Primary Melanocarcinoma of the Esophagus*

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THE GREAT ADVANCES in surgery of the esophagus in recent years have served to focus attention on many previously obscure diseases of this organ. Of the many tumors encountered, melanocarcinoma has been exceedingly rare. Since Bauer's first report[5] in 1906, a total of 11 cases have been recorded, but seven of these have been discovered within the past four years. In a review of 22,000 autopsies at Johns Hopkins Hospital prior to their report, Burnett and St. John[13] found 25 cases of melanocarcinoma, and in none was the tumor found in the esophagus, either primary or secondary.

It has been the experience of most pathologists that in many cases of visceral melanoma it is possible to elicit the information that a superficial mole of some variety had been removed many years previously, long since forgotten by the patient. This experience explains the obvious reluctance on the part of many pathologists to make a diagnosis of primary visceral melanoma. Allen[2] has demonstrated, however, that the presence of junctional changes in the overlying or juxtaposed epithelium is unequivocal evidence that the tumor is primary, and he considers it so reliable that "the absence of junctional change over a dermal melanomatous deposit is strong evidence that the melanoma is metastatic at the site in question." In a later paper[3] Allen and Spitz, after a review of 934 cases of melanoma, broaden this concept to include visceral melanomas, wherever they may arise. Thus, in the group studied, a total of 63 primary melanomas (other than cutaneous) in 52 patients were listed, including one melanoma of the esophagus.

Of the cases of melanoma of the esophagus so far reported only the four most recent ones fulfill the necessary criteria.[11, 12, 16, 17] In each the tumor was unequivocally melanomatous, and junctional changes were demonstrated in all. Of particular importance is the case of Fowler and Sutherland.[16] Their patient succumbed on the third day after operation; careful postmortem examination failed to reveal tumor either in the regional nodes or elsewhere in the body. The remaining cases[5, 13, 14, 18, 20, 25, 30] have not been adequately documented, according to current concepts, to be acceptable as primary tumors.

The following case is one recently encountered, and which we feel fulfills the criteria for the diagnosis of primary melanocarcinoma of the esophagus.

CASE REPORT

History. Mrs. A. W., a 48-year-old white woman, was admitted to The Mount Sinai Hospital for the first time on September 29, 1953. She suffered from duodenal ulcer since 1949, with intermittent attacks of pain that responded well to diet and adherence to a regimen of antacid therapy. Two months prior to admission she noted the onset of difficulty in swallowing solid foods, accompanied by retrosternal pain. Soft and liquid foods were well tolerated. There was no vomiting and no hematemesis. Because of pain, total food intake was voluntarily curtailed, and she lost 12 pounds during the illness. The system review was otherwise negative.

The past history was essentially non-contributory. After the diagnosis was established by operation, the patient and her husband were carefully questioned relative to the removal of moles or cutaneous tumors at any time in the past, with negative results.

Physical Examination. The patient was a well developed, well nourished woman of 48, not acutely ill. Examination of the skin was negative for tu-

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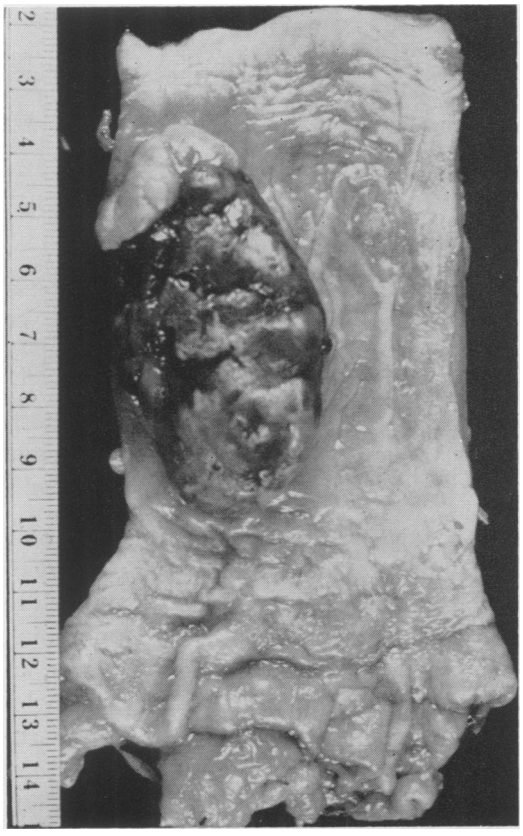

