Case Report

Hypokalemic Rhabdomyolysis due to WDHA Syndrome Caused by VIP-producing Composite Pheochromocytoma: A Case in Neurofibromatosis Type 1

Masahiro Onozawa1, Takashi Fukuhara1, Madoka Minoguchi1, Mutsumi Takahata1, Yasushi Yamamoto1, Takayoshi Miyake1, Koichi Kanagawa2, Makoto Kanda3 and Isao Maekawa1

1Department of Internal Medicine, 2Department of Urology and 3Department of Pathology, Asahikawa City Hospital, Asahikawa, Hokkaido, Japan

Received April 16, 2005; accepted June 1, 2005; published online July 18, 2005

A 47-year-old woman with neurofibromatosis type 1 suffered from general muscle weakness and watery diarrhea. Laboratory findings showed elevated muscular enzymes, severe hypokalemia and excessive production of catecholamines and vasoactive intestinal polypeptide (VIP). A computed tomography scan showed a 10 cm left adrenal mass, in which [131I]-metaiodobenzylguanidine scintigraphy showed high uptake. After she underwent surgical removal of the tumor, all the symptoms and signs subsided. A histological study revealed that the mass consisted of pheochromocytoma and ganglioneuroma, respectively producing catecholamines and VIP. In immunohistochemical staining of neurofibromin, pheochromocytoma and ganglion cells showed positive staining, whereas the staining was negative for nerve bundles and Schwann cells. We concluded that the patient had hypokalemic rhabdomyolysis due to watery diarrhea, hypokalemia and achlorhydria (WDHA) syndrome, which was induced by a VIP-producing composite pheochromocytoma. Composite pheochromocytoma is a neuroendocrine tumor that is composed of pheochromocytoma and ganglioneuroma, both derived from the neural crest. Deficiency of neurofibromin in Schwann cells might have played an important role in the development and the growth of the composite pheochromocytoma in this patient.

Key words: composite pheochromocytoma – vasoactive intestinal polypeptide – hypokalemic rhabdomyolysis – watery diarrhea, hypokalemia and achlorhydria syndrome – neurofibromin

INTRODUCTION

Hypokalemic rhabdomyolysis is a relatively rare presentation of hypokalemia. Gross et al. (1) first described the hypokalemic myopathy caused by licorice ingestion in 1966. Since then, various causes such as usage of laxatives and diuretics, anorexia, chronic alcoholism, infectious enterocolitis, aldosteronism and renal tubular acidosis have been reported to be possible causes of hypokalemic rhabdomyolysis. Here, we present the first case with hypokalemic rhabdomyolysis due to watery diarrhea, hypokalemia and achlorhydria (WDHA) syndrome. The unusual presentation of this case was caused by an unusual tumor, which was revealed to be vasoactive intestinal polypeptide (VIP)-producing composite pheochromocytoma. In this case, the genetic background of neurofibromatosis type 1 (NF1) is considered to play an important role in multidirectional differentiation and proliferation of neuroendocrine cells, resulting in the development of a VIP-producing composite pheochromocytoma.

REPORT OF A CASE

A 47-year-old woman was admitted to the Orthopedic Department of Asahikawa City Hospital in February 2001 for general muscular weakness and myalgia. She could not even stand up or walk for a few days before admission. She had suffered from watery diarrhea and weight loss for 1 month before admission. She had been treated for hypertension for 7 years.

For reprints and all correspondence: Masahiro Onozawa, Department of Gastroenterology and Hematology, Hokkaido University Graduate School of Medicine, Kita 14, Nishi 5, Kita-ku, Sapporo 060-8638, Hokkaido, Japan. E-mail: masahiro.onozawa@mfly.ne.jp

© 2005 Foundation for Promotion of Cancer Research
She was diagnosed as having NF1 when she had a cervical skin neurofibroma removed 14 years earlier. Her mother and daughter were also diagnosed as having NF1. Her height was 150 cm and weight 54.7 kg. Physical examination on admission showed blood pressure of 164/84 mmHg and regular heart rate of 76 beats/min. Multiple café-au-lait macules and neurofibromas were present on her hands and hip. Neurological examination was unremarkable except for general muscle weakness.

