

Intestinal pseudo-obstruction as a complication of paragangliomas: case report and literature review

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ABSTRACT

Intestinal pseudo-obstruction is a rare and relatively unknown complication of phaeochromocytoma/paraganglioma (PCC/PGL). Its pathophysiology can be explained by the hypersecretion of catecholamines, which may reduce the peristaltic activity of the gastrointestinal tract. Clinically, this can result in chronic constipation, intestinal pseudo-obstruction or even intestinal perforation.

We conducted a comprehensive literature search and retrieved 34 cases of pseudo-obstruction caused by either benign or malignant PCC/PGL. We also included a case from our centre that has not been described earlier. We conclude that intestinal pseudo-obstruction is a rare but potentially life-threatening complication of PCC/PGL. Intravenous administration of phentolamine is the most frequently described treatment when surgical resection of the PCC/PGL is not feasible.

signs such as paroxysmal headache, perspiration, pallor, palpitations and high blood pressure.¹ A clinical feature less well known is inhibition of the peristaltic activity of the gastrointestinal tract, which may result in chronic constipation, intestinal pseudo-obstruction or even intestinal perforation.^{2,3} This complication is directly related to the hypersecretion of catecholamines, which may inhibit acetylcholine release from the parasympathetic nerve system and activate α_1 -, α_2 - and β_2 -adrenergic receptors of the intestinal smooth muscle cells. Recently, we encountered a patient with a malignant PGL who had developed an intestinal pseudo-obstruction. Clinical experience with the management of this rare complication is very limited, and we therefore decided to conduct a comprehensive review of the literature on this subject with particular emphasis on the reported responses to the different treatments.

KEYWORDS

Intestinal pseudo-obstruction, paraganglioma, phaeochromocytoma, treatment

INTRODUCTION

Phaeochromocytomas (PCC) and paragangliomas (PGL) are rare catecholamine-secreting neuroendocrine tumours arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia, respectively. The release of catecholamines may lead to typical symptoms and

CASE

A 62-year-old female patient with a malignant PGL caused by a mutation in the succinate dehydrogenase (SDH) subunit B was admitted to our hospital with complaints of constipation and vomiting for the last three days. Her medical history included the surgical removal of a PGL of the bladder when she was 20 years of age. During this operation her left kidney was also removed because at that time a malignant epithelial tumour of the bladder was suspected. In 2009, she was admitted to the hospital because of abdominal pain and a high blood pressure of 211/145 mmHg. Further investigations revealed a

hydronephrosis due to ureteral obstruction secondary to a metastases of the PGL, which was treated by insertion of a double 'J' stent (*figure 1*). Since there were no other treatment options (peptide receptor radiation therapy with ¹¹¹In-octreotide or ¹³¹I-metaiodobenzylguanidine (MIBG) could not be given because there was no uptake on the octreotide and ¹²³I-MIBG scan) she was treated with sunitinib from April 2011 until the time of admission described in this case report (March 2012).

Her last bowel movements had been eight days before admission. Her blood pressure and heart rate were adequately controlled with doxazosin and metoprolol. On physical examination, the abdomen was markedly distended and hypertympanic but not tender to palpation, bowel sounds were absent. The plasma metanephrine and normetanephrine concentrations were 0.24 nmol/l (reference 0.07-0.33 nmol/l) and 149.83 nmol/l (reference 0.23-1.07 nmol/l), respectively. *Figure 1* shows a plain abdominal radiograph of the patient during her hospital stay. Neither administration of laxatives or prucalopride, a selective serotonin-4 (5-HT₄)-receptor antagonist, resulted in any clinical improvement. Subsequently, endoscopic desufflation of the colon was performed because of an imminent risk of a blowout.⁴ Colonoscopy did not reveal any mechanical cause for obstruction. Based on these findings, a diagnosis of intestinal pseudo-obstruction due to high concentrations of circulating catecholamines was considered. Oral treatment with phenoxybenzamine was started and gradually increased to a dose of 30 mg twice a day. Although this was followed by a return of bowel sounds and flatulence, there was no defecation. We therefore decided to administer metyrosine (α -methyl-L-tyrosine) in a dose of 250 mg four times a day. Subsequently,

within one day the intestinal pseudo-obstruction had resolved with restoration of spontaneous defecation and disappearance of the abdominal distension. In addition, plasma normetanephrine levels were reduced to 65.01 nmol/l. Hereafter, the patient could soon be discharged from the hospital. Unfortunately, she died two months later because of progressive disease.

