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CORRESPONDENCE

Gastrointestinal pseudo-obstruction after debulking surgery of malignant pheochromocytoma, improved by intravenous administration of α-adrenergic receptor blocker, phentolamine

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We present a case of a 65-year-old man who suffered from transient ischemic colitis and persistent paralytic ileus complicated with megacolon due to pseudo-obstruction developing after the surgical manipulation of malignant pheochromocytoma. Malignant pheochromocytoma typically metastasizes to the bones, liver, lungs and lymph nodes, and the average 5-year survival rate in the patient with metastases is ~50%.[1–3] Treatment options for malignant pheochromocytoma include surgical debulking, external irradiation and systemic antineoplastic therapy.[4] The survival rate worsens in proportion to tumor size; therefore, the essential therapeutic goal is tumor reduction by debulking surgery even if the surgery is not curative, and control of symptoms of excessive catecholamine secretion.[3,4]

In this report, we focus on the possibility of the gastrointestinal pseudo-obstruction which develops after surgical manipulation of pheochromocytoma producing higher levels of catecholamines, even though other symptoms including hypertension were well controlled. We suggest that in such gastrointestinal pseudo-obstruction, chronic intravenous administration of an α-adrenergic receptor blocker, phentolamine, should be initially considered, especially for the patient who is unable to take meals or drugs efficiently, before embarking on decompression surgery of megacolon.

The patient was diagnosed in 2004 with malignant pheochromocytoma originating in the liver with metastatic lesions in the vertebra. We have previously reported the precise history of the patient till 2005.[5] By 2009, metastases had spread to multiple bones, right hilum of the lung, pleura and liver. The metastatic tumor at the top of the cranial bone had increased remarkably in size (3 cm in the longitudinal diameter) and appeared to be on the point of invading the brain. Therefore, we performed debulking surgery for the cranial metastasis on 17 April 2009 to decrease catecholamine secretion. The surgery was successful, although the blood pressure level was labile during the operation and systolic pressure increased to a maximal level of 300 mm Hg. A histopathological examination revealed that the tumor was compatible with pheochromocytoma. The catecholamine levels of 24-h urine collection decreased slightly (Table 1).

Unexpectedly, after surgery, the patient was unable to tolerate oral nutrition because of vomiting and complained of increasing abdominal gas and nausea, although the symptoms including hypertension were well controlled. Abdominal X-ray and computed tomography showed large dilated loops of the colon with the transverse dilated to 10 cm (Figure 1a). Gastrointestinal pseudo-obstruction showed poor response to conventional treatment including oral administration of α- and β-blockers, yet was relieved promptly with chronic intravenous administration of an α-adrenergic receptor blocker, phentolamine (Figure 1b). However, we could not control the progression and catecholamine secretion of the tumor anymore, and the patient was unable to resume oral food intake. The patient died from spreading of the tumor and pneumonia in September 2009.

In this report, we described that gastrointestinal pseudo-obstruction in the pheochromocytoma can be fatal; however, intravenous administration of phentolamine had an essential effect on paralytic ileus due to overproduction of catecholamines by pheochromocytoma. Refractory ileus in severe pheochromocytoma has been reported previously.[6,7] In some cases, the megacolon with pheochromocytoma was associated with Hirschsprung's disease, which is characterized

Table 1 Time course of catecholamines of the patient in 24-h urine collection

	Normal range	*Diagnosis in 2004*	*Before cranial operation in March 2009*	*After cranial operation in June 2009*
Metanephrine (mg per day)	0.05–0.20	0.11	0.17	0.09
Normetanephrine (mg per day)	0.10–0.28	16	31	30
Adrenaline (μg per day)	1.0–23.0	8.4	30.8	11.9
Noradrenaline (μg per day)	29.0–120.0	7260	19 200	17 900