FIG. 1. Photograph of surgical specimen showing lobulated pedunculated melanoma of the esophagus.

mors or scars. There was neither local nor general lymphadenopathy. The eyes (including fundi), ears, nose and throat were negtaive. Heart and lungs were negative to percussion and auscultation. The liver, spleen and kidneys were not palpable, and the abdomen was free of tenderness and masses. Careful pelvic and rectal examinations were negative.

Laboratory Findings. Urine, blood cell counts and blood chemical determinations were all within normal limits. Stool guaiac tests were negative for occult blood.

Course in the Hospital. Shortly after admission roentgenograms of the esophagus revealed a tumor at the junction of the middle and the lower thirds. The chest film was negative. Esophagoscopy confirmed the presence of a large polypoid tumor filling the lumen of the esophagus at 29 cm. from the upper incisor teeth; biopsy proved it to be melanocarcinoma.

After 48 hours preparation with penicillin aerosol, the left chest was opened through the bed of the 7th rib. The tumor, approximately 2 inches in length, was palpable at the junction of the middle and lower thirds. There was no evidence of local extension beyond the wall of the esophagus, or distant metastases in the chest or abdomen. The superior and anterior walls of the first portion of the duodenum revealed the typical scarring and puckering of a healed duodenal ulcer. Radical esophagogastrectomy with supra-aortic anastomosis and complementary pyloroplasty were performed (J. H. G.). She tolerated the operative procedure well, and postoperatively enjoyed an uneventful convalescence. The patient was discharged on the 12th postoperative day, afebrile and asymptomatic, swallowing soft and semi-solid foods without discomfort.

Follow-up. When last seen, one year after operation, she was well but complained of mild dysphagia. Esophagoscopy revealed slight stenosis at the anastomosis but no indication of tumor recurrence. There was no evidence of regurgitant esophagitis.

Gross Pathological Examination. The specimen consisted of a portion of esophagus measuring 12 cm. in length, with 3 cm. of the cardiac end of the stomach attached. The esophagus was 5 cm. in diameter. Its outer aspect was not remarkable. 2.5 cm. from the proximal resected end and 3.0 cm. from the cardio-esophageal junction a polypoid tumor was noted, measuring 6 x 3.5 x 2.5 cm. and attached to the mucosa by a stalk measuring 3.5 x 1.5 cm. (Fig. 1). The tumor was lobulated in appearance and the mucosa was covered by a gray-green exudate. On cut section the tumor was glistening and fleshy, containing many areas of hemorrhage and necrosis. Near the base, brown-black pigment was noted. The remainder of the mucosa of the esophagus appeared normal except for focal areas of submucosal hemorrhage. The attached portion of cardia of the stomach was normal. Several small, firm lymph nodes found in the serosal fat of the esophagus revealed unaltered architecture, and did not appear to contain metastases.

Sections were taken from the tumor, with adjacent mucosa attached, and from areas of normal appearing mucosa at a distance from the tumor.