REVIEW OF LITERATURE

We performed a comprehensive literature search on the clinical management of intestinal pseudo-obstruction in patients with either benign or malignant PCC/PGL. Case reports written in English, and case reports written in other languages but in Latin script were retrieved from PubMed, Embase, Web of Knowledge and Scholar Google using the following MeSH terms or text words: 'intestinal pseudo-obstruction', 'intestinal obstruction', 'Ogilvie's syndrome', 'paraganglioma' and 'phaeochromocytoma'. Data on age, gender, diagnosis, symptoms and signs, treatment and outcome were collected.

Our search yielded 32 publications, describing 34 cases (*table 1*). There was a slight preponderance of female subjects (59%), and age ranged from 25-70 years (mean 48.8 \pm 13.1 years). Eighteen patients (53%) harboured a benign PCC, two patients (6%) had a benign abdominal PGL, whereas 14 patients (41%), including our own case, had a malignant PCC/ PGL. In nine patients (26%), a paralytic ileus was the initial presenting symptom at the time a diagnosis of benign PCC was made.⁵⁻¹³ Among these subjects, one patient presented with a double perforation of the caecum.⁶ The most frequently reported symptoms and signs were constipation (64%), abdominal pain (61%), nausea (47%), vomiting (44%), and fever (18%). On physical examination, 31 patients (91%) had abdominal distension, 17 patients (50%) had hypoactive or absent bowel sounds and abdominal tenderness was noted in 12 patients (35%). Two patients (6%) had an ischaemic bowel without signs of thromboembolic occlusion of the mesenteric vessels and five patients (15%) developed a bowel perforation. Commonly performed examinations included abdominal X-ray, computed tomography (CT) scan of the abdomen and colonoscopy. Twenty-two patients (65%) underwent adrenalectomy, of which 17 (77%) had a benign PCC. In most cases (77%) adrenalectomy was conducted after pharmacological preparation with drugs such as phentolamine, phenoxybenzamine or neostigmine and β -receptor antagonists. Nine patients (26%) were treated conservatively with either α - and/ or β -receptor antagonists or percutaneous enterogastrostomy/ enterojejunostomy or a combination of these. In one case report the drug treatment was not specified,

Figure 1. A) Abdominal radiograph showing the colon diameter before the start of metyrosine. The maximal colon diameter measured was 12 cm. B) FDG-PET scan showing extensive lymph and bone metastasis of the paraganglioma

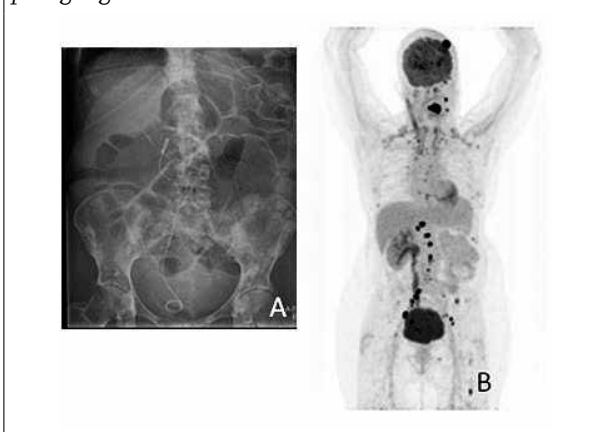


Table 1. Overview of case reports reporting pseudo-obstruction or bowel perforation in patients with PCC/PGL

