

# Intestinal carcinoid tumours in a father and daughter

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**T Pal, A Liede, M Mitchell, A Calender, SA Narod. Intestinal carcinoid tumours in a father and daughter. *Can J Gastroenterol* 2001;15(6):405-409.** Familial cases of carcinoid tumours that are not associated with any known syndrome or disease are extremely rare. All cases reported in the world literature have involved carcinoid tumours of the gastrointestinal tract. Two cases of carcinoid tumours of the small intestine in a father and daughter are presented. Laboratory analyses did not support the hypothesis that the occurrence of carcinoid tumours in this family is a variant of the multiple endocrine neoplasia type 1 syndrome. A review of the literature on familial occurrence of intestinal carcinoid tumours in the absence of any other known carcinoid tumour-predisposing genetic syndrome is provided.

**Key Words:** *Carcinoid tumours; Small intestine*

## Tel père, telle fille : tumeurs carcinoïdes de l'intestin

**RÉSUMÉ :** Les cas familiaux de tumeurs carcinoïdes non associées à des maladies ou à des syndromes connus sont extrêmement rares. Tous les cas signalés dans la documentation scientifique mondiale font état de tumeurs carcinoïdes du tractus gastro-intestinal. Voici deux cas de tumeur carcinoïde du petit intestin : l'un chez le père, l'autre chez la fille. Les analyses de laboratoire ont écarté l'hypothèse de la variante de l'adénomatose polyendocrinienne de type I pour expliquer l'apparition des tumeurs carcinoïdes dans la famille. Suit une revue de la documentation scientifique sur l'apparition des tumeurs carcinoïdes de l'intestin dans des familles en l'absence de tout autre syndrome génétique connu de prédisposition aux tumeurs carcinoïdes.

Carcinoid tumours are derived from the neuroendocrine system and are a morphologically distinct class of tumours. They store 5-hydroxytryptophan and a range of other peptides. Approximately 85% of carcinoid tumours develop in the gastrointestinal tract; the most frequent location is the appendix, followed by the rectum and the ileum (1). They usually occur sporadically, but have also been described as part of a familial tumour complex (2-9).

Multiple cases of carcinoid tumours have been reported in hereditary cancer susceptibility syndromes, most notably, multiple endocrine neoplasia (MEN) type 1, and occasionally MEN2 and neurofibromatosis type 1 (NF1). A case has been reported of carcinoid tumours coexisting with familial adenomatous polyposis (FAP) in a single patient (10).

MEN1 is an autosomal genetic disorder characterized by the familial association of parathyroid, pancreatic islet and

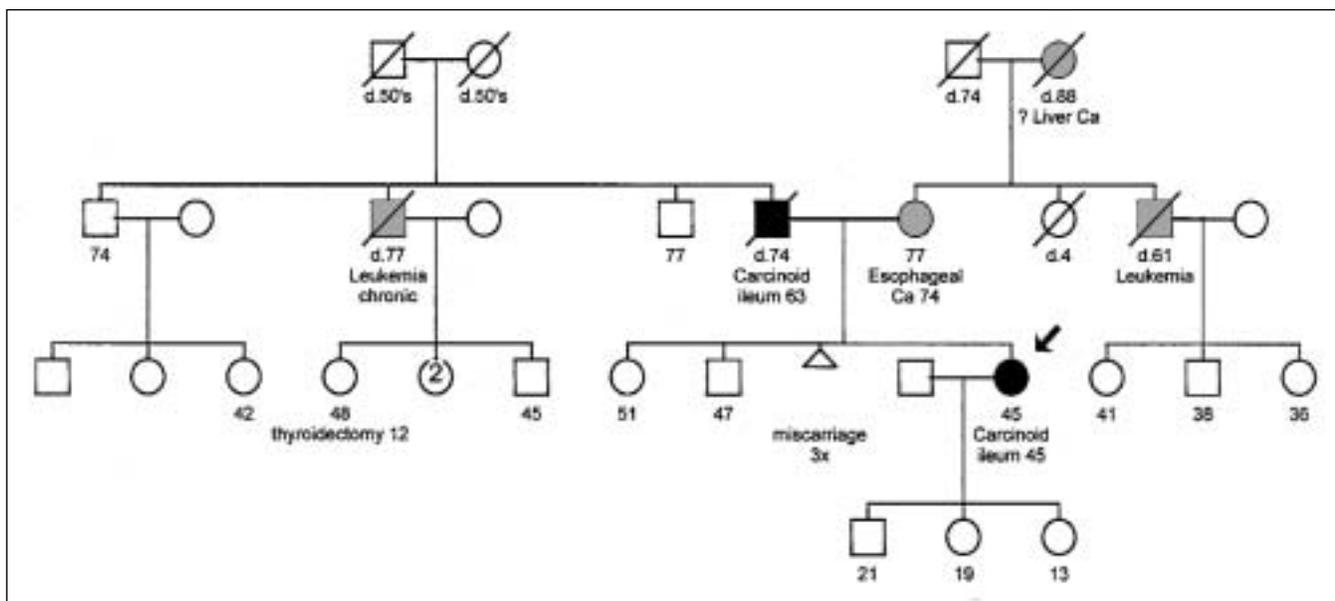
pituitary tumours (11). Hyperparathyroidism is the most common manifestation of MEN1 and is present in 90% to 100% of these patients. Carcinoid tumours are an uncommon manifestation of MEN1 (12,13).

