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LETTER TO THE EDITORS

Cesare Bordi · Maria Luisa Brandi

Ductal adenocarcinoma of the pancreas in MEN-1-patients

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Sirs:
In 1995 we published a typical case of MEN-1 syndrome in which the terminal event was the development of a nonendocrine ductal adenocarcinoma of the pancreas [2]; there was one previous case [9]. Since publication of our paper, we have become aware of two other similar cases, included as case no. 9 in a study of pancreatic endocrine tumours from 14 MEN-1 patients [10] and as patient FW in a series of seven hypergastrinaemic patients [11]. Recently, we have also been informed of a fifth case of this unusual association (G.L. Thomson, personal communication).

Analysis of these five patients shows that four of them were female, a finding at variance with the 2:1 male-to-female ratio reported for pancreatic adenocarcinoma [4]. The age at diagnosis of the pancreatic ductal adenocarcinoma ranged from 32 to 68 years (mean 49.8 years), which is considerably lower then the usual age at onset of pancreatic carcinoma, which is in the seventh and eighth decades [4]. The associated endocrine disorders were heterogeneous: Zollinger-Ellison syndrome in two cases [2, 11], Cushing's syndrome associated with hyperprolactinaemia and hypoglycaemia [9], PP hypersecretion [10], and hyperprolactinaemia with galactorrhoea (Dr. Thomson's case).

Hyperparathyroidism was common to all these patients (no information available in one case [11]), usually showing moderate clinical expression that did not require surgical correction except in one case [10]. The tumours were localized in the pancreatic head in four cases [2, 9–11], with extension to the gastric body in one of them [9]. Multiple islet cell adenomas were found in three patients [2, 10, 11] whereas the report of the remaining two cases lacked the relevant information.

C. Bordi (✉)
Institute of Anatomic Pathology, University of Parma,
Via Gramsci 14, I-43100 Parma

M.L. Brandi
Department of Clinical Physiopathology, Endocrine Unit,
University of Florence, Florence, Italy

We believe that this record of, now, five cases of ductal adenocarcinomas of the pancreas associated with MEN-1 syndrome exceeds the possibility of a coincidental finding and suggests a pathogenetic link. The pathogenetic mechanism remains unknown. The younger age at diagnosis in these patients (32 years in one case [9]) than in patients with sporadic pancreatic adenocarcinomas suggests genetic influences.

The MEN-1 gene is a tumour suppressor gene located on chromosome 11q13 [7]. According to Knudson's two-hit model [6], tumour development in MEN-1 patients must depend on an inherited germ line mutation of the MEN-1 gene and on loss of function of the wild-type allele through chromosomal deletion (loss of heterozygosity, LOH) [3]. Such a mechanism is not restricted to MEN-1 endocrine tumours, having also been detected in nonendocrine tumours associated with the MEN-1 syndrome, such as lipomas [8]. However, LOH has not been found at 11q13 in the pancreatic ductal adenocarcinoma of the single case investigated so far [2]. In one case a rim of gastrin-immunoreactive cells was found surrounding the adenocarcinoma and was associated with slightly elevated gastrin release revealed by a positive gradient in effluent venous blood on selective portal sampling [10]. However, hypergastrinaemia was observed only in two cases [2], whereas no gastrin cells were found in peritumour tissue in another case [9]. These observations make against a gastrin-driven trophic mechanism for tumour development like that involved in ECL cell gastric carcinoids of MEN-1 patients [1]. It has been speculated that pancreatic ductal adenocarcinomas of MEN-1 patients may be examples of "reversed nesidioblastosis", with regression or dedifferentiation from islet cells to adenocarcinoma [10]. Evidence from experimental studies of BOP pancreatic carcinogenesis in hamsters [5] may support this hypothesis. These studies, in fact, have shown that pancreatic islets are critical for the carcinogenetic process and that the neoplastic ductal lesions leading to the development of adenocarcinomas have a close anatomical association with islet tissue.

For these reasons, we suggest that patients with MEN-1 syndrome have an increased risk of developing ductal adenocarcinoma of the pancreas and that this tumour may account for some of the "non-MEN-1 deaths" described in studies of large kindreds affected by MEN-1 syndrome [12].

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