MULTIPLE PRIMARY CANCERS: PRIMARY MALIGNANT LYMPHOMAS AND CARCINOMAS OF THE INTESTINAL TRACT IN THE SAME PATIENT

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Three cases of primary malignant lymphoma and primary mucus-secreting adenocarcinoma of the intestinal tract, occurring in the same patients, are described, and three similar cases reported in the literature are discussed. The carcinomas were present at the same time as the lymphomas, or developed after the lymphomas had been removed. The relationship between malignant lymphoma and carcinoma is uncertain, but there is some evidence to suggest a possible relationship between them. It is important not to assume that a second growth in the intestinal tract is always a recurrence or a metastasis from the original primary tumour.

Since Whipple first described a case of splenic leukaemia and carcinoma of the pancreas in 1878 and Billroth multiple primary cancers of the breast in 1879, multiple primary tumours, benign and malignant, have become a well-recognized and accepted phenomenon. The majority of multiple primary malignant tumours are carcinomas, and they tend to occur more commonly in the same organ, or in paired organs, than in different organs of the body (Slaughter, 1944). Most of the recorded cases are of carcinomas of the skin, colon, stomach, and breasts. If one excludes such diffuse lesions as leukaemia and malignant lymphoma, multiple primary sarcomas are uncommon, the best-recognized examples being the multiple neurogenic sarcomas of von Recklinghausen's disease and liposarcomas.

Carcinoma and sarcoma occurring in the same patient have been reported more frequently than multiple primary sarcomas, and most of these were carcinoma with leukaemia or malignant lymphoma. Moertel and Hagedorn (1957) described 120 such cases seen at the Mayo Clinic, and reviewed 194 similar cases collected from the literature. Weitzel (1958), reporting a further 29 cases seen at the Mallory Institute of Pathology, noted a special relationship between carcinoma and malignant disorders of plasma cells. Many recorded cases were carcinomas of the skin or gastro-intestinal tract, with lymphosarcoma or chronic lymphatic leukaemia. The lymphosarcomas were usually con-

fined to lymph nodes at some distance from the carcinomas and were quite separate from them.

Primary malignant lymphoma and carcinoma, both situated in the intestinal tract of the same patient, is an unusual finding. Kreibitz (1929) described the simultaneous occurrence of a lymphocytic lymphosarcoma of the terminal ileum in a 64-year-old man, with an adenocarcinoma of the caecum. The two tumours were quite separate, both had penetrated the muscle coats, and the lymphosarcoma had spread to the lymph nodes draining the terminal ileum. Cattell and Boehme (1947) described the simultaneous occurrence of a reticulum cell sarcoma of the caecum and an adenocarcinoma of the rectum in a woman aged 26 years. Warren (1959) described the simultaneous occurrence in a man of a primary malignant lymphoma of the rectosigmoid with an adenocarcinoma of the splenic flexure.

In a recent study of 38 cases of apparently primary malignant lymphomas of the small and large intestines, seen at St. Mark's, the Gordon, and Westminster Hospitals, London (Dawson, Cornes, and Morson, 1960), there were three cases of primary malignant lymphoma and carcinoma of the intestinal tract occurring in the same patients.

Case Reports

Case 1.—Mr. D. J., aged 63, first seen in November, 1946, complained of tenesmus, rectal bleeding, and slight weight loss. On examination a hard, friable,

FIG. 1.—Case 1: Large lymphosarcoma lower third of rectum. Small carcinoma below lymphosarcoma, at the ano-rectal junction. Adenomatous polyp at recto-sigmoid junction.

ulcerating tumour was found in the rectum. There was no palpable lymphadenopathy, and a chest radiograph was normal. The haemoglobin was 16.6 g.%, and the white blood cells 8,500 per c.mm. An abdomino-perineal excision of the rectum was performed. At operation the liver and spleen appeared normal, and no enlarged lymph nodes were found. The patient made a quick

FIG. 2.—Case 1: Primary lymphocytic lymphosarcoma of rectum. Haematoxylin and eosin ($\times 250$).

recovery from the operation, and was then given a course of deep x-ray therapy. He died one year after the operation from uraemia, due to urinary obstruction caused by an enlarged prostate. There was no clinical evidence of recurrence of the tumours found in the rectum.