The MEN1 gene has been localized to the long arm of chromosome 11 (11q13) (14-16) and encodes a novel protein consisting of 610 amino acids, referred to as MENIN (17,18). When the specific mutation is not known in a MEN1 family, the optimal screening test for the identification of the gene carrier state is an albumin-adjusted or ionized serum calcium measurement, which may be supplemented by a serum parathyroid hormone measurement (19,20).

Carcinoid tumours have also been seen in individuals with MEN2 (13), although even more rarely than in patients with MEN1. MEN2 is a genetically heterogeneous

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**Figure 1)** Pedigree of a carcinoid family. Note the occurrence of carcinoid tumours in the proband and her father. The proband is indicated by an arrow. Black shaded symbols indicate a diagnosis of intestinal carcinoid tumour, grey shaded symbols indicate another diagnosis of cancer (Ca). Ages are shown directly below the symbol with "d." preceding age at death. Cancer diagnoses are followed by the age at diagnosis

autosomal condition further subcategorized into two variants called MEN2A and MEN2B. MEN2A is characterized by the familial association of medullary thyroid cancer, pheochromocytoma and parathyroid adenoma; MEN2B is also characterized by this tumour spectrum and its hallmark finding of characteristic mucosal neuromas on the distal portion of the tongue, on the lips and subconjunctival areas, and throughout the gastrointestinal tract. The diagnosis of MEN2 is made on a clinical basis.

NF1 is a third autosomal dominant inherited condition in which carcinoid tumours have been described (21,22). NF1 is characterized by a combination of dermatological, ophthalmological and skeletal findings, and the diagnosis is made on a clinical basis by standardized National Institutes of Health Diagnostic Criteria (23).

A case has been reported of recurrent carcinoid tumours in association with duodenal adenomas in a patient with FAP (10). This finding may be a chance occurrence or a true association. FAP is an autosomal dominant, colon cancer-predisposing condition, characterized by more than 100 adenomatous polyps in the gastrointestinal tract that progress to colorectal carcinoma. The diagnosis of FAP is made on a clinical basis in conjunction with a complete family history.

The carcinoid syndrome consists of clinical symptoms including flushing, diarrhea, abdominal pain and congestive heart failure from carcinoid heart disease (the spectrum of which includes valvular heart disease, myocardial metastases and pericardial effusion). Although the exact pathogenesis of the symptoms remains unknown, some symptoms are related to the hormonal production of these tumours. Despite improved diagnostic methods, the recognition of the clinical syndrome, related to hormone production by

carcinoids, is difficult. In the majority of cases of carcinoid syndrome, metastatic carcinoid tumours of the small intestine are present (24).

The case of a father and daughter with carcinoid tumours of the small intestine, both of whom presented with the carcinoid syndrome, is presented (Figure 1). Germline DNA was analyzed for MEN1 mutations and tumour block pathology was reviewed.

