Mixed adenocarcinoma and carcinoid tumour of the colon
A report of 4 cases with postulates on histogenesis

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Summary

Gastro-intestinal tumours which contain both mucinous and endocrine cells have been reported with increasing frequency recently. Four such mixed neoplasms of the colon are described. Macroscopically, the tumours caused muscular hypertrophy resulting in thickening of the wall of the bowel and annular stenosis of the lumen. Microscopic examination showed them to be poorly differentiated adenocarcinomas with a distinct carcinoid component. Both the mucinous and endocrine elements were demonstrated in metastatic deposits of the tumour, so confirming the malignant nature of each component. The neoplasms appear to represent a distinct clinicopathological entity associated with a poor prognosis. The histogenesis is postulated to be a range of neoplasms from pure adenocarcinoma through mixed tumours to pure carcinoids and small-cell undifferentiated carcinoma. Such mixed tumours could arise from neoplastic change of crypt-base stem cells.

Patients and methods

A retrospective study of 4 patients treated by colectomy for colonic neoplasms at Groote Schuur Hospital was undertaken. The colectomy specimens were submitted to the Department of Pathology for routine pathological assessment between 1971 and 1982. Tissues were fixed in 10% formal saline, were described macroscopically, and sampled for histology. Sections were stained with haematoxylin and eosin, Southgate's mucicarmine stain. Immunoperoxidase staining for muramidase (DAKO antibody code A099) using the peroxidase-antiperoxidase method of Sternberger was also performed on the paraffin-embedded material. Tissues were not available for electron microscopy.

Case reports

Case 1
A 62-year-old white woman was admitted to Groote Schuur Hospital with signs of intestinal obstruction. Laparotomy revealed a tumour sited at the hepatic flexure of the colon. Numerous peritoneal nodules of metastatic tumour were also present. A right hemicolectomy was performed. The patient died of malignant disease 2 months later.

Case 2
A 66-year-old coloured woman was admitted in shock from acute peritonitis. A laparotomy showed a perforated caecum and an obstructive tumour of the ascending colon. A right hemicolectomy was performed. The patient died of malignant disease 7½ months later.

Case 3
A 70-year-old white man presented with an obstructive lesion of the rectosigmoid region of the large bowel. The involved segment of bowel was resected but a faecal fistula developed and the patient died of septicaemia 3½ months later.

Case 4
A 20-year-old coloured woman underwent laparotomy to remove a tumour involving the sigmoid colon. Death due to recurrent intestinal obstruction occurred 15 months after the initial operation. Permission for autopsy was refused in all 4 cases.

Pathological findings

The pathological features of all 4 tumours were essentially similar. Macroscopically, all were annular constricting tumours associated with hypertrophy of the muscularis and intestinal obstruction. The tumours extended over 8 - 9 cm lengths of bowel in contrast with the more usual short 'napkin-ring' type of carcinoma (Fig. 1).

Microscopically, all neoplasms arose in the mucosa and were ulcerated. Marked fibrosis of the submucosa and hypertrophy of the muscularis were seen. The neoplasms infiltrated through the muscularis diffusely (Fig. 2). All neoplasms showed the features of...
poorly differentiated adenocarcinoma with formation of irregular glands and acini, columns and strands of cells and individual cells (Fig. 2). Mucicarmine stains were all positive. Areas with a growth pattern resembling insular and trabecular carcinoid tumour were noted in all tumours. These areas maintained the marked cytological atypia seen in the adenocarcinomatous areas. One tumour contained argentaffin-positive cells arranged in nests (Fig. 3), 2 contained argentaffin-positive cells arranged in trabeculae (Fig. 4) and the fourth contained argyrophilic cells and also intracytoplasmic vacuoles of mucin resembling 'goblet cell carcinoid'. In each tumour neoplastic cells stained positively for muramidase; the degree of positivity varied but was strong in 3 neoplasms and weak in 1. Invasion of thin-walled blood vessels and perineural infiltration were noted in all cases. All cases showed metastatic tumour in regional lymph nodes. Both mucin-positive and argyrophil-positive cells were present in the metastases confirming the malignant nature of both elements.

Discussion

Four cases of a distinct variant of colonic carcinoma, which contains both adenocarcinomatous and endocrine components that has been recognised only recently in pathology literature have been described. All patients presented with intestinal obstruction and advanced disease. Despite this, their rapid death appears to indicate a highly aggressive neoplasm with a poor prognosis. The aggressive nature of this neoplasm in appendix 3.14 and stomach has been emphasised. Study of a larger number of colonic neoplasms is necessary to confirm our observation. Common macroscopic features include long segment annular constricting neoplasms associated with hypertrophy of the muscularis and diffuse infiltration of the bowel wall. Histologically these neoplasms exhibited evidence of dual differentiation, containing poorly differentiated adenocarcinoma and endocrine elements. The presence of both cell types in the metastases confirmed the malignant nature of both cell lines. Microscopic features of high invasive potential included invasion of blood vessels and perineural infiltration.

This distinctive neoplasm is of considerable interest histogenetically. Traditionally, adenocarcinomas were considered to be derived from endodermal cells whereas endocrine tumours were thought to originate from amine precursor uptake and decarboxylation cells arising from the neural crest. The presence of both cell lines in the same neoplasm supports the more recent view that both mucinous and endocrine cells arise from common endodermal stem cells. The contention that these mixed tumours represent population of an adenocarcinoma by hyperplasia and entrapment of normal endocrine cells is dispelled by the presence of both mucinous and endocrine cells in the metastases.

Recent experimental work suggests an endodermal origin for these combination neoplasms. Thus Cheng and Leblond, using endodermal stem cells from the crypt base labelled with tritiated thymidine, showed differentiation into four different cell types including columnar villous cells, goblet cells, entero-
endocrine cells and Paneth's cells. Further, Isaacson\textsuperscript{7} has reported that muramidase is a characteristic immunological marker of crypt stem cells. He demonstrated positive staining of goblet cell carcinoids of the appendix for this enzyme and concluded that this mixed neoplasm is of endodermal stem cell origin. The presence of muramidase in the neoplastic cells of the 4 tumours reported here lends support to Isaacson's hypothesis.

Alternative explanations for the histogenesis of intestinal mixed tumours have been proposed. Kubo and Watanabe\textsuperscript{20} postulated transformation of a primary mucinous malignant clone of cells into a clone of endocrine cells. However, this hypothesis does not explain the presence within individual neoplastic cells of both mucin and neurosecretory granules and features of cells containing both mucin and features of Paneth's cells. Warner and Seo\textsuperscript{8} proposed the possibility of hybridisation of neoplastic mucinous and endocrine cell lines to form a hybrid tumour. Alternatively, Hernandes and Reid\textsuperscript{4} suggested that derepression of appropriate genes could explain the presence of cells with dual mucinous and endocrine features. Of added histogenetic interest is the report of a neoplasm with tripartite differentiation,\textsuperscript{10} containing cells exhibiting intracytoplasmic mucin, dense core granules and tonofilaments associated with desmosomes said to be indicative of squamous differentiation. However, the small cell undifferentiated carcinoma of the intestine contains both neurosecretory granules and desmosomes with tonofilaments.\textsuperscript{2,11} This neoplasm may occur as a composite tumour with adenocarcinoma.\textsuperscript{21} A logical explanation of this array of mixed neoplasms and the experimental data is that these mixed neoplasms are derived from endodermal stem cells present in the crypt base. Stem cells have the potential to differentiate along multiple cell lines depending upon expression of the relevant genes governing specific cellular characteristics. This hypothesis is illustrated in Fig. 5.

**REFERENCES**