In the lower third of the excised rectum there was a large, protuberant growth, 8 cm. in diameter, almost completely encircling the bowel (Fig. 1). The overlying mucosa was ulcerated, and, on sectioning, the tumour was dark purple and fleshy in consistency. The tumour breached the muscle coats and infiltrated the surrounding perirectal fat. Just beneath this large tumour mass there was a second, smaller tumour, which on sectioning was seen to consist of numerous, small, cystic spaces, filled with mucus. A pedunculated polyp was present at the rectosigmoid junction, and the superior haemorrhoidal lymph nodes were slightly enlarged. Sections taken for histology showed a benign, adenomatous polyp of the rectosigmoid, a lymphosarcoma of the rectum, and a mucus-secreting adenocarcinoma of the rectum. The regional lymph nodes were free of growth. The large tumour mass was composed of small, round cells, with round, hyperchromatic nuclei, and scanty cytoplasm (Fig. 2). The muscle coats appeared to be eaten away by this tumour mass, and the lack of any surrounding fibrous reaction was striking. The appearances were

FIG. 3.—Case 1: Well-differentiated adenocarcinoma of rectum. Haematoxylin and eosin ($\times 250$).

those of a lymphocytic lymphosarcoma. The small tumour nodule was composed of large acini filled with mucus and lined by mucus-secreting columnar epithelium (Fig. 3). Although touching each other in the perirectal fat, the two tumours were quite discrete, and there was no invasion of one tumour by the other.

Case 2.—Mr. A. B., aged 52, first seen in April, 1946, complained of colicky abdominal pain, vomiting, and anorexia, for 10 days. On examination the abdomen was distended, but no other abnormality was found. The haemoglobin was 14.0 g.%, and the white blood cells 3,700 per c.mm. (84% neutrophils, 1% basophils, 1% eosinophils, 9% lymphocytes, and 5% monocytes). A chest radiograph was normal, and a plain radiograph of the abdomen showed the appearances of a small bowel obstruction somewhere in the lower ileum. A laparotomy was performed, and an area of thickening, 8 cm. long, was found in the terminal ileum. A diagnosis of regional ileitis was made, and the involved area was by-passed by a side-to-side ileo-ileal anastomosis. Two weeks later a second laparotomy was performed and the isolated loop of bowel was excised.

This operation specimen consisted of 21 cm. of ileum. In the area of growth the bowel wall was thickened, and the lumen grossly narrowed. On sectioning, the tumour was white and could be seen growing right through the muscle coats into the mesenteric fat. The overlying mucosa was intact. Sections taken for histology showed a lymphosarcoma. The histological appearances were

similar to the lymphocytic lymphosarcoma of the first case (Fig. 4).

Following a course of deep x-ray therapy the patient remained in good health for 18 months, when he began to complain of colicky abdominal pain, vomiting, and constipation. A laparotomy was performed, and a stricture was found in the sigmoid colon. This stricture was resected, but the patient died four days later from a paralytic ileus. A necropsy was performed.

The operation specimen showed an adenocarcinoma of the sigmoid colon, completely encircling the lumen of the bowel. The tumour breached the muscle coats, and was infiltrating the surrounding pericolic fat. Microscopy showed a moderately well-differentiated adenocarcinoma penetrating the muscle coats and invading the local lymphatics (Fig. 5). At necropsy no tumour deposits of lymphosarcoma or carcinoma were found.

Case 3.—Mr. D. C., aged 52, first seen in November, 1955, complained of periodic attacks of abdominal pain after a gunshot wound of the abdomen in 1942. The pains became progressively more severe and generalized, and he developed anorexia and lost weight. On examination the abdomen was tender, there was no palpable abdominal mass, and no palpable superficial lymphadenopathy. The haemoglobin was 7.4 g.%, and the white blood cells 8,000 per c.mm., with a normal differential count. A chest radiograph was normal, and a barium meal with follow-through showed a stricture in the

FIG. 4.—Case 2: Primary lymphocytic lymphosarcoma of terminal ileum. Note the punched-out appearance of the muscle coats and the absence of any fibrous reaction. Haematoxylin and eosin ($\times 120$).

ascending colon, multiple metallic fragments in the right iliac fossa, and stones in the gall-bladder. At laparotomy, in January, 1958, a large mass was found in the ascending colon, with the terminal ileum adherent to it in two places. The ileo-caecal lymph nodes were enlarged, but no other enlarged nodes were found at laparotomy, and the liver and spleen appeared normal. A right hemicolectomy was performed.

The operation specimen consisted of 25 cm. of terminal ileum and 21 cm. of caecum and ascending colon. The tumour mass in the ascending colon extended along the bowel for a distance of 13 cm. On sectioning, the tumour could be seen growing right through the bowel wall into the pericolic fat and mesentery, and at two sites the tumour was infiltrating the adjacent terminal ileum. Sections from the tumour mass showed a reticulum cell sarcoma. The cells were large and pleomorphic, with abundant pale-staining cytoplasm and large oval nuclei (Fig. 6). Silver stains demonstrated an abundant reticulin network amongst the tumour cells. The regional lymph nodes were free of growth.

