CASE REPORT

Optimal Management of a Synchronous Diagnosis of Pheochromocytoma and Colorectal Neoplasia

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Abstract The incidence rates of pheochromocytoma and colorectal cancer (CRC) are approximately 1 and 65 per 100,000 per year, respectively. Simultaneous presentation of these conditions is rare and poses unique management challenges. We report on treatment strategies and clinical outcomes in a series of patients with colorectal neoplasia and pheochromocytoma. Demographic and clinical details of four patients over a 4-year period were reviewed. The median (range) age at first presentation was 66 (52–70) years. Pheochromocytoma (2.5–12.5 cm) was confirmed on biochemistry after incidental detection of an adrenal mass on CT scan—three had CT for staging of CRC and one had CT scan for weight loss. Adrenalectomy (three retroperitoneoscopic and one open procedure) was first performed after maximally tolerated alpha blockade; no significant complications were observed. Normalisation of biochemistry was confirmed and the patients then underwent colorectal surgery—laparoscopic right

hemicolectomy, open right hemicolectomy (with further extensive surgery) for locally advanced cancer, laparoscopic low anterior resection and open high anterior resection. One respiratory infection and a seroma were the post-operative complications seen. In patients with a simultaneous diagnosis of pheochromocytoma and CRC, surgical interventions should be staged. Adrenalectomy should first be performed to avoid haemodynamic instability during colorectal resection. A retroperitoneoscopic approach to the adrenal in patients with ipsilateral colonic tumours avoids transgressing the planes for colorectal resection. The synchronous diagnosis of these two rare conditions and the reported stimulatory effect of catecholamines on colorectal epithelia raise the possibility of an increased incidence of colorectal neoplasia in patients with pheochromocytoma.

Keywords Colorectal · Cancer · Neoplasia · CRC · Synchronous · Simultaneous · Diagnosis · Pheochromocytoma · Adrenal · Incidentaloma · Hypertensive · Crisis · Biochemical · Series · Bowel cancer screening · Retroperitoneoscopic · Adrenalectomy · Staging · Alpha blockade · Catecholamines · Metanephrines · Investigations

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Introduction

Colorectal cancer (CRC) is the fourth most common cancer in the UK. A national screening programme for early detection and optimal treatment of colorectal cancer was initiated in 2006 and fully implemented in 2010 [1]. The programme is aimed at men and women aged 60–74 years, and participants are asked to provide stool samples

biannually [2]. An abnormal result warrants a colonoscopy for diagnosis of pre-malignant and/or malignant lesions. Any malignant lesions are then staged and treated appropriately. Patients with polyps are stratified by risk to determine subsequent management [3].

The incidence of phaeochromocytoma in the UK is 1 in 100,000 per year [4] and the incidence for bowel cancer is roughly 65 per 100,000 [4]. If there is no association between these two cancers and both lesions are sporadic, the chance of a person getting both of these cancers in 1 year would be very low (1 in 150 million per year). Interestingly, four cases of phaeochromocytoma and colorectal neoplasia (three cancers and one adenoma) were managed in Sheffield Teaching Hospitals over a 4-year period. This hospital has a catchment population of roughly 1.8 million.

The aim of this report is to present these cases and discuss the management issues in patients presenting with this rare association.

Methods

Over a 4-year period, four cases were identified from the log of the senior authors. Data regarding the four patients was obtained from case note review and from electronic records. Details of the demographics, age, presentation, investigations, diagnosis, surgical treatment and outcome were collected and a descriptive analysis was performed.

Results

The details of the cases are presented in Table 1 and briefly discussed below.

Case 1

A 64-year-old, otherwise well, male patient presented with a positive faecal occult blood (FOB) test. A colonoscopy demonstrated obstruction at level of the sigmoid. A CT scan confirmed a large sigmoid tumour and a 2.5-cm left adrenal mass. Twenty-four-hour urinary normetanephrine, noradrenaline, dopamine and plasma normetanephrine levels were raised confirming a phaeochromocytoma. (Values and reference ranges are presented in Table 2.) He was alpha-blocked with phenoxybenzamine and a stent was inserted into his bowel to prevent obstruction. After excluding a contralateral adrenal lesion by MIBG scan, a left retroperitoneoscopic adrenalectomy was performed. Post-operative biochemistry confirmed cure and histology showed a completely resected phaeochromocytoma. Three weeks later, a high anterior resection of the sigmoid colon was performed: histology demonstrating a moderately differentiated adenocarcinoma of the colon with multiple background hyperplastic polyps. Pathological staging was pT4, N0, V1 and R0. Lymph node examination was negative (0/15). Following surgery, capecitabine was started. The patient is free of disease 5 months after diagnosis.