Microscopic Study. Sections taken from the main tumor mass show a highly cellular neoplasm extending downward from the epithelial surface. The cells are compactly arranged, and generally polyhedral in outline; some are round or ovoid. The stroma is extremely scanty in amount and consists mainly of condensations of connective tissue around small blood vessels. The latter are relatively few in number, and are widely separated. The surface epithelium is largely ulcerated, and extensive zones of necrosis and hemorrhage are noted in the superficial aspects of the tumor. No organized formations are seen but the tumor cells show some tendency

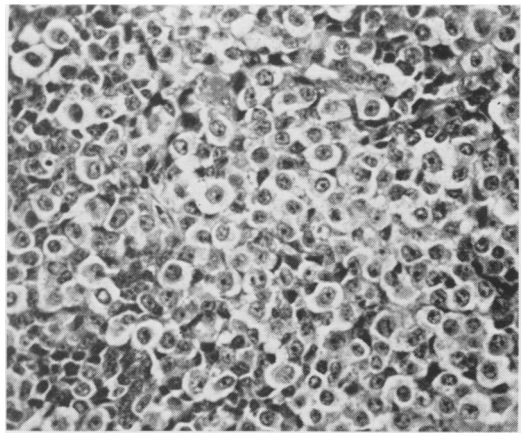

FIG. 2. High power photomicrograph illustrating typical melanoma cell type (x525).

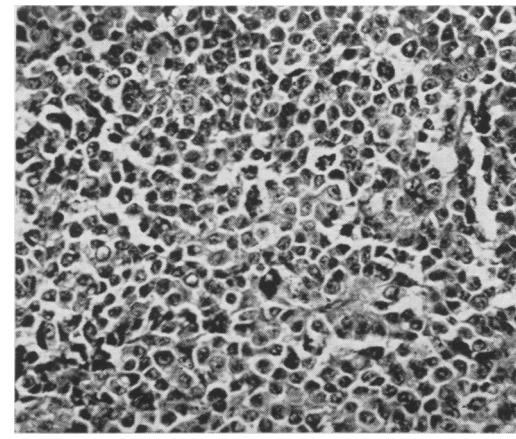

FIG. 3. Scattered cells containing clusters of melanin pigment (x425).

toward perithelial growth around blood vessels and the formation of indistinct nests and clusters.

The individual tumor cells have, as a rule, indistinct outlines; their cytoplasm is scanty in amount, and finely granular or vacuolated. The nuclei are large, round or oval, and fill the cells. All are hyperchromatic and vesicular, and many contain prominent nucleoli (Fig. 2). Many deeply stained pyknotic nuclei are present but mitotic figures are relatively rare. Although occurring in a minority of the cells, pigment is readily found in the cytoplasm of the tumor cells principally in the form of small clusters of golden to dark brown granules (Fig. 3).

Sections from the margins of the lesions in areas where the overlying epithelium is intact show a well marked junctional change (Fig. 4). Small clusters of cells are seen in the basal layers of the epithelium, rounded off and well demarcated from the adjacent epithelial cells. Their cytoplasm is vacuolated and heavily dusted with golden-brown, finely granular pigment. This alteration, typical of junctional change, is found over tumor tissue as well as over an area not occupied by tumor. In the latter regions the lamina propria is heavily infiltrated by lymphocytes and macrophages. Many of the last named are filled with dark brown melanin pigment granules.

Multiple sections show the neoplasm to be confined entirely to the *lamina propria*. There is no evidence of invasion of the muscular wall of the esophagus. No involved lymph nodes are found.

Diagnosis. Polypoid malignant melanoma of the esophagus, primary.

DISCUSSION

The establishment of the junctional nevus as the precursor of melanoma, and the general acceptance of its presence as the only certain indication that a tumor is primary or metastatic at a given site has done much to clarify the general confusion surrounding cutaneous melanocarcinoma. However, as one reviews the literature relative to moles and melanoma, particularly the experimental biological and embryological literature, several disconcerting questions arise as one attempts to carry over the theories and data to primary melanocarcinoma of the esophagus and other visceral organs. These questions have proven intriguing not only to us as surgeons but also to our pathologists as well. Our purpose in stressing the following discussion is twofold: (1) to review the available information on the subject, and (2) by calling attention to controversial features to stimulate further research in allied fields.

