TRIPLE PRIMARY MALIGNANCY

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The occurrence of more than two primary malignant neoplasms in the same person has long been recognized as rare. Drooker (1), on analyzing the figures reported in the excellent review by Warren and Gates (2), states that multiple cancer constitutes 1.84 per cent of autopsied cases of malignancy, of which triple carcinomas comprise 2.9 per cent. In round figures, approximately one in two thousand cancer autopsies, or in twenty thousand routine autopsies, reveals more than two primary malignant lesions.

In 1879 Billroth, reporting the earliest recognized cases of true multiple malignancy, postulated that each tumor must have a different histologic appearance, must arise in a different location, and must produce its own metastases. Mercanton, in 1893, added that there must be no reappearance on removal. In the numerous case reports and several general reviews that have appeared since, notably the contribution of Seecoff (19), these criteria have been discarded as too strict in that they would exclude early cancer of such characteristically non-metastasizing or late metastasizing types as basal-cell carcinomata or adenocarcinomata of the uterine fundus. Warren and Gates (2) emphasized that each tumor must afford a picture of malignancy, each must be distinct, and the probability of one being a metastasis of the other must be ruled out. They criticize many records of supposedly multiple malignant tumors, especially on this last score. For example, it is at present conceded that in bilateral breast cancers, the probability of metastasis to one breast from the other is very strong. Similarly we now recognize that many cases of coincident gastric and ovarian or multiple ovarian tumors may very well come under the category of metastases. In view of the newer concepts of the range of cellular anaplasia and metaplasia, numerous so-called carcinosarcomas, especially when of the same organ, may also be open to question. Moreover, lesions which ordinarily are either multiple or multicentric, as myelomas or certain hepatic carcinomas, are not usually to be included as multiple malignancies. Reasonably practical rules for establishing true multiplicity of new growths were formulated by Goetze (3). He suggested that the macroscopic and microscopic appearance of the tumors must be that of the usual carcinomas of the organs involved. To this he added that exclusion of metastasis must be certain, constituting the very crux of the problem, and that diagnosis might be confirmed by the character of metastasis in each case.

The incidence of the various combinations of multiple malignancy varies as reported by different writers. In a recent review, Schreiner and Wehr (4), describing more than eleven thousand cases over a twenty-year period, found, in part substantiating the previous work of Owen (5), that the most common primary multiple cancer was the basal-cell epithelioma of the skin, with
squamous-cell epidermoid skin carcinoma next in frequency. Tumors of the mucous membranes of the oral cavity associated with malignant lesions of the skin came third. Collins (31) points out that the accessibility of even multiple cutaneous cancers to successful therapy means that the majority of patients survive. It is for this reason that the cases go unreported in pathological protocols. Hurt and Broders (6) believe that multiple primary malignant neoplasms occur most frequently in the same organ or organ system, thus, in agreement with most authors, denying the conclusion of Abell (7), who stated that multiple malignant tumors have no predilection, excluding paired organs, for organs of the same system, but appear more commonly in unrelated structures.

Warren and Gates (2) acknowledge that coexistent antecedent skin carcinomata may not have received adequate representation in the literature. They list, however, the large intestine, breast, skin, stomach, and pharynx as involved by double carcinoma in approximately that order of frequency. Among combinations of different organ systems affected, the gastro-intestinal and genito-urinary tracts come first. Despite the supposed rarity of coexistent carcinoma of the female breast and genital organs, genito-urinary and gastro-intestinal cancers in association with mammary carcinoma are next in frequency, in approximately equal numbers.

Kretschmer reiterates the fact that case reports of coincident primary gastric and ovarian neoplasms must be scrutinized critically because of the predilection of cancers of the stomach and intestine to metastasize to the ovary, frequently with an alteration in histopathology, as is characteristic of the Krukenberg tumor. It must be remembered that multiple cancers of the colon, particularly in association with polyposis or adenomatosis of that organ, constitute roughly 5 per cent of malignant lesions of the large bowel. The group of multiple tumors under discussion is quite distinct from this more common clinical entity.

