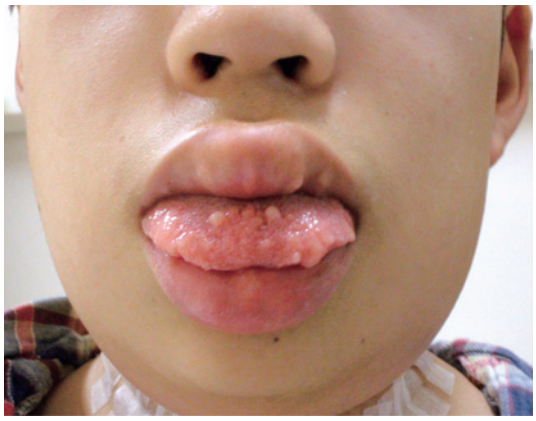

Fig. 2

jugular vein. Pathologically nodal metastases were found in 6 among 15 nodes. She received chemotherapy using paclitaxel, but died 9 years after diagnosis due to distant metastasis to the lung.

Case 2: A 39-year-old woman, the mother of the patient in Case 1 (**Fig. 1**), underwent genetic testing for the *RET*918 mutation after her daughter's diagnosis. MEN2B with MTC and pheochromocytoma was diagnosed. She also presented with mucosal neuromas. Serum CEA and calcitonin at diagnosis were 27 ng/mL and 2,300 pg/mL, respectively. A left adrenalectomy (tumor size was 50 mm) by laparotomy through a retroperitoneal approach was conducted. Afterwards, a total thyroidectomy and bilateral neck dissection were performed. The thyroid tumor was 26 mm in diameter and invaded the trachea. Lymph node metastases were found in 6 among 29 nodes. Since distant metastases to the bone, lungs, and liver had progressed, she entered a clinical trial using vandetanib for 3 years. She remains alive, and was 59 years old at the time of writing.

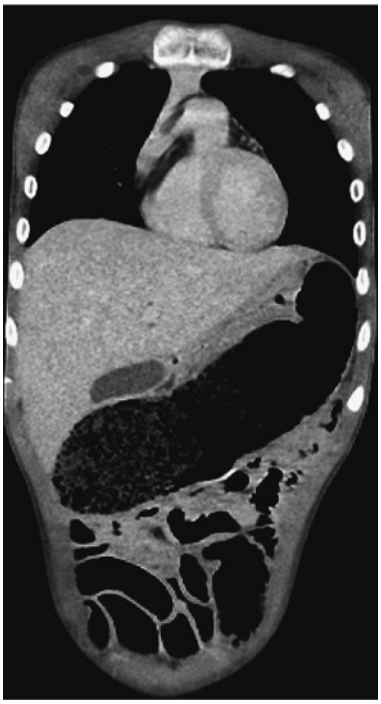

Fig. 3

Case 3: A 36-year-old woman was diagnosed with MTC and underwent a total thyroidectomy in another hospital. Serum CEA and calcitonin at diagnosis were 46 ng/mL and 4,603 pg/mL, respectively. The 30 mm tumor invaded the patient's strap muscle. Twenty-four metastasized nodes were seen among 65 lymph nodes. She presented with mucosal neuromas, but showed no gastrointestinal manifestations. After pheochromocytoma was detected, MEN2B was diagnosed. She underwent left and right adrenalectomies at 37 and 42 years old, respectively. The left adrenal gland, with a 40 mm tumor, was resected by laparotomy through a retroperitoneal approach and the right adrenal gland, with a 39 mm tumor, was removed by laparotomy through a transperitoneal approach. MTC recurrence was detected at 52 years old. She died due to metastasis to the liver.

Case 4: A 13-year-old boy was referred to our department with a palpable neck mass. He had experienced chronic constipation and flatulence since infancy. He presented with mucosal neuromas in the lips and tongue (**Fig. 2**), and megacolon (**Fig. 3**). Serum CEA and calcitonin were 837 ng/mL and 9,865 pg/mL, respectively. MEN2B with MTC was diagnosed and a total thyroidectomy with bilateral lymph node dissection was performed. The 41 mm tumor invaded the left recurrent laryngeal nerve and lymph node metastases were found in 16 among 30 nodes. Lung metastases were suspected. As of 1 year postoperatively, he remains alive with no sign

of progression of lung metastases or development of pheochromocytoma.