There seems to be almost universal agreement that melanomata arise from melanoblasts. There is by no means such accord with respect to the nature and specificity of these cells. Allen[2, 3] has emphatically and repeatedly stated that melanoblasts are "not likely to be previously invisible or highly specialized cells that have proliferated, but rather are the basal and other epidermal cells that are transformed just where they lie." The cytoplasm of the transformed cells may be powdered with fine granules of mela-

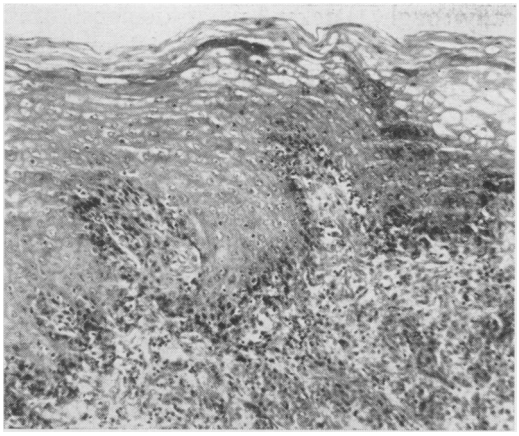

FIG. 4. Squamous epithelium adjacent to main tumor mass with characteristic junctional change (x200).

nin, or may be free of pigment. It is his impression that the pigment is formed *in situ* in these altered cells, and does not reach them by transcellular migration of the pigment granules. Finally, based on the work of Peck[28] with Thorium X, it is his opinion that the "dopa" positivity attributed solely to melanoblasts may obtain in cells that are unequivocally epidermal.

Masson,[22] on the other hand, has maintained that the melanoblast (or dendritic cell of Bloch) is a specific cellular entity located within the basal layers of the epidermis. Also, that it is the only cell of the epidermis that is dopa-positive (producing melanin via its dopa oxidase), and discharges its melanin pigment into the adjacent epidermal cells in contradistinction to the theory of "*in situ*" production of pigment. In so far as their origin is concerned, he feels that it is still obscure, being possibly from the epidermis or from the embryonic neural crest, although in man these cells may denote instead "a placodic potentiality spread throughout the epiblast."

Strong support has been accorded Masson's views, particularly by the observations of Billingham.[9, 10] In exquisitely meticulous histological work on sections of pigmented and non-pigmented skin of the guinea-pig, rabbit, and man (including Caucasian, Negro and Indian skin), he found branched dendritic cells in a single layer interspersed among the basal (Malpighian) cells. From these cells (called pigmented dendritic cells) branches are given off, which travel along the intercellular spaces between the ordinary epidermal cells and ultimately terminate in caps closely applied to the ordinary epidermal cells. His evidence indicates that pigment granules are elaborated within the dendritic cells and passed to the basalar epidermal cells across the end-caps.

The dendritic cells are dopa-positive, and he points out that although chromatophores elsewhere in the body may be dopa-positive, the dendritic cells are the only dopa-positive cells in the epidermis, and the stain is unequivocally specific. Mitoses and cell division have been observed in dendritic cells, and it is his belief that they have a cell-lineage of their own, not being derived from ordinary epidermal cells of the basal layer.

Additional support is offered Masson's views by Willis,[32] Ackerman[1] and Becker.[7] It is Becker's opinion that "the ordinary palisade basal cell gives rise to benign epitheliomas and carcinomas," while "the clear cell 'the melanoblast' gives rise to benign melanomas (nevi) and malignant melanomas." Ackerman points out that malignant melanoma is a radio-resistant tumor, while the basal-cell and squamous cell tumors, derived from ordinary epidermal cells, are radio-sensitive.