Bugher (8), after a thorough statistical analysis, concluded that the incidence of multiple malignant neoplasms is equal to or greater than may be expected from chance alone. This finding is concurred in by Burke (9) and Warren and Gates (2), who accept it as indicating the existence of a cancer dyscrasia or predisposition in a proportion of the general population as yet undetermined. Interestingly enough, Williams (10) as far back as 1908 made the same observation. As further proof of this, Warren and Gates point out that there is no significant difference in the age of female patients with one, two, or three cancers, and that the average duration of life in patients with multiple cancers is less than a year longer than the two-year average for a single malignant growth. Certainly, as appears to have been shown, multiplicity of cancers must be due to a factor other than a prolonged time interval during which additional tumors may make their appearance. The opposing contention of Hanlon (3), however, that patients with multiple malignant growths are generally several years older than those dying with a single new growth, somewhat confuses the issue.

Stalker et al (25), reporting the experience at the Mayo Clinic, state that 26.6 per cent of patients with multiple lesions have a family history of cancer.
It is noteworthy, also, that in more than a quarter of the cases there was a five-year interval between the observed occurrence of the first and second tumor. In additional reference to the bearing of hereditary diathesis or predisposition on the problem of cancer, Stalker cites the findings of McFarland and Meade (26), who collected reports of twenty cases of identical tumors occurring simultaneously in the same organs of identical twins. It has been assumed that within such a group one deals with truly comparable genetic constitutions. We have, however, been puzzled by one apparent paradox. Such relatively common multicentric lesions as lymphosarcoma or multiple myeloma, if they bespeak a marked individual susceptibility to the development of neoplasia, are almost never found in association with other cancers, even those as frequent as carcinoma of the breast, cervix, stomach, or large bowel.

The reviews mentioned above, the inclusive monographs of Ewing (11), Willis (12), and Stout (13), interesting isolated instances of triple or quadruple malignancy more recently reported by Portuondo (23), McNamara (20), Davis et al (21), Kulikowski and Hoerner (22), Friedman and Golden (14), Mayo (15), Herly (16), and Kretschmer (18), and a painstaking search of the literature of the past half century fail to reveal the combination of primary malignant tumors to be presented here. Eisenstaedt (17), Markowitz and Huerta (24), Stalker et al (25), Drooker (28), Webb and Wynne (29), and Sweetser (30), have likewise described cases during the past decade. As only about 10 per cent of the examples of true triple malignancy, of which approximately 135 appear to have been described, do not include the more common multiple skin tumors, it is felt that the following case warrants recording among the fifteen or so in the literature.

**Case Report**

A seventy-year-old Jewish male was admitted to the Brooklyn Cancer Institute March 0, 1938. His chief complaint was a mass in the right thigh, of three months' duration. An attempt had been made elsewhere to remove this but failed because of the presence in the tumor of large blood vessels. Subsequently an unknown amount of radiation therapy had been given, with apparently no reduction in the size of the mass.

The patient was debilitated and had an enlarged heart and gallop rhythm. The abdomen was protuberant and flabby. In the left inguinal region was a matted collection of nodes and on the right side, just below Poupart's ligament, was an indurated mass about 6 cm. in diameter, involving the skin of the inner third of the thigh. On the surface of the mass was an old operative scar.

Before therapy could be instituted, signs of bronchopneumonia developed and the patient died, ten days after admission. The diagnosis, based on the anatomical and pathological findings, was as follows: papillary adenocarcinoma of the colon with obstruction, perforation into the mesentery, and localized abscess formation; a colonic polyp; lymphosarcoma (lymphoblastic type) of the right and left inguinal nodes and right thigh; clear-cell adenocarcinoma of the right kidney; acute purulent bronchopneumonia, acute tracheobronchial lymphadenitis, and anthracosis, but no pulmonary metastases; generalized arteriosclerosis with coronary and renal arteriolar sclerosis.

