

Case Report

Solitary Breast Metastasis: First Manifestation of an Occult Carcinoid of the Ileum

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Summary. A metastasis to the breast was the first manifestation of a clinically occult ileal carcinoid in a 53 year old woman. Modified radical mastectomy was performed after the breast neoplasm had been interpreted clinically and pathologically as a primary carcinoma. Permanent sections demonstrated the tumor to be composed of sheets of small uniform cells subdivided into lobules by delicate vascular septa. Silver impregnation revealed the presence of argentaffin cytoplasmic granules. This feature, with the added ultrastructural findings which showed pleomorphic neurosecretory-type granules within the cytoplasm of the tumor cells strongly suggested a metastasis to the breast from a midgut carcinoid. The subsequently performed barium study of the small bowel showed an infiltrating neoplastic lesion in the terminal ileum, which after surgical excision and histologic examination proved to be two typical argentaffin carcinoids with pleomorphic cytoplasmic granules. This report thus clearly demonstrates the importance of a combined light microscopic, histochemical and ultrastructural analysis of this breast neoplasm in order to establish its metastatic origin and to separate it from a primary carcinoma or a primary carcinoid of the breast.

Key words: Carcinoid – Argentaffin – Metastasis – Breast.

Introduction

Tumors metastatic to the breast are rare. The statement by Virchow (1863) that almost all organs which show a strong tendency to develop primary neoplasms are seldom the site of metastases, remains true for the breast. However, even though a breast tumor may appear to be a primary neoplasm, the possibility of a metastasis to the breast from a tumor localized elsewhere has to be considered. The most frequent secondary carcinoma found in the breast is a carcinoma

from the opposite breast (Sandison, 1959). Other recorded tumors metastatic to the breast include with decreasing frequency, malignant melanoma, lymphoma, bronchogenic, gastric, ovarian and renal carcinoma (Dawson, 1936; Charache, 1952; Sandison, 1959; Deeley, 1965; Hajdu, 1972; Pressman, 1973).

Metastatic carcinoid tumors to the breast are far less frequent than the tumors mentioned above; 6 definite cases have been reported. Primary tumors included 3 ileal, 1 appendiceal, 1 duodenal and 1 bronchial carcinoid (Zetzel and Scully, 1957; Chadoff, 1965; Hawley, 1966; Turner and Galager, 1969; Haagensen, 1971; Harrist and Kalisher, 1977). In 5 cases the breast metastasis presented as an isolated tumor and it was considered clinically and pathologically to be primary breast carcinoma. Mastectomy was performed in each instance. In fact, as demonstrated later, a primary carcinoid preceded the appearance of the breast metastasis in 4 cases for periods varying from 1 to 15 years, whereas in 1 case a carcinoid syndrome developed 2 years following mastectomy. In the 6th case numerous bilateral breast metastases were part of a terminal generalization of a carcinoid.

In this report, we describe a metastatic carcinoid to the breast which presented as an isolated mass and in which the correct diagnosis was made, following mastectomy, on permanent sections including silver impregnation and electron microscopy. These studies subsequently permitted the discovery of a clinically occult carcinoid of the terminal ileum.

Case Report

A 53 year old obese woman in apparent good health was admitted to the hospital because of a mass in the left breast. On palpation, a tumor measuring approximately 4×3 cm was found in the lower medial quadrant. No axillary lymph nodes were palpable. Mammography showed an irregular mass with poorly defined margins which was located deep in the lower medial quadrant of the left breast. No calcification was seen and the mass did not show hypervascularization. Chest films were negative and technetium 99-m methyl diphosphonate bone scan was normal as were all the routine laboratory tests. A fine needle aspiration biopsy was not conclusive because of insufficient material. Modified radical mastectomy was performed after a biopsy of the tumor was taken for frozen section. The diagnosis entered after examination of the frozen section was infiltrating carcinoma. The histologic aspect of the tumor was somewhat unusual, being composed of several nodules made up of sheets of small uniform cells. A portion of the biopsy was therefore processed for electron microscopy. Silver impregnation of the paraffin sections revealed that the tumor cells contained numerous argentaffin granules. This feature with the added electron microscopic findings strongly suggested a metastasis from a distant carcinoid rather than a primary breast tumor. It was then suggested that the primary neoplasm could be located in the midgut, where argentaffin carcinoids are most frequently observed.