Case 2

A 67-year-old woman underwent colonoscopy for rectal bleeding. Biopsy showed low- and high-grade dysplasia with invasive cancer of the rectum 5–6 cm from the anal verge. Abdominal CT scan showed a small polypoid rectal tumour and a 12.5-cm right-sided adrenal mass. Biochemistry showed raised 24-h urine metanephrine, normetanephrines, noradrenaline, adrenaline and dopamine and plasma normetanephrine. Following maximal tolerated alpha blockade with phenoxybenzamine, a right open adrenalectomy was performed. Histology demonstrated a 450-g phaeochromocytoma. Post-operative biochemistry

Table 1 Demographic and management details of patients with synchronous diagnosis of phaeochromocytoma and colorectal neoplasia

No.	Age	Sex	Colorectal tumour			Phaeochromocytoma		
			Presentation	Location of tumour (staging)	Surgery	Presentation	Location	Surgery
1	64	Male	FOB	Sigmoid (pT4N0R0Mx)	High anterior resection	Incidental	Left PASS ^a 10	Retroperitoneoscopic adrenalectomy
2	67	Female	Rectal bleeding	Rectum (pT2N0R0Mx)	Lap low anterior resection	Incidental	Right	Open adrenalectomy
3	70	Female	FOB	Caecum (tubulovillous adenoma)	Lap right hemicolectomy	Incidental	Right PASS ^a 2	Retroperitoneoscopic adrenalectomy
4	52	Male	Weight loss	Hepatic flexure/transverse colon (pT4bN0R0Mx)	Right open hemicolectomy	Flushing, fainting, headaches	Left	Retroperitoneoscopic adrenalectomy

^a Phaeochromocytoma of the adrenal gland scaled score (PASS) is a histomorphologic classification of phaeochromocytoma into benign and malignant. PASS ≥ 4 is considered malignant and PASS < 4 is considered benign [5]

Table 2 Pre- and post-adrenalectomy biochemistry results with references ranges

Biochemistry	Case 1		Case 2		Case 3		Case 4	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
24-h urinary metanephrines (reference range 0–1.7 μ mol)	1.0	0.4	54.2	0.5	9.6	0.3	N/A	0.3
24-h urinary normetanephrines (reference range 0–3.0 μ mol)	14.2	1.6	80.3	1.9	22.8	1.5	N/A	2.5
24-h urinary adrenaline (reference range 0–93 nmol)	36	16	766	23	378	13	1090	50, 32
24-h urinary noradrenaline (reference range 0–490 nmol)	3633	313	2791	202	378	261	2310	555, 388, 325
24-h urinary dopamine (reference range 0–3400 nmol/l)	4856	2368	4609	1101	1090	1144	N/A	1963
Plasma metanephrines (reference range 0–510 pmol/l)	168	49	N/A	242	2467	74	1698	77
Plasma normetanephrines (reference range 0–1180 pmol/l)	4370	265	2018	711	1330	415	4320	375
Plasma 3-methoxytyramine (reference range 0–180 pmol/l)	<75	<75	166	<75	<75	<75	<75	<75
Cortisol level after 1 mg dexamethasone suppression (<50 nmol/l)	128	NA	51	NA	28	NA	NA	NA

Values in italics indicate elevated levels

confirmed cure. The patient then had long-course radiotherapy, and 8 months following adrenal surgery, a low anterior resection with defunctioning ileostomy was performed. Histology demonstrated a moderately differentiated invasive rectal carcinoma with staging of T2 N0 R0 Mx. The patient had a post-operative respiratory infection. She was disease-free at 2-year follow-up.

Case 3

A 70-year-old female with a positive faecal occult blood test underwent colonoscopy. This showed a 40-mm tubular villous adenoma (TVA) of the caecum. This was confirmed on CT scan which also showed a 42-mm right adrenal mass. Biochemical investigation confirmed a pheochromocytoma with raised 24-h urinary adrenaline, metanephrine and normetanephrine, as well as plasma metanephrine, and normetanephrine. After appropriate alpha blockade with phenoxybenzamine, the pheochromocytoma was removed via a right retroperitoneoscopic approach. After confirmation of biochemical cure, a laparoscopic right hemicolectomy was performed. Histology of the tumour showed no signs of malignancy of the polyp. The patient had a seroma at the umbilical port site. There was no evidence of recurrence at 5-month follow-up.

Case 4

A 52-year-old man had two emergency admissions over a 3-month period with severe headaches, palpitations, fainting

episodes and significant weight loss. On the second admission, he had transient hyperglycaemia and a borderline oral glucose tolerance test (OGTT). A CT scan showed an 11-cm soft tissue mass at the hepatic flexure extending into his duodenum and liver. In addition, a 41-mm mass in his left adrenal gland was found. Subsequent biochemical investigations showed raised 24-h urinary adrenaline and noradrenaline levels, plasma metanephrine and normetanephrine. After adequate alpha blockade with phenoxybenzamine, a retroperitoneoscopic adrenalectomy was performed. Histology showed a completely resected pheochromocytoma and normalisation of post-operative urinary catecholamine and metanephrine. Further surgery for colorectal cancer included a laparotomy, right hemicolectomy, duodenectomy, cholecystectomy, partial hepatectomy and a biliary reconstruction. Histology showed a poorly differentiated adenocarcinoma with invasion through the bowel wall into surrounding structures. Staging of the tumour was pT4b N0 Mx. The patient was well at 4 years of follow-up.