In the light of this evidence, we are inclined to accept the specificity of the melanoblast (the dendritic cell) as the site of origin of melanoma. Although the origin of the melanoblast of the epidermis is obscured in mystery, we are puzzled as to how such a tumor could arise in the esophagus, an organ in which dendritic cells have not previously been described. The whole problem becomes more confusing when one considers Allen's all-inclusive viewpoint that one may not only find junctional changes and melanoma in the stratified squamous mucous membranes (*e.g.*, esophagus) but also in

(a) the ciliated pseudostratified columnar epithelium of the nasal cavity, paranasal sinuses, larynx and bronchus, (b) pseudostratified columnar epithelium of the urethra, and (c) the columnar epithelium of the rectum. He reports a total of 14 cases from these regions.[3] It should be pointed out that these regions (esophagus, respiratory tract and upper rectum) are of endodermal origin, while the juxtacutaneous mucous membranes (nasal cavity, mouth, and ano-rectum) are ectodermal in origin. As Willis points out the juxta-cutaneous epithelia normally possess pigment-formative capacities, and in some cases developmentally heterotopic epidermis may be found.

A generalized, non-specific *in situ* transformation of cells of different germ layers into one specific tumor cell type appears less appealing as a concept than tumor formation from one structure, however wide and apparently disorganized its distribution might be. Occurrence of melanoblasts in the esophagus must be exceedingly rare. If they are of moderate frequency, one would expect to see more reports of melanosis of the esophagus, especially in Addison's disease and other disorders accompanied by systemic stimulation of pigment forming cells. According to Becker,[8] the only references to such melanosis are in connection with melanoma. Of the previously reported cases of melanoma of the esophagus, only Fowler and Sutherland[16] found evidence of non-neoplastic pigmentation in areas of mucous membrane at a distance (4.5 cm.) from the tumor. In addition to Becker, Klemperer[21] and Masson[23] are of the opinion that, rare as it may be, melanoblasts must be present in those esophagi in which melanomas arise.

Standard texts of embryology[4, 27] and histology[24, 26] do not mention dendritic cells of the esophageal mucosa. Careful examination of the developing mucous membrane of the gastro-intestinal tract in the human embryo[19] failed to demonstrate these cells. In a critical study of 30 consecutive autopsy cadavers in which melanoblasts were specifically sought, Becker,[6] while demonstrating pigmented cells in 70 per cent of the mucosae from mouth to pharynx, failed to demonstrate any evidence of pigmentation in any of the esophagi.

According to Weidenreich,[31] the five pigment layers of the body are (1) ectodermal, (2) dermal, (3) peri-coelomic, (4) perineural, and (5) perivascular. In the case of the esophagus, the source would be the peri-coelomic layer. While this layer is usually pictured as subserous, Weidenreich's Table IV, Figure 16, illustrating a cross-section of a salamander larva, shows the pigment cells immediately beneath the esophageal epithelium. It is therefore conceivable that such pigment cells may have a phylogenetic background."[8] DuShane[15] has demonstrated that the pigment cells of vertebrates originate in the neural crest, and that these pigment cells migrate to their definitive positions early in embryonic life. The dermal and visceral chromatophores are thus of neural crest origin. Rawles,[29] working on embryonic mouse tissue grown in the coelom of chick embryos, also concluded that melanophores arise from an outside source, the neural crest. The accumulated evidence to date, therefore, would seem to indicate that the melanoblast, the precursor to melanoma, is not a normal component of the esophageal mucosa but in rare cases ectopic foci of such cells will localize in the esophagus as a result of an aberration in embryonic distribution.

SUMMARY AND CONCLUSIONS

A case of primary melanocarcinoma of the esophagus in a 48-year-old woman is presented, the fifth such case to be recorded. The absence of any other primary site was carefully ruled out by history and thorough physical examination. The identifying junctional change was found within 1 cm. of the main tumor mass.

We agree with the theory that melanoma arises only from the melanoblast (the dendritic cell), and suggest that primary melanocarcinoma of the esophagus arises not by

in situ transformation of squamous mucosa but from melanoblasts ectopically located in the esophagus.

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