The search for a primary midgut carcinoid was then initiated. Urinary 5-hydroxy indole-acetic acid assays were normal. Specifically questioned, the patient recalled that occasional periods of diarrhea had occurred over the past 10 years. X-ray study of the small bowel showed a polypoid tumor in the terminal ileum measuring approximately 1.5 cm in diameter which was located 4.5 cm from the ileo-coecal valve. Barium study of the large bowel was normal except for a rigidity of the wall of the caecum and part of the ascending colon due to the infiltrating neoplastic process in the terminal ileum. A scan of the liver and the spleen using colloid sulfur technetium 99-m was normal. $2\frac{1}{2}$ months following left mastectomy, ileo-colic resection was performed and two tumors were found in the terminal ileum. At exploration, the liver was free of metastases. The patient is in apparent good health 6 months after ileo-colic resection, and repeated urinary 5-hydroxy indole-acetic acid assays are normal.

Material and Methods

For light microscopy, tissue from the breast and ileal neoplasms was fixed in 10% neutral buffered formal, postfixed in Bouin's solution, then dehydrated and embedded in paraffin. Sections cut at 3–5 μm were stained with haematoxylin-phloxine-saffron (HPS), Masson's trichrome stain, Laidlaw's reticulin stain, Alcian Blue Periodic Acid-Schiff (AB-PAS) and were impregnated with both modified Grimelius argyrophil (Lack and Mercer, 1977) and Fontana Masson's argentaffin methods.

For electron microscopy, tissue samples of the tumors were cut into 1-mm³ fragments, fixed for 2 h in 3% glutaraldehyde buffered with 0.1 M phosphate buffer at pH 7.4, and postfixed for 1 h in 2% osmium tetroxide in the same buffer. The fragments were then dehydrated in graded acetones and embedded in Epon 812. Semi-thin sections were stained with toluidine blue, thin sections were double stained on copper grids with uranyl acetate and lead citrate and examined in a Philips 201 electron microscope.

Results

Breast Metastasis

a) Gross Appearance. The specimen contained a firm yellowish tumor measuring 2.5 cm in diameter with irregular stellate margins and central necrotic foci.

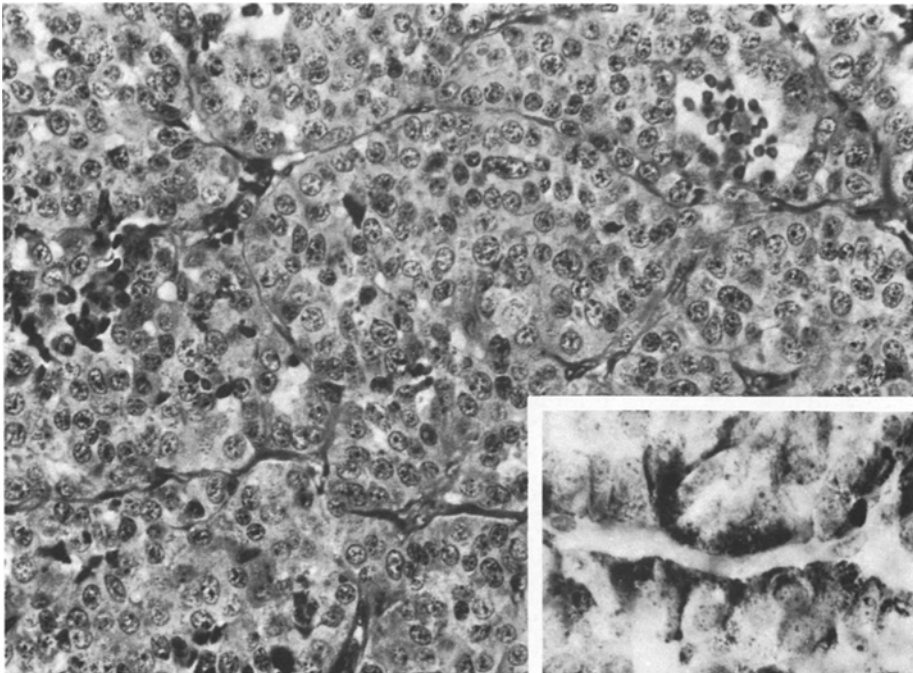


Fig. 1. Breast metastasis. Light micrograph showing small uniform tumor cells arranged in lobules separated by thin and delicate vascular septa. Several small foci of necrosis are present. The inset demonstrates numerous argentaffin granules within the cytoplasm of tumor cells. H.P.S., $\times 400$; Inset: Fontana-Masson's silver impregnation, $\times 600$