Discussion

Two patients were hereditary cases from the same family, and two were considered *de novo* cases with phenotypically normal parents. The mean age at diagnosis was 25.5 years (range, 13–39 years). Although all patients had shown mucosal neuroma on the lips and tongue, in addition to gastrointestinal symptoms (except for Case 3) from infancy, diagnoses were made from symptomatic MTC even for hereditary cases. Genetic testing for *RET* mutations revealed the M918T mutation in all patients. Two patients developed pheochromocytoma, two died from distant metastases of MTC, and two received treatment for multiple metastases of MTC (one with vandetanib).

MTC in patients with MEN2B is the most aggressive form of hereditary MTC. The American Thyroid Association (ATA) guidelines showed that the risk level for MTC in patients with the *RET*918 mutation was "Highest"[1]. One report stated that the clinical course of MTC in MEN2B in Japanese patients is not particularly aggressive, with a 10-year survival rate of 92%, compared with about 50% for Caucasians[2]. In our series of patients, the patient in Case 2, who was the oldest at diagnosis, has remained alive for over 20 years. Establishing the diagnosis of MEN2B at an early age is important when there is a possibility that thyroidectomy will be curative. ATA guidelines recommend thyroidectomy in the first year of life for children who have inherited MEN2B, and perhaps even within the first months of life[1]. This recommendation is considered to be aimed only at hereditary cases of MEN2B. Indeed, very few patients are able to undergo prophylactic total thyroidectomy as recommended before MTC progresses.

Over 90% of patients with MEN2B present with *de novo* mutations, while the remaining 10% of cases occur in families with previous or current manifestations of MEN2B[3]. This might be due to reduced fertility of patients carrying the MEN2B phenotype. In a study of 44 children with MEN2B, Brauckhoff et al. reported that only 3 patients (7%) were identified as hereditary cases and underwent thyroidectomy during the first year of life, with the remaining 41 patients (93%) considered *de novo* cases[3]. Of the 41 patients with *de novo* RET mutations, 12 were diagnosed upon recognition of non-endocrine manifestations of MEN2B, comprising: ganglioneuromatosis (n=6), oral symptoms (n=5), ocular manifestations (n=4), and skeletal abnormalities (n=1). The remaining 29 patients were diagnosed because of symptomatic MTC (n=28) or pheochromocytoma (n=1). In a Japanese study of 23 patients with MEN2B, Yoshimoto et al. reported that only 3 patients (13%) were hereditary cases and 19 patients (83%) were *de novo* cases (the remaining 1 case was unspecified)[2]. In a small number of cases, children with familial MEN2B have undergone prophylactic total thyroidectomy before 1 year of age[4–6]. Few reports have described prophylactic thyroidectomy for children with MEN2B, with only two such reports confirmed in Japan[7,8]. Ages at the time of total thyroidectomy in those cases were 8 and 6 years old, above the age recommended in the ATA guidelines. For patients with *de novo* mutations, prophylactic total thyroidectomy is difficult.

Unique physical characteristics and gastrointestinal symptoms caused by mucosal neuroma are observed from infancy in patients with MEN2B, including flatulence (86%), megacolon (63%), and constipation or diarrhea (43%)[9,10]. A unique physical appearance is also evident, characterized by atypical facies, ophthalmological abnormalities (inability to make tears in infancy, thickened and everted eye-lids, mild ptosis, and prominent corneal nerves), and skeletal malformations (Marfanoid habitus, narrow long face, pes cavus, pectus excavatum, high-arched palate, scoliosis, and slipped capital femoral epiphyses). Recognizing unique physical characteristics and abdominal symptoms are key to the early diagnosis of MEN2B.

Conclusion

In our series of patients with MEN2B, prophylactic or early thyroidectomy could not be performed. The characteristic phenotype associated with MEN2B is almost always seen prior to detection of MTC or pheochromocytoma. Recognizing unique physical characteristics and abdominal symptoms are key to achieving an early diagnosis of MEN2B. Knowledge of the non-endocrine manifestations of MEN2B needs to be shared among pediatricians and gastroenterologists.

Conflict of Interest: None.

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