European Journal of Cancer, Vol. 34, No. 10, pp. 1639–1640, 1998

Printed in Great Britain
0959-8049/98/$—see front matter

PII: S0959-8049(98)00157-9

Does the Syndrome of Familial Medullary Thyroid Carcinoma Describe a Distinct Clinical Entity?

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MEDULLARY THYROID carcinoma (MTC) occurs in sporadic and hereditary forms. The hereditary form is autosomal dominant. The syndromes associated with the hereditary forms have been divided into familial MTC (FMTC), when MTC alone is present [1], MEN 2A when phaeochromocytomas and parathyroid hyperplasia are found with MTC, and MEN 2B when there are mucosal neuromas, altered facies, marfanoid habits, corneal nerve hypertrophy. Hirschsprung disease and other abnormalities are found in addition to MTC [2].

Germline point mutations of the *RET* proto-oncogene have been identified in the FMTC and MEN 2 syndromes [3]. In MEN 2A, mutations are present in one of five codons in exon 10 and exon 11 [4]. New mutations, involving codon 768 of exon 13 and codon 804 of exon 14, have recently been described [5–7]. A strong correlation exists between the specific positions of the *RET* mutations and the phenotype of the syndrome [8]. In FMTC, the *RET* mutations affect the same codon as in MEN 2A. Phenotypically, the syndrome of FMTC has been defined as MTC in a minimum of four members of a family without evidence of phaeochromocytoma or parathyroid disease in living affected or at risk individuals [3].

We encountered two families with alleged FMTC, but the occurrence of phaeochromocytoma in a member of one family led to a revision of the diagnosis for that family to MEN 2A. The particular member of the family had a phaeochromocytoma removed after the diagnosis of MTC was established (Figure 1). This family had been followed for 21 years, over four generations, since the proband had a thyroidectomy. 11 of 31 members of the family had histologically confirmed MTC. 6 members, who were positive for *RET* mutations, had not had any surgical treatment. 10 members had normal serum levels of calcitonin, and 4 had no mutations of the *RET* proto-oncogene. None of the members of this family have died of MTC. The examination of this family has been conducted mainly on an annual basis and includes: plasma calcitonin levels at 2 and 5 min after intravenous administration of pentagastrin plus calcium gluconate, a 24 h urine for vanillyl mandelic acid (VMA) by liquid chromatography, and norepinephrine, epinephrine and dopamine by high performance liquid chromatography (HPLC). Magnetic resonance imaging and ^{131}I-metaiodobenzylguanidine scintigraphy were performed when a phaeochromocytoma was suspected biochemically. Serum intact parathyroid hormone, ionised calcium, albumin and calcium were measures of parathyroid function. In the patient previously alluded to, a total thyroidectomy and modified neck dissection was performed in 1988 for MTC. Five years later, bilateral phaeochromocytomas were removed. An attempt was made to detect mutations in the *RET* proto-oncogene by digesting polymerase chain reaction products containing the mutated