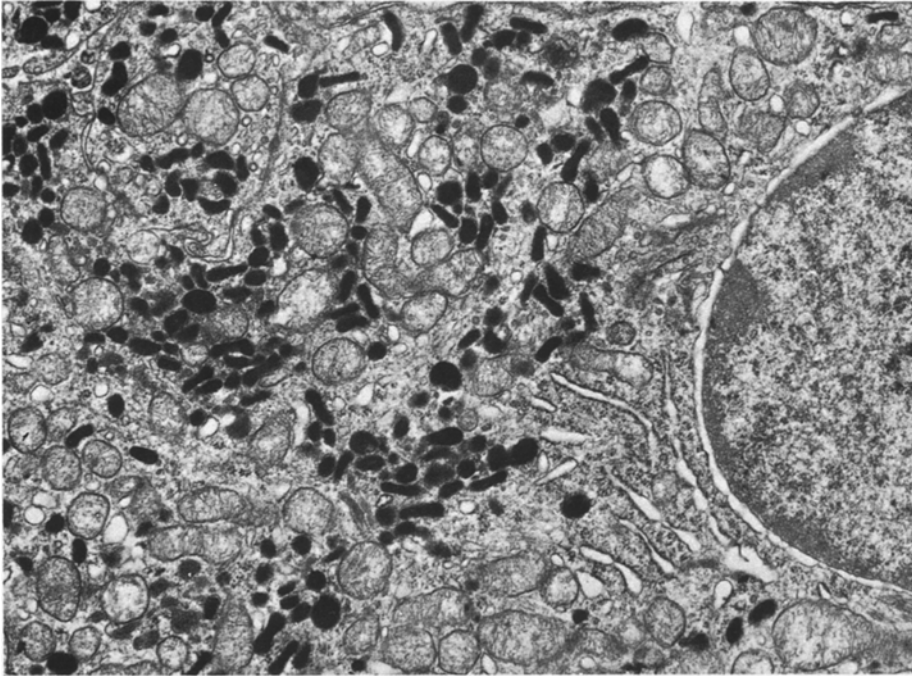


Fig. 2. Breast metastasis. Electron micrograph demonstrating numerous pleomorphic secretory granules (round, oval, rod-like, kidney-shaped and biconcave) within the cytoplasm of a tumor cell. The granules are separated from the limiting membrane by a clear halo. Uranyl acetate and lead citrate, $\times 16,500$

b) Light Microscopy. The tumor was composed of several nodules separated by large bands of dense connective tissue. The nodules were grouped around the fibrous center containing several areas of necrosis. They were made up of sheets of small uniform cells subdivided into small lobules by thin and delicate vascular septa (Fig. 1). At the periphery of the nodules an occasional ribbon or nest-like pattern was seen, while glandular or acinar differentiation and mucus production in AB-PAS stained section were absent. Mitotic figures were extremely rare. No intraductal or in situ carcinoma was found in the breast parenchyma surrounding the tumor and axillary lymph nodes were free of metastases.

Cytologic features of the neoplastic cells included small round or oval nuclei containing fine regularly dispersed chromatin and one or two small nucleoli. The cytoplasm was slightly eosinophilic and the cells were round or polyhedral in shape. When impregnated with silver nitrate using the modified Grimelius technique, the tumor cells contained abundant brown to black argyrophil granules. The subsequently performed Fontana-Masson reaction revealed the cytoplasmic granules to be also silver-salt reducing, i.e. argentaffin (Fig. 1, inset).

c) Electron Microscopy. The tumor cells were mostly polyhedral, presenting straight plasma membranes with a few interdigitations and numerous desmo-