The mass in the right thigh was intimately adherent to the surrounding fatty tissue; it measured 14 × 11 × 5 cm., and weighed 350 grams. On section it was found to consist of multiple nodules of varying size, gray-white in color, fairly firm in consistency, and showing many areas in various stages of degeneration. The mass encroached upon the underlying muscle, apparently compressing it. No gross invasion of the femoral vessels was observed. The corresponding inguinal lymph nodes had an appearance similar to the
mass in the thigh. They were large, roughly 4 to 5 cm. in diameter, of soft consistency, discrete, and homogeneously gray on section. The pelvic colon and ileum were bound to each other by many fibrous bands. In the colon, 20 cm. from the anal orifice, was a firm mass 10 cm. in diameter, including adherent fat, omentum, and gut. On opening the gut the wall was found to be replaced in its entire circumference by an irregularly nodular, fairly firm, grayish-white mass extending through into the surrounding fatty tissue. The mucosa was absent, leaving a shallow ulcerated area with grayish tissue as its base over a
width of 4 cm. proximal to the lesion; the right lateral wall was the seat of three small, punched-out stercoral ulcers, averaging 0.5 cm. in diameter, and leading into a necrotic mass, roughly 6 cm. in diameter, in the mesenteric fatty tissue. Eight centimeters below the distal edge of the lesion was a polyp with a base 1.5 × 0.2 cm., and 2.5 cm. in length.

The cortex of the right kidney presented a grayish-red, soft, discrete nodule 1 cm. in diameter, bulging above the cut surface.

Microscopically the mass in the thigh (Fig. 1) was found to be composed of sheets of small cells with deeply staining nuclei identical with the type of cell in the inguinal nodes. These cells extended widely into the fatty tissue and among the voluntary muscle bundles, causing atrophy of the latter. Collections of hemosiderin-laden phagocytes were seen.

In the inguinal lymph nodes the normal follicular outline was completely destroyed. The entire node consisted of sheets of round or polygonal cells, with scanty pink cytoplasm, discrete outlines, and deeply staining round or irregular nuclei occupying almost the entire cell. Sheets and rows of these cells extended through the capsules of the nodes at many points and invaded the surrounding fibrous and fatty tissues. Large areas had undergone complete coagulation necrosis.

The kidney nodule (Fig. 2) was found on section to consist of sheets of rather well defined, large cells with a pale, clear cytoplasm and ovoid or irregular vesicular nuclei varying moderately in size. These cells were closely crowded together, but at several points reproduced a distinct tubular picture. Within the tumor were large dilated vascular spaces, the tumor cells at several points invading the lumina. The neoplasm extended into a pseudocapsule formed of adjacent compressed renal parenchyma. Several areas of partially organized hemorrhage contained numerous hemosiderin-laden phagocytes.

Sections through the nodular mass in the colon (Fig. 3) showed masses of neoplastic cells in papillary and pseudo-glandular arrangement. The individual cells were columnar, with poorly defined boundaries and nuclei varying considerably in size, shape, and staining qualities. The majority were vesicular, with prominent single or multiple nucleoli. Occasional regular mitotic figures were observed. The lumina of the pseudoglands were filled with a granular pink necrotic material. Masses of tumor cells extended through the gut wall and into the surrounding fatty tissue. There were a moderate desmoplastic reaction and a heavy cellular infiltrate consisting of plasma cells, lymphocytes, and polymorphonuclears.
Conclusion

A case is reported of a previously undescribed combination of coexistent triple primary malignant neoplasms. Each of the three lesions demonstrated the classical picture of a characteristic neoplasm of the structure involved, namely, lymphosarcoma of the right inguinal region, clear-cell adenocarcinoma of the right kidney, and papillary adenocarcinoma of the pelvic colon. No distant metastases to viscera were observed from any of the tumors, despite the clear-cut microscopic picture of malignancy and gross local invasiveness. A benign polyp of the colon and two lipomata of the forehead were present in the same patient.

Bibliography