

## Case report

## Synchronous multiple adenocarcinomas of the colon in a patient with von Recklinghausen disease: a case report

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### SUMMARY

The type-I neurofibromatosis (von Recklinghausen disease) (NF-1), is a dominantly inherited syndrome with varying disease manifestations with the consistent feature that tissues derived from the neural crest is most commonly affected. In addition to the nearly uniform development of neurofibromas, NF1 patients are at elevated risk of developing pheochromocytomas, schwannomas, neurofibrosarcomas, and primary brain tumours.

Although gastrointestinal tumours have been well described in patients with von Recklinghausen disease, and numerous case studies have been reported, colonic cancer is rarely associated with the disease.

We report a case of multiple synchronous colonic tumours, in a patient who fulfilled two of the seven criteria proposed by the NIH (National Institute of Health) for the diagnosis of NF1.

**Key words:** neurofibromatosis-1, von Recklinghausen disease, multiple adenocarcinoma of colon, phacomatosis

phenotypes. The most common clinical picture is neurofibromatosis-1 (NF1), (von Recklinghausen's disease), which was described more than a century ago.<sup>1</sup>

The disease is characterised by the presence of a variety of tumours of neural crest-derived cells and other systemic disorders and pigmentary changes. The numerous manifestations of neurofibromatosis often present challenging diagnostic and treatment dilemmas. Diagnosis is established when any two of the following criteria proposed by the NIH are present: six or more café-au-lait spots; two or more neurofibromas or one plexiform neurofibroma; axillary or inguinal freckling; optic gliomas; osseous lesions e.g. sphenoid wing dysplasia or congenital bowing or thinning of long bone cortex with or without pseudoarthrosis; lesions of iris known as Lisch's nodules; or a first-degree relative with NF1.<sup>2</sup>

Adenocarcinomas of the gastrointestinal tract have rarely been reported in these patients. We present here the case of a patient with four synchronous adenocarcinomas of the colon, who also fulfilled two of the above-mentioned criteria for the diagnosis of NF-1.

### INTRODUCTION

Neurofibromatosis (NF) is one of the most common genetic disorders, with an estimated birth incidence of 1 in 3000-4000 live births. Inherited in an autosomal dominant pattern with variable penetrance, neurofibromatosis has many

### CASE REPORT

A 58-year-old man was admitted to the First Department of Surgery of Evangelismos Hospital of Athens, with malaise and history of passing blood mixed with stools.

Clinical examination revealed anemia and multiple dermal and subcutaneous nodules of a hard consistency, mainly in the chest, lower back and right forearm. We, also, counted over six café-au-lait spots (bigger than 1,5 cm) which were located all over his body, mainly on his

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face and trunk. (Figure1)

From his past history we learned of an appendectomy, and a transurethral excision of a papilloma in the bladder. Five of his relatives suffered from different kinds of malignancies. His mother had died from gastric cancer and three of his six brothers had lymphoma, renal cell carcinoma and cancer of pharynx, respectively. One of his cousins had familial adenomatous polyposis (FAP).

Laboratory investigations showed an hematocrite value of 35%, a hemoglobin 11 gr/dl, a white cells count of 14.190 mm<sup>3</sup> with 82% leukocytes, with the carcinoembryonic antigen (CEA) increased to 38,9ng/ml. Other cancer markers (a-FP, CA-19.9, PSA etc) were normal. Biochemistry, chest X-ray and electrocardiogram (ECG) were normal.

Colonoscopy revealed two tumours at 35cm and 18cm from the anal verge, and a third one in the ascending colon, at 14 cm from the ileocecal valve.

Intravenous pyelography (IVP) showed silence of the right kidney, which was investigated by cystoscopy and retrograde pyelogram and which showed obstruction of the right ureter near the bladder, due to external compression. A pig-tail catheter was successfully inserted.

Computed tomography of the abdomen and thorax did not revealed distant metastasis.

The patient was treated by total proctocolectomy with



**Figure 1.** Café-au-lait spots in the torso of the patient

permanent ileostomy.

