

Case report

A family case of a new dermointestinal syndrome: an unknown variant of Gardner's syndrome?

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SUMMARY

The dominantly inherited gastrointestinal polyposis syndromes are divided into adenomatous and hamartomatous varieties, depending on the histology of the polyps. Unfortunately, because the age of onset of polyps varies, to exclude the presence of these syndromes, bowel screening must be continued until at least 40 years of age.

A 67 year-old man was admitted to our hospital because of altered bowel movements, anemia and a weight loss of 7-Kg during the previous couple of months. Physical examination revealed multiple subcutaneous nodules in his neck, upper and lower extremities. Colonoscopy revealed three colonic adeno-carcinomas and subtotal colectomy was successfully performed. The patient was discharged but came one month later complaining of continuous headache and was diagnosed with malignant meningioma. Two months later the patient came again complaining of severe dysphagia and was diagnosed with esophageal adenocarcinoma.

The family tree showed that all male first-degree relatives had megalacric appearing faces with bilateral eyelid lipomas and multiple subcutaneous nodules in neck, upper and lower extremities. The patient's younger brother was operated on at the age of 63 for gastric cancer and one year later three adenomatous polyps were diagnosed. Their

father died at the age of 76 years because of bowel adenocarcinoma. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) was noted in the brothers with bowel carcinomas.

We have presented a family with a dermointestinal syndrome probably representing a new variant of Gardner's syndrome.

Key words: FAP (familial adenomatous polyposis), CHRPE (congenital hypertrophy of retinal pigment epithelium), GS (Gardner's syndrome), dermointestinal syndrome, lipoma, inherited colorectal cancer.

INTRODUCTION

The dominantly inherited gastrointestinal polyposis syndromes are divided into adenomatous and hamartomatous varieties. The adenomatous polyposis syndromes include familial adenomatous polyposis coli (FAP), Gardner's syndrome (GS) and Turcot's syndrome (TS). The hamartomatous polyposis syndromes include Peutz-Jeghers syndrome, familial juvenile polyposis, Cowden's syndrome, intestinal ganglioneuromatosis and the Ruvalcaba-Myhre-Smith syndrome¹. A familial colon

Abbreviations used in the text:

GS (Gardner's syndrome),

TS (Turcot's syndrome),

CHRPE (congenital hypertrophy of retinal pigment epithelium),

ECM (extracolonic malignancies),

APC (adenomatous polyposis coli),

CRC (colorectal cancer),

HFAS (hereditary flat adenoma syndrome),

FAP (familial adenomatous polyposis),

HNPCC (hereditary non polyposis colorectal cancer).

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cancer syndrome has been identified, in which nearly all affected members develop cancer but with features distinct from the polyposis syndromes; this has been termed hereditary nonpolyposis colorectal cancer syndrome (HNPCC) or Lynch syndrome (type I and II). This syndrome, inherited as an autosomal dominant gene that produces colon cancer two to three decades earlier than typically seen, is associated with multiple primary colonic neoplasms both synchronous and metachronous. In the hereditary flat adenoma syndrome (HFAS) the principal phenotypic marker is multiple colonic adenomas (usually less than 100) with a tendency for proximal location.² Congenital hypertrophy of the retinal pigment epithelium (CHRPE) has been reported in association with FAP and GS syndrome and the presence of multiple CHRPE lesions has been correlated with the presence and development of polyposis in these conditions.³ The APC (adenomatous polyposis coli) gene is located in on the long arm of the chromosome 5.⁴ It is noteworthy that one third of the newly diagnosed cases represent new mutations.⁵

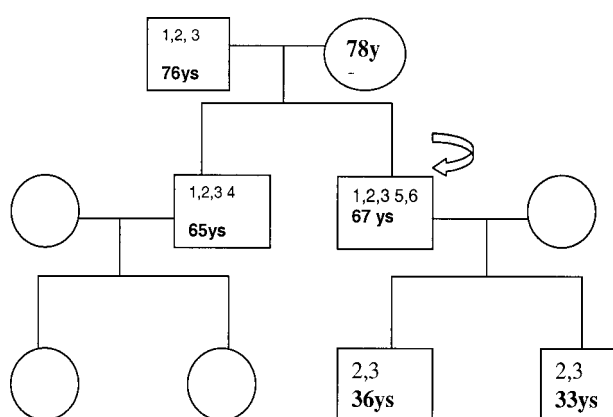
We present here a family with a dermointestinal syndrome probably representing a new variant of Gardner's syndrome.