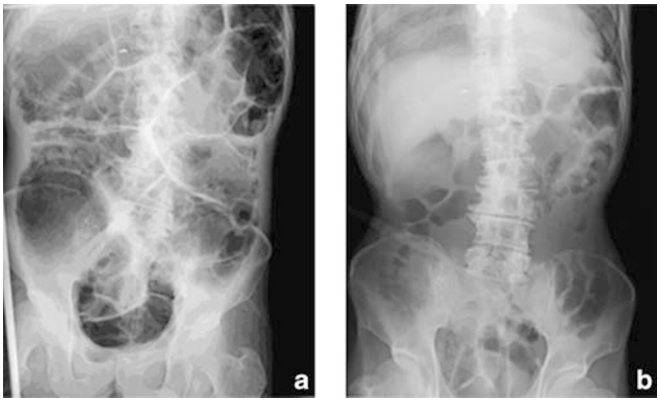

Figure 1 Abdominal X-ray findings of the gastrointestinal pseudo-obstruction after surgery. (**a**) The abdominal X-ray findings of the megacolon on postoperative day 16. Whole colon was dilated to >10 cm. (**b**) The abdominal X-ray findings after treatment with intravenous administration of phentolamine. The gastrointestinal pseudo-obstruction and megacolon had almost resolved.

by the disappearance of normal enteric nerves. Both pheochromocytoma and Hirschsprung's disease can be associated with MEN-2.[8] However, the patient had no family history of pheochromocytoma or related endocrinopathies. This report has novel characteristics in that the patient unexpectedly developed megacolon soon after the operative removal of the cranial metastasis, even though other symptoms including hypertension were well controlled.

Gastrointestinal pseudo-obstruction can be caused by pheochromocytoma with higher levels of circulating catecholamines, which would act on intestinal smooth muscle cells to decrease peristalsis through α1-adrenergic receptors. In addition, they would act on vascular smooth muscle cells to induce vasoconstriction of the mesenteric arteries, which would lead to ischemic colitis and necrosis of the intestines.[6,7] In this case, the patient presented with colonic stricture caused by ischemia and megacolon due to paralytic ileus and pseudo-obstruction soon after the operative removal of cranial metastasis. Ischemic colitis was transient and subsided without specific treatment as reported previously.[7] In contrast, the paralytic ileus that developed after the operation persisted in the present patient. In this manner, we show that surgical manipulation of the tumor can trigger this type of ileus in a patient with pheochromocytoma by stimulation of catecholamine secretion during the operation, which simultaneously induces ischemic colitis due to vasospasm and paralytic ileus due to persistent intestinal paralysis.[7]

The megacolon in the patient was dilated to >10 cm and accompanied by abdominal pain and leukocytosis, and consequently, we were obliged to consider surgical decompression by means of colostomy to prevent perforation. We found that the intravenous administration of phentolamine was effective for the treatment of severe megacolon due to α-adrenergic stimulation by pheochromocytoma, even though conventional treatment including oral administration of α- and β-blockers showed poor response. Phentolamine is an α1- and α2-adrenergic receptor blocker, which is useful for controlling hypertensive episodes in a patient with pheochromocytoma. Intravenous administration of phentolamine would inhibit α1-mediated effects of catecholamines on intestinal and vascular smooth muscle cells, and accordingly would be effective for gastrointestinal pseudo-obstruction. At first, we attempted to increase intestinal peristalsis of the patient by oral administration of α-blocker, β-blocker and anti-cholinesterase (distigmine); however, these oral medications were ineffective. On the other hand, the intravenous administration of phentolamine was dramatically effective for gastrointestinal pseudo-obstruction. We speculate that intravenous administration would be effective, especially for the patient who was unable to take meals or drugs efficiently.

In summary, we reported a case of malignant pheochromocytoma at the terminal stage, with persistent paralytic ileus and megacolon. In severe pheochromocytoma, pseudo-obstruction and abdominal symptoms could be present after surgical manipulation of pheochromocytoma, and this condition could be fatal. We suggest that in such cases, intravenous administration of an α-adrenergic receptor blocker, phentolamine, should be initially considered. This may be especially appropriate for the patient who is unable to take meals or internal drugs, before embarking on a decompression surgery of megacolon due to pheochromocytoma with high levels of catecholamines, which stimulate the α-adrenergic receptor.

The precise history of the patient is reported in Supplementary information available at *Hypertension Research*'s website.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)