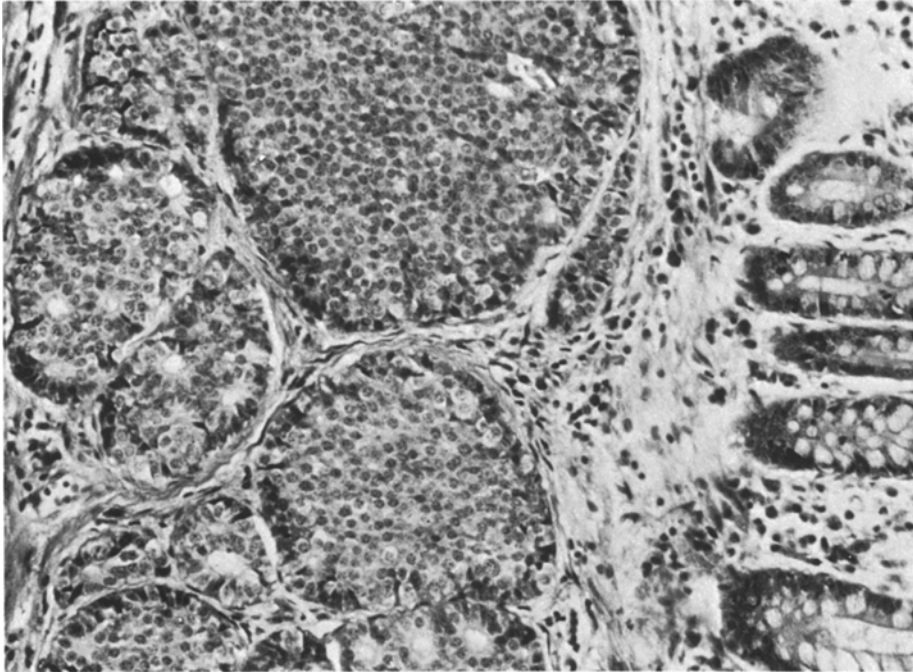


Fig. 3. Primary ileal carcinoid. Light micrograph which shows a typical carcinoid composed of nests of small uniform cells which frequently form glandular acini. H.P.S., $\times 240$

somes. No intra- or extracellular acini were found. Numerous dense-core neurosecretory granules were randomly distributed within the cytoplasm. The granules were pleomorphic (round, oval, kidney-shaped or biconcave) and measured from 120 to 450 nm in diameter. The central core of most granules was separated from the limiting membrane by a clear halo (Fig. 2).

Primary Ileal Carcinoid

a) Gross Appearance. The specimen consisted of a segment of terminal ileum in continuity with the cecum, the appendix and the ascending colon. Two tumors were found within the terminal ileum, one 0.5 cm from the ileo-cecal valve measuring 0.5×0.3 cm, the other 4.5 cm from the valve measuring 1.1×0.7 cm. The smaller tumor was localized mainly within the submucosa and bulged slightly into the lumen of the ileum. The larger was distinctly polypoid and infiltrated the muscularis, the serosa and the mesenteric adipose tissue. The cut surface of both tumors was yellowish.

b) Light Microscopy. Both tumors of the terminal ileum were typical carcinoids composed of nests of small regular cells separated by a delicate connective tissue framework. Frequently, acini were observed within the nests (Fig. 3).

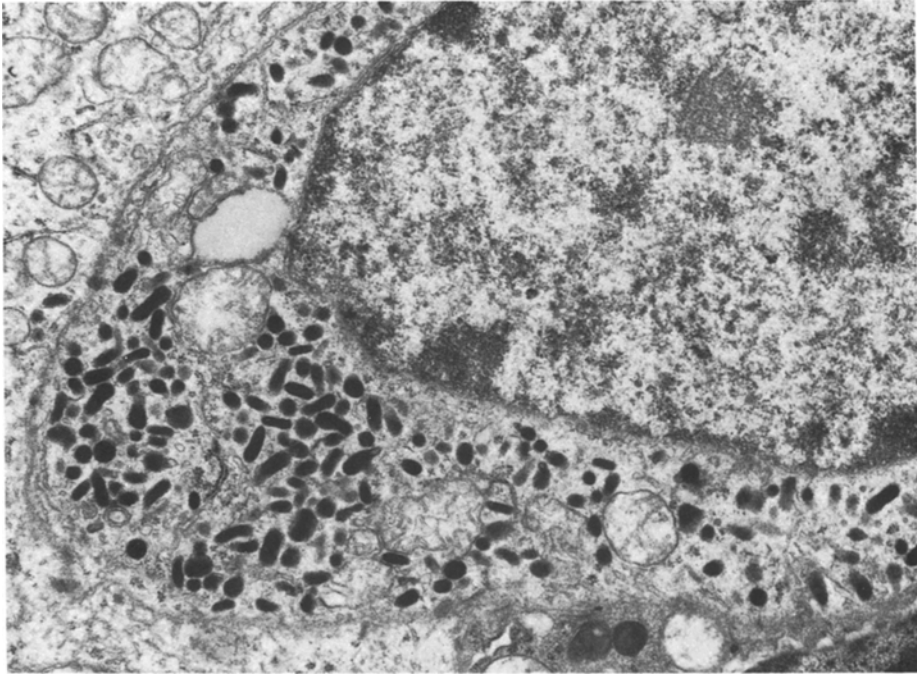


Fig. 4. Primary ileal carcinoid. Electron micrograph of a tumor cell which contains numerous pleomorphic cytoplasmic secretory granules, identical to those observed in the tumor cells of the breast metastasis. Uranyl acetate and lead citrate, $\times 16,500$