CASE REPORT

A 67 year-old man was admitted to our hospital because of altered bowel movements, anemia and a weight loss of 7 Kg during the previous couple of months. The patient had no history of previous hospital admissions and was not taking any kind of drugs. Physical examination revealed a megalacric appearing face with bilateral eyelid lipomas and multiple subcutaneous nodules in neck, upper and lower extremities. Rectal digital examination was negative but occult blood test was positive. Laboratory tests showed iron deficiency anemia and levels of carcino-embryonic antigen (CEA) were 3-fold increased above reference values. Colonoscopy revealed three polypoid masses in the descending colon and biopsies were compatible with colonic adenocarcinomas. Thoracic and abdominal computed tomography was negative for secondary lesions. Subtotal colectomy was successfully performed and the patient was discharged with instructions to perform all screening tests for inherited polyposis syndromes, including genetic screening, but the patient refused. One month later the patient came again, complaining of continuous headache. Brain computed tomography showed a mass in the right temporal area which proved to be a malignant meningioma. Two months later the patient came again, complaining of

severe dysphagia and upper gastrointestinal endoscopy revealed a polypoid mass in the lower esophageal segment, which proved to be a well-differentiated adenocarcinoma.

Careful investigation of his family tree (Figure 1.) showed that all his male first-degree relatives had megalacric appearing faces with bilateral eyelid lipomas and multiple subcutaneous nodules in neck, upper and lower extremities. Those nodules were histologically proven lipomas. The patient's younger brother was operated on at the age of 63 for gastric cancer and one year later three adenomatous (dysplastic) polyps were successfully removed from his bowel. Their father died



Abbreviations: 1=multifocal synchronous bowel adenocarcinoma, 2=multiple subcutaneous lipomas, 3=megalacric appearing face with bilateral eyelid lipomas, 4=gastric cancer, 5=esophageal cancer, 6=malignant meningioma

Figure 1. Family tree of a new dermointestinal syndrome. Five male siblings are affected, one of them (arrow) diagnosed with synchronous gastrointestinal cancers and meningioma.

at the age of 76 years because of bowel adenocarcinoma. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) was noted in both brothers.

It is noteworthy that in all three generations, no female sibling was affected by any of the above mentioned conditions nor had anything remarkable on physical or laboratory examination.

The patient's two sons, now aged 33 and 36, have multiple subcutaneous nodules in neck, upper and lower extremities, no CHRPE at the moment, and have been informed about the importance of bowel screening. Genetic counselling about the probability of neoplasia was also offered to all family members who accepted it.

DISCUSSION

The development of extracolonic malignancies (ECM) in FAP has, since 1953, been termed Gardner's syndrome.⁶ Atypical GS or variants of GS with skin or subcutaneous tissue involvement and not necessarily APC involvement have been reported in several cases. A cutaneo-intestinal syndrome with perifollicular fibromatosis cutis and APC was reported, in which one parent and two siblings were diagnosed with fibromas on face, neck and trunk.⁷ One female sibling was diagnosed with malignant transformation of bowel adenomatous polyps while in the other two family members most features of GS were absent. Nevertheless, authors suggest that this family probably represent a new cutaneo-intestinal syndrome. Subcutaneous lipomas and acromegalic appearance have been correlated with gastric cancer, colon tubular adenoma with moderate atypia, and pancreatic mucinous cystadenoma in one case.⁸ It is noteworthy that all male members of the family tree described here had a megalacric appearance.

The description of a mother and her two daughters with desmoid fibromas represent another atypical GS family case.⁹ The two daughters had single colonic polyps, while one of them and her mother had mandibular osteomas. A single family case of GS was also reported, in which a member diagnosed with gastric adenomatous polyps was operated on for biliary obstruction due to a common bile duct adenoma, and another member died at the age of 24 because of brain tumour.¹⁰ Moreover, a case of APC, craniofacial exostosis and astrocytoma suggestive of concomitant occurrence of the Gardner's and Turcot's syndromes was once reported¹¹. However Gardner's and Turcot's syndromes represent FAP gene mutations, the majority of which have already been identified. Familial adenomatous polyposis gene has been identified at chromosome 5q, distal to 5' terminal, Peutz Jegers syndrome at chromosome 19p13.3, Turcot's syndrome has both FAP and HNPCC variants while HNPCC is an autosomal dominant condition with germline mutations of many mismatched repair genes (*hMSH2*, *hMLH1*, *hPMS1*, *hPMS2*).¹² In Turcot's syndrome, neural tumours associated with FAP normally develop at a very young age, often before the onset of the polyps and are a good marker for the disease if the parent is already known as an FAP patient. Basically, there are two surgical options for these patients-subtotal colectomy with ileorectostomy on the one hand or total colectomy with pouch-anal anastomosis or terminal ileostomy on the other. The first option leaves a residual rectum with the sometimes not inconsiderable risk of