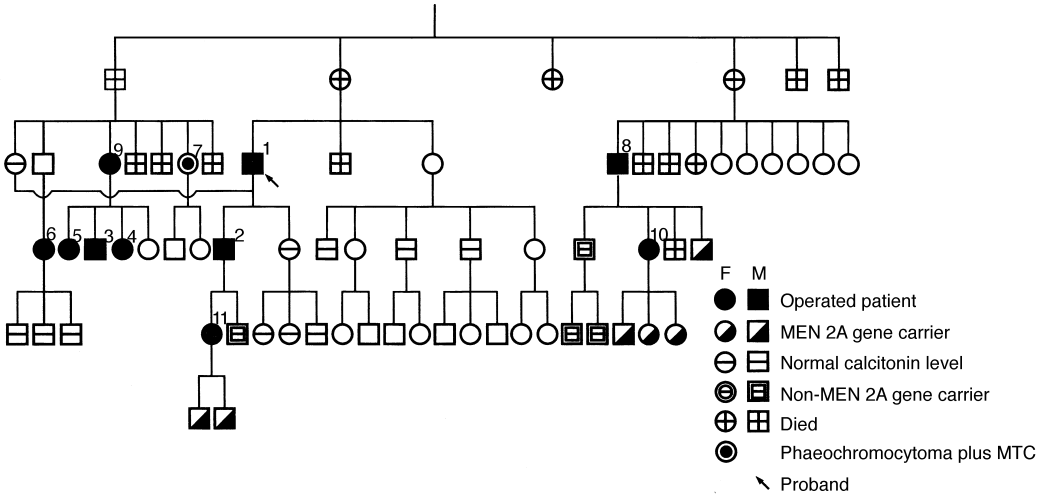

Figure 1. Pedigree of the family with medullary thyroid carcinoma (MTC) investigated, showing family members affected and unaffected by MTC and the disease gene carrier state as assessed by DNA analysis.

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Received 17 Feb. 1998; accepted 4 Mar. 1998.

codons with restriction enzymes for cleavage sites produced by the specific genetic alteration [9]. A mutation was found in exon 10, which alters codon 618 from TGC (Cys) to GAC (Ser). Cysteine codon 618 is associated with a milder course and less frequent involvement of the adrenal and parathyroid glands [3, 10].

Our findings raise the question of whether the separation of FMTC as a separate syndrome is warranted. It appears from our one example that the longer a family with presumed FMTC is followed, the greater the chance for the development of a phaeochromocytoma or parathyroid hyperplasia. The syndrome of FMTC appears to need a better definition to include the number of families that need to be examined, the length of the follow-up, the frequency of the follow-up examinations, and the screening methods for phaeochromocytomas and parathyroid hyperplasia. One alternative is to eliminate the designation and substitute in its place the use of FMTC and MEN 2A syndromes by their specific mutations.

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European Journal of Cancer, Vol. 34, No. 10, pp. 1640–1641, 1998

Printed in Great Britain
0959-8049/98/$—see front matter

PII: S0959-8049(98)00145-2

Gastric, Duodenal and Rectal Multifocal Malt Lymphoma: the Possible Co-existence of Two Different Cell Populations

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In the last few years several studies have reported regression of gastro-intestinal MALT lymphomas after anti-*Helicobacter pylori* therapy [1–4]. In this regard, the regression of intestinal MALT lymphomas originating outside the stomach is particularly interesting, suggesting that the association between *H. pylori* and MALT lymphoma might not be limited to the stomach [5–7]. In this letter, we report a case of multifocal MALT lymphoma, in which the co-existence of two different cell populations is possible, and the role of *H. pylori* infection seems to represent an important, but not the sole, pathogenetic event.

A 56-year-old male was found to be affected by concurrent gastric, duodenal and rectal low-grade MALT lymphoma. Despite a high serum titre of anti-*H. pylori* antibodies, routine sections of gastric, duodenal and rectal biopsies did not show the presence of *H. pylori*, and six courses of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) were administered. Complete regression in the rectum and partial regression in the stomach and duodenum were achieved. However, the serum titre of anti-*H. pylori* antibodies increased after chemotherapy, and restaging gastric biopsies showed the presence of *H. pylori*, suggesting that the number of histological samples examined at the time of the diagnosis was probably inadequate. Eradication treatment consisting of Omeprazole, Clarithromycin and Tynidazole was administered for 7 days. *H. pylori* was eradicated and complete remission was endoscopically and histologically documented after 2 months. Twenty-eight weeks later, rectal, gastric and duodenal relapse was observed. Multiple biopsies taken from the gastric fundus, body and antrum excluded *H. pylori* recurrence, and the serum titre of anti-*H. pylori* antibodies was lower than that of previous assays. The patient was treated with chlorambucil and, at present, is clinically well.

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Received 24 Nov. 1997; revised 25 Feb. 1998; accepted 25 Mar. 1998.