#### CASE PRESENTATIONS

**Case 1:** A 45-year-old woman was found to have a carcinoid tumour of the ileocecal region in 1996 (proband in Figure 1). She had a 10-year history of gastrointestinal problems and flushing. Her gastrointestinal symptoms included diarrhea, bloating, postprandial nausea and vomiting, excessive flatus production and abdominal discomfort. Results from ultrasound studies of the gastrointestinal tract suggested a right lower quadrant mass with possible intussusception. Computed tomography scan confirmed the presence of a lower quadrant small bowel intussusception at the ileocolic junction. Laparotomy in December of 1996 revealed a 3 cm carcinoid tumour of the ileocecal region with extension through full thickness of the bowel wall into the serosa and pericolic fat. Two regional lymph nodes were positive for metastatic tumour, and perineural involvement was described. The resection margins were negative, and no evidence of distant spread of disease was present. The patient had normal serum ionized calcium and normal parathyroid hormone levels. The patient is currently well. She had none of the clinical stigmata associated with MEN2 or NF1. There were no findings suggestive of FAP.

**Case 2:** The father of the proband presented at age 63 years, after several years of lower back discomfort and

**TABLE 1**  
**Published reports of familial carcinoid syndrome in the absence of any known carcinoid-predisposing genetic syndromes**

Report	Number of families	Number of affected members	Relation	Tumour location	Clinical manifestations
Eschbach and Rinaldo (2)	1	2	Brother and sister	Ileum	Serum calcium (normal)
Anderson (3)	1	2	Father and daughter	Appendix	No tests reported
Moertel and Dockerty (4)	1	3	Sister, brother and niece	Ileum	No tests reported
Wale et al (5)	2	2	Sisters	Ileocecum	No tests reported
Yeatman et al (6)	1	3	Sister and brother	Ileum	No tests reported
			Father and two sons	Duodenum	Serum calcium, phosphorus, PTH and calcitonin (normal)
Lengyel et al (7)	1	2	Father and daughter	Jejunum	No test reported
Yoshikane et al (8)	1	2	Two sisters	Stomach	Serum gastrin (elevated)*
Babovic-Vuksanovic et al (9)	9	19	All first-degree	Small bowel and colon	No tests reported
Present case	1	2	Father and daughter	Ileum	Testing negative <sup>†</sup>

\*Likely type A chronic atrophic gastritis; <sup>†</sup>Standard screening for multiple endocrine neoplasia type 1 by serum ionized calcium, parathyroid hormone (PTH), gastrin and prolactin

chronic gastrointestinal problems with diarrhea and flushing. On physical examination, he had infra-umbilical tenderness and a palpable mass. Laparotomy was done in mid-1976, at which time the primary tumour was resected. The pathology report revealed an infiltrating carcinoid tumour of Meckel's diverticulum and the wall of the ileum. Metastatic disease was present in the liver and mesenteric nodes. He was given several courses of chemotherapy with 5-fluorouracil; the last treatment was given in November 1984. Following resection of the tumour, he did well at home aside from daily episodes of flushing and a mild degree of diarrhea, controlled with medication. The cardiac manifestations of his carcinoid tumour consisted of damage to his tricuspid valve resulting in mild ankle swelling. In mid-1987, at the age of 74 years, he started to develop increasing weight loss, fatigue, anorexia, increased abdominal girth with ascites and bilateral pleural effusions. He died in December 1987 at the age of 74 years of metastatic disease. **Laboratory analysis:** The pathology of paraffin-embedded tumour blocks was reviewed for both the proband and her father. There was concern that this family may be a MEN1 variant because multiple carcinoid tumours in a family have been described for this syndrome (25). The proband and her two siblings were screened with the standard blood testing regimen for MEN1, including serum ionized calcium, parathyroid hormone, gastrin and prolactin, all of which were normal. These tests detect over 90% of MEN1 carriers after age 40 years (26).

To investigate further the possibility of MEN1, mutation analysis was performed on the proband's DNA with heteroduplex analysis and full gene sequencing as previously reported (27). Mutations in 75% to 80% of patients with MEN1 are detected using this method (28).

## RESULTS

The pathologic tumour material from each of the patients was reviewed, and typical carcinoid histology was confirmed. No germline MEN1 mutations were detected in the

proband by heteroduplex analysis and full gene sequencing. Nevertheless, this analysis did not exclude a mutation in the uncharacterized 5' regulatory region of the MEN1 gene nor the presence of a large germline deletion as reported by Kishi et al (29) who used quantitative polymerase chain reaction methods.