Pathological examination of the resected specimen revealed five macroscopically distinct tumours of white-gray colour and hard consistency, located 3,5 cm and 17,5 cm from the anal verge and 14,5 cm, 12 cm and 8 cm from the ileocecal valve, respectively. (Figure 2)

The microscopic findings were:

- A poorly differentiated adenocarcinoma of the rectum with intracellular mucus production (signet-ring cells). This tumour was ulcerative, located at 2,5 cm from the anal verge and measured 4.5 × 4 × 15 cm. This cauliflower tumour resulted in partial obstruction of the lumen. The tumour infiltrated the perirectal fat, with metastasis in three lymph nodes of the mesorectum.
- A moderately differentiated adenocarcinoma with extracellular mucus production (CK20+) in the rectosigmoid junction, 17,5 cm from the anal verge. This tumour was also ulcerative and measured 3.5× 2.5× 1.5 cm. The tumour invaded the serosa and extended into the pericolic fat.
- A poorly differentiated adenocarcinoma with extracellular mucus production (CK20+) 12 cm from the ileocecal valve. This tumour measured 2.5× 2.5× 1cm and infiltrated the serosa, extending to the pericolic fat.
- A moderately differentiated adenocarcinoma of the ascending colon 8 cm from the ileocecal valve,



**Figure 2.** Operative specimen showing multiple tumours of large bowel

growing on the base of a pre-existent tubulovillous adenoma. The dimensions of this adenoma were 2.5 × 1.5 × 0.7 cm. This infiltrating adenocarcinoma was extended into the bowel wall infiltrating the muscularis.

- e. A tubulovillous adenoma of the ascending colon, with mild epithelial dysplasia 14.5 cm from the ileocecal valve. This tumour was a sessile polyp with 2 cm maximal diameter at the apex.

The surgical margins of the resected bowel were free of disease and no metastatic invasion of the lymph nodes, in the territory of the ileocecal and right colic vessels was found.

Three of the subcutaneous nodes were excised for histology purposes. The diagnosis of solitary neurofibromas was retained because of their appearance as well circumscribed but nonencapsulated spindle cell tumours on routine stained sections, with curved or "S" shaped nuclei of the spindle cells and an increase in the number of mast cells within the tumour. A neural origin for these tumours was further supported by a positive cholinesterase stain of the tumour cells, which were also positive for CD34 and for S100 protein, but negative for CD117.

After an uneventful recovery he was discharged on the 14<sup>th</sup> postoperative day. The Astler-Coller stage of the disease was considered to be C2, and the patient received 12 courses of adjuvant chemotherapy with 5FU-Levamisole. Today, sixteen months after the initial operation he is alive and well, although under investigation for an isolated gradual rise in the CEA levels (from 14ng/ml the first month after surgery to 43ng/ml).

## DISCUSSION

The diagnosis of neurofibromatosis can still be challenging because of the disease's progressive nature, with the appearance of symptoms and signs later in adult life or during periods of high hormonal activity. Furthermore, a negative family history should not exclude the disease, because half of all new cases represent new, sporadic mutations. Patients with NF1 have an average life expectancy shortened by at least 10 to 15 years, with a mean age at death of 61.6 years. Malignancy is the leading cause of death, but causes of death in general follow age-related trends. In childhood, death most commonly results from intracranial tumours, followed by malignant peripheral nerve sheath tumours, leukemia, embryonal tumours, or the spread of plexiform neuro-

fibromas to surrounding vital structures. In the adults the most common cause of death is malignant peripheral nerve sheath tumours or soft tissue sarcomas, vasculopathy, acute hydrocephalus or complications from hypertension.<sup>3,4</sup>

Several studies have estimated the frequency of malignancy in NF1 to be somewhere between 5% and 29%. Several authors have estimated the risk of malignancy in NF1 patients to be only approximately 5% above the general population risk. However others have questioned whether there is actually an increased frequency of malignancies in NF1.

In a recent study from Sweden, the risk incidence in these patients was approximately four times as high as that expected in the general population. Clinical malignant and benign tumours were found in as many as 25 of 70 NF1 patients (36%) during their lifetime. A relatively large number of pheochromocytomas (6%), sarcomas (7%) and carcinomas (16%) were found.<sup>5</sup>

In fact, colorectal cancer is rarely reported in patients with NF-1, where gastrointestinal involvement occurs in three principal forms i) hyperplasia of the submucosal and myenteric nerve plexuses and mucosal ganglioneuromatosis, which leads to disordered gut motility; ii) gastrointestinal stromal tumours showing varying degrees of neural or smooth muscle differentiation; and iii) a distinctive glandular, somatostatin-rich carcinoid in the periampullary region of the duodenum that contains psammoma bodies and may be associated with pheochromocytoma.