Laboratory tests showed marked hypokalemia of 1.8 mEq/l and elevated muscular enzymes: AST, 164 IU/l; LDH, 629 IU/l; CPK, 12 920 IU/l. White blood cell count (11.77 \times 10^9/l) and C-reactive protein (1.0 mg/dl) were slightly elevated. Results of other biochemical tests were within normal ranges. She was diagnosed as having rhabdomyolysis due to severe hypokalemia and was referred to our department for additional systemic examination. Although treatment with an intravenous infusion of potassium resulted in steady clinical improvement of symptoms and signs of rhabdomyolysis, watery diarrhea persisted despite treatment with several antidiarrhetics. Repeated stool cultures were negative for bacterial infection. An abdominal computed tomography scan revealed a mass of 10 cm in diameter in the left adrenal gland (Fig. 1). 131I-labeled metaiodobenzylguanidine scintigraphy showed uptake in the left adrenal gland. An endocrinological study was then performed. Plasma levels of catecholamines were markedly increased. The plasma level of VIP was also elevated to 645 pg/ml (Table 1). Plasma levels of other adrenal hormones (cortisol, aldosterone and deoxycorticosterone) and other gastrointestinal hormones (gastrin, somatostatin and glucagons) were within normal ranges.

We concluded that she had hypokalemic rhabdomyolysis due to WDHA syndrome, which was assumed to be induced by a VIP-producing pheochromocytoma. She underwent surgical removal of the tumor. Catecholamine and VIP levels returned to normal ranges (Table 1) and the diarrhea subsided soon after removal of the tumor. The patient was discharged and has not received any medication since discharge. She has been physically well without any signs of recurrence.

The tumor measured 11 × 13 × 7 cm and weighed 460 g. It was soft, brownish and had a thin capsule. Multiple cystic degeneration and necrosis were seen on a section view (Fig. 2). In the low power observation, the tumor was well demarcated from the normal tissue. The adjacent adrenal gland was intact. Two different components were recognized in the tumor. The first component showed the typical zellballen pattern with high cellularity, and the second component showed a relatively loose wavy pattern with fibrous stroma. The two components were separated but partially merged into each other (Fig. 3A).

<table>
<thead>
<tr>
<th>Table 1. Pre-operation and post-operation hormone levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone</td>
</tr>
<tr>
<td>Plasma catecholamines (ng/ml)</td>
</tr>
<tr>
<td>Adrenaline</td>
</tr>
<tr>
<td>Noradrenaline</td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>Plasma VIP (pg/ml)</td>
</tr>
<tr>
<td>24 h urinary catecholamines (μg/day)</td>
</tr>
<tr>
<td>Adrenaline</td>
</tr>
<tr>
<td>Noradrenaline</td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>24 h urinary metabolic products (mg/day)</td>
</tr>
<tr>
<td>VMA</td>
</tr>
<tr>
<td>HVA</td>
</tr>
<tr>
<td>Metanefurine</td>
</tr>
</tbody>
</table>

VIP, vasoactive intestinal polypeptide; VMA, vanillylmandelic acid; HVA, homovanillic acid.
In the high power observation, pleomorphic small cells with abundant granules were arranged in nests (pheochromocytoma) (Fig. 3B). Cells of each component were well differentiated, and no mitosis was observed. A diagnosis of composite pheochromocytoma was made on the basis of these findings.

Immunohistochemical staining of formalin-fixed, paraffin-embedded tissue was performed using EnVision System (DakoCytomation, Glostrup, Denmark), which is based on peroxidase-labeled polymer conjugated with secondary antibodies. The antibodies against the following antigens were used for staining: chromogranin A (DakoCytomation, Glostrup, Denmark), synaptophysin (DakoCytomation, Glostrup, Denmark), neuron-specific enolase (NSE) (DakoCytomation, Glostrup, Denmark), VIP (Biomed, Foster City, CA, USA), vimentin (DakoCytomation, Glostrup, Denmark), S-100 protein (DakoCytomation, Glostrup, Denmark) and neurofilament (DakoCytomation, Glostrup, Denmark). The immunohistochemical staining of neurofibromin was kindly performed by Dr N. Kimura (Department of Pathology and Laboratory Medicine, Tohoku Rosai Hospital, Sendai) as described previously (2). Pheochromocytoma cells and ganglion cells were stained positively for chromogranin A, synaptophysin and NSE. The ganglion cells were strongly positive for VIP stain (Fig. 4A). Nerve bundles and Schwann cells were immunoreactive for vimentin, S-100 protein and neurofilament. Pheochromocytoma and ganglion cells showed positive staining for neurofibromin, whereas nerve bundles and Schwann cells showed negative staining (Fig. 4B). Tumor cells showed negative immunoreactivity to pancreatic polypeptide, calcitonin, glucagon, serotonin, somatostatin and gastrin.