Following a course of deep x-ray therapy the patient remained in good health for nine months, when he began to complain of passing blood and mucus per rectum. Sigmoidoscopy revealed multiple tumours and several small polyps in the rectum and sigmoid colon. An abdomino-perineal excision of the rectum, with removal of the sigmoid and part of the descending colon, was performed, and three months later the patient was alive and well.

The operation specimen was 30 cm. long. Numerous, small, sessile polyps were present throughout the rectum and sigmoid colon. Two large pedunculated polyps and three obviously malignant growths were also present (Fig. 7). The malignant growths were situated at 5, 13, and 20 cm. respectively from the ano-rectal junction. Microscopy showed all the tumours to be mucus-secreting adenocarcinomas, the two lowermost growths arising in villous papillomas. In addition, one of the pedunculated polyps had undergone a malignant change, and the stalk and adjacent submucosa were invaded by growth. The tumour at 5 cm. had invaded the submucosa

FIG. 5

FIG. 5.—Case 2: Moderately well-differentiated adenocarcinoma of sigmoid colon. Haematoxylin and eosin ($\times 120$).

FIG. 6.—Case 3: Primary reticulum cell sarcoma of ascending colon. Haematoxylin and eosin ($\times 650$).

FIG. 6

Fig. 7.—Case 3: Multiple carcinomas of rectum and sigmoid colon.

only, but those at 13 and 20 cm. had breached the muscle coats. The neighbouring lymph nodes were invaded by adenocarcinoma, but the more distant lymph nodes were free of growth.

Discussion

Primary malignant lymphomas of the intestinal tract are frequently multiple, and in the series of 38 cases reported by Dawson *et al.* (1960) there were eight cases of this type. The occurrence of malignant lymphoma and adenocarcinoma of the intestinal tract in the same patient, on three occa-

sions, is, however, a most unusual and remarkable finding. Clinically the lymphomas appeared to be primary in the intestines, because there was no palpable lymphadenopathy, chest radiographs showed no obvious mediastinal glandular enlargement, and repeated blood counts excluded the possibility of leukaemia. At laparotomy, the liver and spleen appeared normal in all cases, and the only lymph nodes obviously involved were those in the immediate neighbourhood of the bowel tumours. Post-operatively none of these three cases developed a generalized lymphoma or leukaemia, and in the second case a necropsy showed no tumour anywhere else in the body. In all cases the lymphomas penetrated the muscle coats and infiltrated the surrounding fat, a feature regarded by Stout (1955) as an important feature of primary malignant lymphomas in the gut. The carcinomas were all mucus-secreting, and were readily distinguished from the malignant lymphomas.

In the cases described by Cattell and Boehme (1947) and Warren (1959), the malignant lymphomas and carcinomas occurred in cases of long-standing ulcerative colitis. Carcinoma is a well-recognized complication of chronic ulcerative colitis (Dawson and Pryse-Davies, 1959), but lymphosarcoma complicating this disease has been less frequently described (Cornes, Smith, and Southwood, 1960).

No significant relationship between malignant lymphoma and carcinoma has yet been established. Moertel and Hagedorn (1957), describing 68 cases seen at the Mayo Clinic, concluded that the presence of a malignant lymphoma did not seem to predispose to the development of any other specific type of primary malignancy, and that the incidence of another primary malignant lesion in patients with a malignant lymphoma only slightly exceeded that in any other segment of the general population of similar age. Tissue culture studies and animal inoculation experiments offer some suggestion of a relationship between malignant lymphoma and carcinoma. In tissue cultures, the lymphocyte is the only cell to be attracted to areas of mitosis, is the only motile cell to attach itself to other cells for long periods of time, easily enters and leaves malignant cells, and can wander freely about inside their cytoplasm (Pulvertaft, 1959). Salaman (1959), using cell-free filtrates of mouse leukaemic tissue injected subcutaneously into newborn mice, produced 40 tumours in 15 out of 23 inoculated mice which survived for three months or more. Twenty-six of these were carcinomas, and no case of leukaemia was found. It is interesting to note that of the three present cases, and the three cases reported

in the literature, there was no case of carcinoma preceding the lymphoma. In four cases the tumours were synchronous, and in two cases metachronous, the carcinomas following the lymphomas within 18 months.

The finding of a second primary cancer in the intestinal tract is of considerable clinical importance, since the results of surgical removal of primary malignant lymphomas of the gut are most encouraging, and the prognosis for carcinomas of the colon and rectum, if removed early enough, is equally encouraging. It is therefore most important to have an adequate clinical follow-up in all cases, and not to be too ready to assume that a second growth in the intestinal tract is a recurrence or a metastasis from the original primary tumour.

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