The above-mentioned Swedish study included two adenocarcinomas of the rectum, one of the transverse colon and one of the sigmoid colon. In another case a 73-year-old woman with NF1 who developed cancer of the colon, multiple tubulovillous adenomas and a polypoid ganglioneuroma has been reported by Shousha S and Smith PA<sup>6</sup>, as well as two cases of children with NF1 and cancer of the colon reported by Shearer P *et al*<sup>7</sup>, in addition to the case of a case of a 61-year-old man with von Recklinghausen disease who developed an adenocarcinoma at the right colonic flexure, reported by Kim.<sup>8</sup>

To our knowledge, there is only one previous report of multiple colorectal carcinomas and NF<sup>9</sup> This patient also had polyposis coli, as well as his younger brother who also suffered from NF and polyposis coli, and died from mediastinal T-cell lymphoma.

A small proportion of patients with colorectal carcinoma (CRC) have synchronous tumours at the time of diagnosis. A subset of sporadic CRCs display the

microsatellite instability (MSI) that is associated with MLH1 silencing due to promoter methylation. MSI characterises a unique clinical and pathologic phenotype, known as hereditary nonpolyposis colorectal cancer syndrome (HNPCC). In this case, an increased incidence of synchronous and metachronous tumours has been reported, but there are few reports with standardised criteria of MSI in HNPCC-associated tumours. The phenotype of hereditary nonpolyposis colorectal cancer includes an 80 percent lifetime risk of colorectal cancer, a predominance of lesions proximal to the splenic flexure, and a high incidence of synchronous and metachronous neoplasia. A subset of sporadic colorectal carcinomas show microsatellite instability, usually as a result of the biallelic hMLH1 gene promoter, methylation. Synchronous tumours occur in up to 5 percent of patients with colorectal cancer, but their cause is poorly understood. It is hypothesized that in the setting of sporadic microsatellite instability cancers, synchronicity may reflect a global predisposition of the colorectal epithelium to tumour development because of gene hypermethylation.<sup>10,11</sup>

The *NF1* gene was initially localized to the pericentromeric region of chromosome 17q by linkage analyses. The *NF1* gene is large, spanning roughly 350 kb of DNA, and it encodes a protein product with a molecular mass of about 300 kDa. Although germline mutations in the *NF1* gene are believed to underlie the development of the associated disease features in all or very nearly all NF1 patients, specific germline *NF1* mutations have been identified in about half to two-thirds of NF1 patients. Difficulties in identifying germline mutations in the *NF1* gene in the remaining NF1 patients may be due to the inherent inefficiencies and insensitivity associated with mutation detection strategies in such a large gene. In addition to germline *NF1* mutations in those with NF1, the *NF1* gene is affected by somatic mutations in a fraction of colon cancers, melanomas, neuroblastomas, and bone marrow cells from patients with the myelodysplastic syndrome. Consistent with its presumed tumour suppressor role, the mutations inactivate *NF1*. Like the *RBI*, *p53*, and *APC* genes, the *NF1* gene is expressed ubiquitously, so, as for other inherited cancer syndromes, the basis for the tissue-specificity of the malignant tumours seen in neurofibromatosis patients remains puzzling. The *NF1* protein product, termed neurofibromin, is a cytoplasmic protein with high similarity to GTPase activating proteins (GAPs). Perhaps the best studied GAP is Ras-GAP, which markedly enhances the GTPase activity of the wild-type K-Ras, H-Ras, and N-Ras proteins. Although the means through which *NF1* defects altered cell growth is not well understood, it is

likely that inactivation of neurofibromin function leads to alterations in signalling pathways regulated by small Ras-like G proteins.<sup>12,13</sup>

Because the *NF1* gene is a tumour suppressor gene and is involved in growth regulation, the progress of the disease and the risk of malignancy for the individual patient are of special interest. It seems that patients with NF1, compared with individuals in the general population, run a significantly higher risk of developing malignant tumours, including colorectal adenocarcinomas if the observation period is long enough.

The natural history of NF is such that, in any given affected individual, the signs and symptoms can be expected to worsen as the patient ages. In fact, as the development of malignant and benign tumours is part of the NF1 disease process, and cutaneous manifestations may precede or follow the manifestation of the internal malignancy. When such a lesion is detected, the individual should be put in a surveillance programme. Scrupulous investigation for associated neoplasia may be justified, and family counselling should be considered.

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