## DISCUSSION

There have been a limited number of families reported with familial carcinoid tumours in the absence of any other known carcinoid tumour-predisposing genetic syndrome (Table 1). The carcinoid tumours in all affected individuals in these families have been limited to the gastrointestinal tract. Eschbach and Rinaldo (2) described the first familial case in a brother and sister who had metastatic carcinoid tumours of the ileum. The ionized calcium in the proband was normal. Anderson (3) described a father and daughter who both had nonmetastasizing carcinoid tumours of the appendix discovered incidentally at appendectomy with no evidence of carcinoid syndrome. Moertel and Dockerty (4) described three cases of multicentric and metastasizing carcinoid tumours originating in the terminal ileum in two generations of a family. The patients all had evidence of carcinoid syndrome. Wale et al (5) described two family groups with familial carcinoid tumours and evidence of carcinoid syndrome. Their first family consisted of two sisters with metastatic carcinoid tumours in the ileocecal region; the other family consisted of a sister and brother with metastatic carcinoid tumour in the terminal ileum. Yeatman et al (6) reported a father and two sons with proximal duodenal carcinoid tumours. Lengyel et al (7) described a father and daughter with intestinal carcinoid tumours. Recently, Yoshikane et al (8) described the familial occurrence of gastric carcinoid tumours associated with type A chronic atrophic gastritis in two sisters. There was an elevation in serum gastrin in both sisters and the father. Because gastric carcinoid tumours can arise in the presence of type A chronic atrophic gastritis (the most common type

of gastric carcinoid), the hereditary factor in this family may be a predisposition to chronic atrophic gastritis. The gastric carcinoids may be a secondary finding.

In a more recent chart review conducted at the Mayo Clinic on patients with malignant carcinoid tumours of the gastrointestinal tract diagnosed between 1988 and 1996, nine of 245 patients (3.7%) had at least one first-degree relative with the same malignancy; one patient had two affected relatives (9). Of the 10 relatives with carcinoid tumours, five had tumours located in the small bowel, and two in the colon, and information about the location was unavailable in three. The authors described the rate of carcinoid tumour in first-degree relatives of probands as higher than expected ( $P < 0.0001$ ) based on the surveillance, epidemiology and end result population data. It was estimated that the cumulative probability of a first-degree relative developing a carcinoid tumour is 1.5% to age 80 years (9). Neither patients with carcinoid tumours nor their first-degree relatives had an increased incidence of other malignancies according to this study.

The presence of small intestinal carcinoid tumours in two generations is strongly suggestive of a genetic etiology. Possibilities include a variant of a known carcinoid-predisposing genetic condition (ie, MEN1, MEN2 or NF1) or a new syndrome of familial carcinoid tumours of the gastrointestinal tract. The likelihood that the family described in the present case is a MEN1 variant is low. The diagnosis of MEN1 is based on a family history of pituitary, parathyroid and pancreatic islet cell tumours, and none of these characteristics were present in the family. Hyperparathyroidism, the most commonly associated manifestation of MEN1, was also investigated and found not to be present in the proband and her siblings. The age-related penetrance of hyperparathyroidism, based on serum calcium and prolactin, exceeds 90% by age 45 years (26). These negative clinical findings reduce the likelihood of MEN1 involvement in this family. Additionally, DNA analysis with full gene sequencing did not identify any mutations in the MEN1 gene.

Previously reported cases (2-9) were published after the recognition of the MEN1 syndrome (30), did not have any

MEN1-associated tumours and were not suggestive of MEN1 based on the clinical information available in the reports. As previously mentioned, in rare instances carcinoid tumours occur in MEN2 (13), an autosomal dominant syndrome characterized by the familial association of medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia or adenomatosis. Mutations in the RET gene are associated with MEN2 (31,32), and mutational analysis is a useful test for detection of the condition (33) when clinically indicated. Based on the absence of MEN2-associated tumours and hyperparathyroidism, it was not thought that mutational analysis of the RET proto-oncogene was indicated in the present proband. Carcinoid tumours have also rarely been described in NF1 (21,22). There was no evidence to support the clinical diagnosis of NF1 as the etiology of the carcinoid tumour in the present proband. More recently, a patient with FAP and recurrent carcinoid tumours located at the bases of duodenal adenomas was reported (10). This finding may represent a true association between FAP and recurrent carcinoid tumours, or be a chance occurrence. There was no evidence of FAP in the present proband or any family history suggestive of the condition.

There is evidence to support that these cases of familial carcinoid tumours of the gastrointestinal tract (2-9) represent a new genetic entity. Diagnostic criteria for this new syndrome should include exclusion of MEN1 through screening for hyperparathyroidism and any MEN1-associated tumours in the family. A detailed family history and complete physical examination should be performed to rule out MEN2, NF1 and possibly FAP.

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