While the typical carcinoid pattern predominated, sheets of tumor cells subdivided into small lobules by thin vascular septa were seen in some areas. This histological feature was similar to that observed in the breast metastasis. AB-PAS stained sections revealed neutral and/or acid mucosubstances within a few acini. 12 mesenteric lymph nodes were free of metastases. Fontana-Masson silver impregnation demonstrated the tumor to be composed of argentaffin cells.

c) Electron Microscopy. The ultrastructural appearance of the ileal carcinoids was identical to that observed in the breast metastasis. The neurosecretory-type granules were pleomorphic, similar in size to those observed in the breast tumor, and were randomly distributed within the cytoplasm (Fig. 4). Extra- and intracellular acini were frequently observed.

Discussion

This report clearly shows the importance of the combined light microscopic, histochemical and ultrastructural study of the breast tumor in order to establish its metastatic origin. The positive argentaffin reaction of the breast tumor and

its pleomorphic cytoplasmic granules at the ultrastructural level pointed to a primary carcinoid tumor in the midgut which proved to be localized in the terminal ileum and which was clinically occult. Gastrointestinal carcinoid tumors are most commonly located in the ileum, followed by rectum and appendix (Kuiper et al., 1970). Carcinoids of the small intestine and of the appendix are nearly all argentaffin (Lillie and Glenner, 1960), whereas those from the hindgut are argentaffin only infrequently (Stout, 1942). Argentaffin cells are present in small numbers in a minority of bronchial carcinoids (Williams and Azzopardi, 1960) and carcinoid tumors of the stomach tend to be argentaffin-negative (Williams and Sandler, 1963). Capella et al. (1976) using Masson's argentaffin reaction on specimens examined electron-microscopically, demonstrated that the argentaffin cells of the rectum, colon, appendix and ileum, and some of those of the jejunum and duodenum showed a prevalence of rod-like, biconcave or kidney-shaped granules. The majority of argentaffin cells in the duodenum and a minority of those from the jejunum showed a prevalence of ovoid, angular and irregular granules. These studies thus clearly demonstrate that in a metastatic carcinoid the argentaffin reaction and the morphology of the granules may help to specify the site of the primary tumor.

Since recent reports have established the existence of primary mammary carcinoids, (Cubilla and Woodruff, 1977; Kaneko et al., 1978; Devitt, 1978; Taxy et al., 1979) determining the true nature of a carcinoid tumor in the breast has become somewhat complex. In addition, primary breast carcinomas may present a carcinoid-like pattern, but these tumors also usually show areas of a conventional appearance. The reported cases of primary breast carcinoids all contained argyrophil cytoplasmic granules, except one which was argentaffin (Devitt, 1978). This latter tumor may represent a metastasis of a clinically occult intestinal carcinoid. Ultrastructurally, primary carcinoids of the breast showed round cytoplasmic granules (Cubilla and Woodruff, 1977). These authors found intraductal carcinoma in 3 of 8 mammary carcinoids and observed in one area of intraductal proliferation argyrophil cytoplasmic granules suggesting a ductal origin of these neoplasms. In addition, Taxy et al. (1979) noted that their breast carcinoid was associated with areas of typical in-situ and infiltrating ductal carcinoma. According to Farrow (1956) the presence of foci of in-situ carcinoma is the only absolute proof of the primary nature of a breast carcinoma.

In conclusion, a breast carcinoma composed of small cells arranged in nests separated by connective tissue septa with a positive argyrophil reaction, round uniform secretory granules at the ultrastructural level, and a pattern of intraductal or in-situ proliferation suggest a primary carcinoid of the breast. In the absence of intraductal lesions a metastasis to the breast from an argyrophil carcinoid should be excluded. If the tumor gives a negative argyrophil reaction, but electron microscopy reveals neurosecretory-type granules, the tumor might represent a metastasis from an extra-mammary non argyrophil carcinoid. Finally, if both argyrophil and argentaffin reactions are positive, a metastasis from an intestinal carcinoid is likely. The ultrastructural morphology of the granules (Capella et al., 1976) may then help to specify the localization of the primary carcinoid.

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