Author (year of publication)	Diagnosis	Therapeutic intervention	Outcome
Zahor (1955) ⁴³	Malignant PCC	Resection of tumour	Died because of ventricular fibrillation just after surgery
Hughes (1962) ⁵	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Bernstein (1967) ⁴⁴	Bilateral benign PCC	Phentolamine	Died after a collapse 15 hours after start phenoxybenzamine
Petrin (1967) ⁴⁵	Benign PCC	Coecostomy	Died one day after coecostomy
Korhonen (1970) ¹²	Benign PCC	Died before intervention	Died because of tumour progression
Cruz (1972) ⁴⁶	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Garijo (1973) ⁴⁷	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Sznajderman (1975) ⁴⁸	Benign PCC	Resection of tumour	Died of haemodynamic shock after surgery
Short (1976) ⁴⁹	Malignant PCC	Colostomy	Died because of tumour progression
Fisch (1976) ⁵⁰	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Turner (1983) ¹¹	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Thurtle (1984) ⁵¹	Malignant PCC	Phentolamine and neostigmine; transverse colostomy	Died after surgery because of a bowel perforation
Mullen (1985) ³⁵	Case 1: Malignant PCC	Phenoxybenzamine, metyrosine, metoprolol	Died because of tumour progression
	Case 2: Malignant PCC	Phentolamine, phenoxybenzamine, metyrosine	Full recovery of pseudo-obstruction; FU one year
Baba (1985) ³²	Malignant PCC	Prazosin, propranolol, nifedipine	Died of tumour progression
Khafagi (1987) ⁷	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Noguchi (1990) ³⁶	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Hashimoto (1990) ²³	Malignant PCC	Phentolamine, propranolol, midaglizole	Died of organ failure caused by tumour progression
Oliver (1990) ³³	Malignant PCC	Phentolamine	Full recovery of pseudo-obstruction
Sacks (1993) ³⁴	Benign PCC and HNPG	Resection of tumour	Died of embolus 4 days after surgery
Sweeny (2000) ¹⁰	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Salazar (2001) ⁹	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Mazaki (2002) ⁸	Benign PCC	Colon perforation; hemicolectomy	Full recovery; FU several visits oncologist
Sawaki (2003) ³²	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Murakami (2003) ³⁵	Malignant PCC	Ileostomy	Died of tumour progression
Karri (2005) ⁶	Benign PCC	Right hemicolectomy; resection of tumour	Full recovery of pseudo-obstruction
Wu (2008) ³³	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
De Lloyd (2010) ³⁷	Case 1: benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
	Case 2: malignant PCC	Resection of tumour	Died 6 days after surgery because of DIS
Yamaguchi (2010) ²²	Malignant PCC	Phentolamine	Died of tumour progression and pneumonia
Edling (2011) ⁵⁶	Malignant PCC	Colectomy, ileostomy and gastrostomy tube placement	Full recovery of pseudo-obstruction
Coupe (2012) ³⁴	Malignant PCC	Phenoxybenzamine, β -blockade; colostomy, PEG and PEJ	Died of septicaemia four weeks after discharge
Lin (2012) ³³	Abdominal PGL	Resection of tumour	Full recovery of pseudo-obstruction
Osinga (2013)	Malignant PGL	Phenoxybenzamine, doxazosin, metyrosine	Died of tumour progression

PCC = phaeochromocytoma; FU = follow-up; HNPG = head and neck paraganglioma; PEG = percutaneous enterogastric; PEJ = percutaneous enterojejunostomy; PGL = paraganglioma; DIS = disseminated intravascular coagulation.

and a diagnosis of phaeochromocytoma-associated intestinal pseudo-obstruction was made post-mortem.¹² Intravenous administration of phentolamine was the most frequently applied drug treatment (7 out of 9 patients; 78%). Eventually, 18 patients (53%) fully recovered from the intestinal pseudo-obstruction, whereas 16 died (47%). Causes of death were tumour progression (n=9), treatment-related complications (n=5), intestinal pseudo-obstruction (n=1), or unknown (n=1).