Discussion

Two patients presented with a positive FOB test which warranted further investigation for colorectal cancer. One presented with rectal bleeding, and the other had non-specific weight loss in addition to several symptoms that were attributable to a pheochromocytoma. The pheochromocytomas were found incidentally. In all these patients, adrenal surgery under adequate alpha blockade was performed first. Of these, three

patients had adrenal surgery done retroperitoneoscopically, and the fourth had an open operation for a large phaeochromocytoma. The colorectal tumours were resected after confirmation of biochemical cure of the phaeochromocytoma (Table 2).

The synchronous diagnosis of both neoplasms poses unique management dilemmas, chiefly due to the high circulating catecholamine levels in these patients. Any procedure without adequate alpha blockade carries a significant risk of a hypertensive crisis [6]. In a study [7], incidental adrenal masses in four patients with varying cancers were assumed to be metastases and did not have biochemical investigations and appropriate alpha blockade. Three of these four patients developed hypertensive crisis intra-operatively.

The standard recommendation would be to perform the adrenalectomy **before** the colorectal operation. This would allow catecholamine levels to return to normal before the second operation, thereby reducing the risk of cardiovascular instability at the second operation. Some surgeons may consider performing adrenal and colorectal surgery simultaneously. This may potentially reduce anaesthetic risk and hospital stay. However, after removal of the phaeochromocytoma, perioperative hypotension is relatively common. A reduction in blood pressure is an independent risk factor for anastomotic leak [8, 9], which in turn increases risk of pelvic sepsis, risk of reoperations, increased hospital stay and mortality [10]. Simultaneous surgery is also likely to significantly increase the duration of surgery and potential need for blood transfusions, both of which increase the risk of complications after colorectal resection [11]. For these reasons, adrenalectomy for phaeochromocytoma should be performed prior to and as a separate procedure from the colorectal operation.

Another approach would be to perform the adrenalectomy retroperitoneoscopically [12, 13] if suitable equipment and trained staff are available [12]. This would be particularly important with small ipsilateral lesions, since it would avoid the need for transgressing the planes opened in the first operation during colorectal resection. It may also decrease adhesions and make the second operation easier.

Three out of the four phaeochromocytomas were found incidentally on CT scan. Adrenal incidentalomas are found in 7–10% of abdominal CT scans in those above the age of 70 and their incidence increases with age [14]. The vast majority (around 70%) are benign non-functioning adenomas, while phaeochromocytomas and adrenal metastases account for 5% and 2% of these lesions, respectively [5]. In the presence of concurrent or previous malignancy, the likelihood of an adrenal incidentaloma being a metastasis would be higher. In a study of 33 patients with a previous history of malignancy with adrenal masses [15], 20 masses were metastases and eight were found to be phaeochromocytomas, representing a much higher proportion of metastases or phaeochromocytomas compared to patients without a history

of cancer. Given the risk of a fatal outcome if a phaeochromocytoma is overlooked, a thorough biochemical investigation is warranted in all cases.

Given the expected rarity of this association and the presentation of four such cases, it is possible that a biological explanation underlies the association. It has been shown that adrenaline upregulates factors that increase the proliferation of colon cancer cells, while noradrenaline increases their locomotive capabilities [16, 17]. In a patient with untreated, recurrent phaeochromocytoma [18], rectal adenocarcinoma occurred 12 years later. Immunohistochemical staining showed strong staining for choline acetyltransferase (ChAT), the principal enzyme for acetylcholine production. Increased expression of M3R acetylcholine receptor was found in biopsies of colon cancer. Acetylcholine produced by phaeochromocytomas is thought to be a growth factor for colon cancer [18]. These studies suggest that high levels of circulating catecholamines in patients with phaeochromocytomas may drive colorectal neoplasia.

Our study has a few limitations. One of them is the small sample size of four patients. Also, given the lack of temporal information, it is difficult to speculate about the biological plausibility of a causative relationship between the two conditions. The term ‘neoplasia’ has been used to include the three patients with cancer as well as the one with a tubulovillous adenoma. The reason for the inclusion of the patient with adenoma is because this patient had similar management problems as the other patients with colorectal cancer.

With the introduction of a bowel cancer screening programme, more adrenal incidentalomas are likely to be detected. Synchronous diagnosis of colorectal neoplasia and phaeochromocytoma is a rare occurrence. Nonetheless, it poses specific management problems which can be circumvented by performing the adrenalectomy as a separate procedure before the colorectal surgery and ensuring that a biochemical cure is achieved following adrenalectomy. A retroperitoneoscopic approach should be considered as it will avoid transgressing the planes for the colorectal resection in patients with ipsilateral colonic tumours and phaeochromocytomas. Further work is required to test the hypothesis of a significant association between colorectal neoplasia and chromaffin tumours.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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