carcinoma developing in the preserved rectum.¹³

Initially it was believed that CHRPE was associated only with GS. Subsequent studies from the USA, Japan and the UK have shown CHRPE to be present in a high proportion of FAP family members (65-100%) with and without ECM of Gardner's syndrome.¹⁴⁻¹⁶ Multiple patches of congenital hypertrophy of the retinal pigment epithelium (CHRPE) have recently been described in a large number of relatives with Gardner's syndrome; they are specific and sensitive clinical markers of this disease (specificity 0,952 and sensitivity 0,780)¹⁷. CHRPE might also occur in patients who manifest hereditary polyposis of the colon in the absence of Gardner's syndrome.¹⁷⁻²⁰

A major problem in many studies that could affect conclusion is the diagnosis of individuals (and not families) as having GS with extracolonic manifestations (ECM) as opposed to GS syndrome without this kind of manifestations. As is the case with most multi-system dominant syndromes, various expressivities is the rule. Within families with GS, many patients with polyposis will not show ECM, except for possibly the ocular lesions which are probably the most common.²¹

It has been suggested that when we label pedigrees of families as GS because at least one member of each family had ECM other than congenital hypertrophy of the retinal pigment epithelium (CHRPE), we must be skeptical.²² The absence of CHRPE in individuals at risk for APC cannot preclude regular colonic screening, and this dictum should be followed up in the management of all families. All groups studying the genetics and extracolonic manifestations of adenomatous polyposis should use family diagnosis and not individual diagnosis as a basis for labeling patients as having Gardner's syndrome. On the other hand it was supported²³ that anachronistic labelling of affected families complicates individual management and long-term screening to map out the unknown spectrum of extracolonic manifestations occurring in any combination in any one patient, as may have happened in our case. Results argue for a combined screening program of DNA analysis, indirect ophthalmoscopy and bowel examination.²² Unlike repeated bowel screening, both of these tests can be performed at a single hospital visit and their accuracy for predictive diagnosis can be improved by combined risk analysis.²⁰ In these series, the youngest affected patient examined was 13 months old.²⁴

The rarity of reported cases of multiple synchronous primary cancers including malignant meningioma means that it has not yet been well registered and classified

among probable hereditary forms of cancers. According to the Annual Pathological Autopsy Cases in Japan, 156 cases of multiple primary cancers in a 16-year period were reported. However only two cases with multiple primary cancers including malignant meningioma were reported in those sixteen years, although no correlation with Gardner's syndrome was implicated.²⁵ We cannot exclude the coincidental diagnosis of meningioma in this case, but its synchronous diagnosis (within one month) with the other gastrointestinal malignancies cannot exclude the possibility of common aetiopathology.

The principal difficulty in making the diagnosis of HNPCC in a family tree is that the phenotype is not necessarily distinctive and no definite pre-morbid markers have been identified. Criteria for a working definition of HNPCC for clinical studies have been developed by an international collaborative group and have been referred to as the Amsterdam criteria.²⁶ The diagnosis is made if a family has had all of the following; three or more relatives with verified colorectal cancer, with one person being a first-degree relative of the other two; colorectal cancer involving at least two generations; and one or more cancers diagnosed in family members younger than 50 years of age. It is obvious that the family reported here is not another case of Lynch II syndrome (cancer family syndrome) nor a case of Torre's syndrome,²⁷ a rare familial condition characterized by multiple sebaceous gland neoplasms and colorectal cancer being clinically a subset of Lynch syndrome type II. It has been suggested that multiple mandibular osteomas, similar to those found in FAP, may be found in patients with Lynch type II syndrome (cancer family syndrome), however this has not been accepted as a general rule.²⁸ Finally, Cowden's syndrome, although extremely rare, should also not be overlooked in this family case. Cowden's syndrome is also called multiple hamartoma syndrome and is characterized by multiple hamartomatous polyps of the skin and mucous membranes. The hallmark of the syndrome is the presence of multiple facial trichilemmomas. In Cowden's syndrome the occurrence of multiple cancer including visceral tumours and meningiomas has been observed. If the gastrointestinal tract is involved, numerous hamartomatous but non-dysplastic polypoid lesions are found throughout, including the esophagus. However, gastrointestinal investigation does not appear necessary unless referable symptoms are present.

In conclusion, we have reported a family with a new dermointestinal syndrome with megalacric appearance, lipomas and late onset of gastrointestinal cancer which was multifocal with meningioma in one case. We suggest

that this family phenotype is due to PTEN (phosphatase and tensin homologue) mutations (Cowden's syndrome), may represent a variant of Gardner's syndrome or a new dermointestinal syndrome.

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