DISCUSSION

Intestinal pseudo-obstruction is a clinical syndrome characterised by signs and symptoms suggestive of a mechanical intestinal obstruction in the absence of a demonstrable lesion blocking the intestinal lumen. In a large series of patients with acute intestinal pseudo-obstruction, the most frequently reported clinical features were abdominal distension (100%), abdominal

pain (80%), nausea (63%) and vomiting (57%).¹⁴ As shown in *table 2*, this syndrome may arise from several aetiologies and may present as either acute colonic pseudo-obstruction (ACPO or Ogilvie's syndrome) or chronic intestinal pseudo-obstruction.^{2,14,15} The diagnosis can only be made after exclusion of mechanical obstruction or a toxic megacolon.^{2,14,15} The pathogenesis of intestinal pseudo-obstruction in PGL/PCC is a direct consequence of the elevated levels of circulating catecholamines, which activate α_1 , α_2 and β_2 receptors in the gastrointestinal tract. The gastrointestinal tract has its own intrinsic nervous system. This enteric nervous system is composed of two plexuses, an outer myenteric plexus and an inner submucosal plexus. The outer myenteric plexus mainly controls the gastrointestinal movements, and the inner submucosal plexus gastrointestinal secretion and local blood flow. The intrinsic activity of the enteric nervous system is modulated by the activity of the parasympathetic and sympathetic nervous system. The parasympathetic nerve endings release acetylcholine, which stimulates the activity of the plexus of the entire enteric nervous system through activation of muscarinic receptors.¹⁶ Activation of muscarinic receptors is followed by stimulation of bowel movements, gastrointestinal secretion and blood flow. In contrast, the sympathetic nerve endings release norepinephrine, which inhibits both the plexus of the enteric nervous system through activation of the α_1 -, α_2 - and β_2 -adrenergic receptors.¹⁷⁻¹⁹ In addition, based on *in vitro* electrical recordings from the outer myenteric plexus,

it has been shown that the effects of the sympathetic nervous system on the gastrointestinal tract are further augmented by a presynaptic norepinephrine-mediated inhibition of parasympathetic acetylcholine release.^{16,20} Circulating epinephrine may also inhibit gastrointestinal peristaltic activity through stimulation of β_2 receptors.³ Moreover, catecholamine-induced stimulation of the α_1 and α_2 receptors can cause vasoconstriction, which may result in intestinal ischaemia and its complications such as ischaemic colitis, necrosis and intestinal perforation.^{3,6,21-23}

In general, treatment of intestinal pseudo-obstruction can initially be conservative if there is no abdominal pain and if the colonic distension measured on a plain abdominal radiograph is less than 12 cm.^{2,24} Conservative management includes fasting, nasogastric suction, intravenous replacement of fluids and electrolytes, and discontinuation of drugs which could adversely affect colon motility, such as narcotics and anticholinergic agents.^{2,24} The risk of colonic perforation increases when the colon diameter exceeds 12 cm and when the distension has been present for more than six days.²⁵ Spontaneous perforation has been reported in 3-15% of patients with acute intestinal pseudo-obstruction, which carries a high mortality rate of at least 50%.²⁴ If conservative treatment is not successful, endoscopic desufflation or pharmacological treatment with neostigmine, a competitive acetylcholinesterase inhibitor, should be considered.^{26,27} The initial response after treatment with intravenous neostigmine in patients with acute intestinal pseudo-obstruction is 89%, and in 61% of patients this response was sustainable.^{27,28} Immediate surgical intervention is indicated in case of clinical signs of ischaemia or perforation.^{14,29}

The incidence of PCC/PGL is low and intestinal pseudo-obstruction is an uncommon complication in this setting, as reflected by a total number of only 34 case reports in the literature, including our case. Consequently, clinical experience with the management of PCC/PGL-associated intestinal pseudo-obstruction is very limited.³⁰ In 26% of the cases, intestinal pseudo-obstruction was the presenting symptom of PCC/PGL. Mortality rate is high, as from this review can be concluded that 47% of patients are no longer alive within one year after development of the intestinal pseudo-obstruction. If the PCC/PGL can be resected successfully, the chances of complete recovery are high (88%).