In electron microscopic analysis, high electron density core granules with a wide halo (norepinephrine granules) and relatively low electron density core granules without a halo (epinephrine granules) were observed in pheochromocytoma cells.

**DISCUSSION**

WDHA syndrome is caused by VIP-producing tumors (VIPomas). Although most VIPomas arise in the pancreas, as many as 20% occur in extra-pancreatic sites (3). Adrenal pheochromocytoma could be one of the extra-pancreatic VIPomas. Previously, 16 cases of VIP-producing adrenal pheochromocytoma have been reported (4–19). Thirteen of those cases had clinical symptoms of watery diarrhea. Muscle weakness (4,6,10,12,17) was commonly observed in these cases, possibly related to associated hypokalemia. All patients became free from such symptoms after resection of the tumor. However, many patients did not show typical symptoms of pheochromocytoma such as hypertension (6,8,10,12,13,15,16,18). It is suggested in some reports that excessive VIP acts as a vasodilator and masks the vasospastic symptoms of catecholamines. Eleven cases were histologically diagnosed as pheochromocytoma (5–10,12,15,17–19), but only five cases were diagnosed as composite pheochromocytoma like ours (4,11,13,14,16). In cases of composite pheochromocytoma, it has been reported that the pheochromocytoma component...
and the ganglioneuroma component produced catecholamines and VIP, respectively, as in our case (4,11,13,14,16). Only one case was reported to have a genetic background of NF1 among these 16 cases of WDHA syndrome due to VIP-producing pheochromocytoma (18).

NF1 or von Recklinghausen’s disease is characterized by proliferation and malignant transformation of neural crest derivatives. NF1 is an autosomal dominant disorder, which is caused by single loss-of-function allele of the gene designated NF1 (20). Neurofibromin, the product of NF1, contains a region homologous to mammalian RasGTPase-activating proteins that function as negative regulators of Ras by accelerating the conversion of Ras-GTP to Ras-GDP (21). The NF1 gene appears to act as a tumor suppressor gene. Thus, it is conceivable that patients with NF1 have a higher incidence of malignancy. It has been reported that the incidence of pheochromocytoma in patients with NF1 is 10 times higher than that in the general population (22). Composite pheochromocytoma, known as mixed neuroendocrine and neural tumor, has been reported to be associated with NF1 (2). The role of neurofibromin in neurofibromas of NF1 patients has been extensively studied. Neurofibromin is a mixed tumor that comprises all neural crest derivatives. It has been reported that only Schwann cells lose neurofibromin expression, whereas the other components of neurofibroma retain neurofibromin expression (23). Zhu et al. demonstrated that loss of neurofibromin in Schwann cells (NF1−/−) is sufficient to generate a neurofibroma in a heterozygous (NF1+/−) mouse, which is considered to be the counterpart model of human NF1 (24). Composite pheochromocytoma is also a mixed neuroendocrine tumor that is composed of pheochromocytoma and ganglioneuroma, both of which are neural crest derivatives. Similar to neurofibroma, Schwann cells of composite pheochromocytoma in NF1 patients have been reported to lose neurofibromin expression as in our case (2). In our case, loss of neurofibromin in Schwann cells might also have played an important role in multidirectional differentiation and proliferation of neuroendocrine cells, resulting in the development of VIP-producing composite pheochromocytoma.

Acknowledgments

We thank Dr N. Kimura (Department of Pathology and Laboratory Medicine, Tohoku Rosai Hospital, Sendai) for the immunochemical staining of neurofibromin.

References

12. Fisher BM, MacPhee GJA, Davies DL, McPherson SG, Brown IL, Goldberg A. A case of watery diarrhea syndrome due to an adrenal