Intravenous administration of phentolamine, a competitive α_1 - and α_2 -adrenergic receptor antagonist, was the most frequently applied pharmacological treatment (78%). Phentolamine inhibits α -mediated effects of catecholamines on intestinal and vascular smooth muscle cells and is usually administered preoperatively in PCC/PGL patients with drug-resistant

Table 2. Overview of the different aetiologies of intestinal pseudo-obstruction

Acute colonic pseudo-obstruction (Ogilvie's syndrome)^{2,14}
Trauma (non-operative; e.g. fractures, burns)
Infection (pneumonia and sepsis most common)
Cardiac (myocardial infarction, heart failure)
Obstetric or gynaecological disease
Abdominal/ pelvic surgery
Neurological (Parkinson's disease, spinal cord injury, multiple sclerosis, Alzheimer's disease)
Orthopaedic surgery
Miscellaneous surgical conditions (urologic surgery, thoracic surgery, neurosurgery)
Chronic intestinal pseudo-obstruction¹⁵
Degenerative neuropathies (e.g. Parkinson's disease, amyloidosis, diabetes mellitus)
Paraneoplastic immune-mediated pseudo-obstruction (small cell lung cancer, carcinoid and phaeochromocytoma/ paraganglioma)
Immune-mediated pseudo-obstruction (e.g. dermatomyositis, systemic lupus erythematosus)
Infectious (Chagas' disease)
Radiotherapy/ Chemotherapy
Genetic diseases (e.g. Hirschsprung's disease)

hypertension or a hypertensive crisis.³¹ In the majority of the reported cases, treatment with phentolamine was followed by clinical improvement. However, the intestinal pseudo-obstruction often recurred after discontinuation of this drug.^{7,22,23,32-37} Another limitation of phentolamine is that it can only be administered intravenously and under close haemodynamic monitoring in the intensive care unit, because of the risk of severe hypotension.^{38,39} Metyrosine could be considered as an alternative treatment in PCC/PGL patients with pseudo-obstruction. Metyrosine is a tyrosine analogue that competitively inhibits tyrosine hydroxylase. This enzyme catalyses the conversion of tyrosine to dihydroxyphenylalanine (DOPA), the rate-limiting step in catecholamine biosynthesis. Metyrosine results in a depletion of the catecholamine stores inside the chromaffin tumour cells, which was also reflected by the significant decrease of plasma normetanephrine in our patient.^{40,41} The use of metyrosine in patients with intestinal pseudo-obstruction might have several advantages, including oral administration without the need of blood pressure monitoring in the intensive care unit, allowing patients to use this drug at home. In clinical practice, however, the use of metyrosine is limited because of the high costs, limited availability and adverse effects in high doses.³¹ Common side effects of metyrosine are sleepiness, depression, anxiety and galactorrhoea. Occasionally extrapyramidal signs may arise, because of inhibition of the catecholamine biosynthesis in the brain. Metyrosine can cause diarrhoea and crystalluria, which has been described in rats and dogs receiving 50 mg/kg metyrosine per day.⁴² Although human data are scarce, patients are advised to drink approximately two litres per day.^{41,42}

In conclusion, intestinal pseudo-obstruction is a rare, potentially life-threatening complication in patients with PCC/PGL as a result of high circulating levels of catecholamines. While awaiting surgery or in case curative surgery is no longer possible, treatment with catecholamine-antagonising drugs, such as phentolamine and metyrosine, or neostigmine should be considered.

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