ADENOACANTHOMA (ADENOSQUAMOUS CARCINOMA) OF THE PANCREAS
腫瘍の腺類癌（腺扁平上皮癌）

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OF THE PANCREAS

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SUMMARY

Four cases of adenocanthoma of the pancreas were collected and the literature reviewed. This uncommon histological variant appears as aggressive and malignant as the more common adenocarcinomas. Two of these four cases had originally been diagnosed as squamous cell carcinomas and were shown to be adenocanthoma in type only after additional sections were examined microscopically. It is the authors' opinion that any squamous cell carcinoma of the pancreas must be thoroughly examined for adenocarcinomatous elements before it can be classified as being purely squamous in type. Also because metastases may be predominantly of either squamous or adenomatous type, the presence of squamous carcinoma in a metastatic lesion does not eliminate the possibility of a pancreatic primary nor does the finding of two distinct histological types of metastases necessarily imply two separate primary malignancies. The terminology and origin of this histologic type of pancreatic tumor are discussed.

INTRODUCTION

Originally we intended to report the characteristics of a squamous carcinoma of the pancreas found at

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はじめは著者の一人が剖検で認めた膵臓の扁平上皮癌
an autopsy performed by one of us and an additional case in the ABCC autopsy files. However, as we reviewed the literature and reexamined our material, it became evident that our diagnoses were at fault and, more important, that a similar error might underlie some of the relatively few reported cases of squamous carcinoma of the pancreas in the literature. For, only after extensive sampling of the tumors in our cases were we able to demonstrate the presence of unequivocal malignant glandular elements in these two predominantly epidermoid carcinomas. The ABCC autopsy files contained two additional pancreatic carcinomas which showed mixtures of squamous and adenomatous features.

The four cases, which are the basis for this report, illustrate how much the proportion of the two cell types can vary in different tumors and suggest that perhaps small foci of malignant squamous cells might be found frequently in pancreatic tumors if a thorough search was made for them. Further, they indicate that the presence of epidermoid carcinoma in metastatic foci does not necessarily rule out primary pancreatic carcinoma nor is the presence of metastatic foci with adenocarcinoma and others with squamous carcinoma prima facie evidence of origin from multiple primary carcinomas.

Several terms have been used for carcinomas containing both adenomatous and squamous elements including adenocanthoma, adenosquamous carcinoma, mucoepidermoid carcinoma, and mixed carcinoma. For reasons to be discussed later we prefer and will use the term adenocanthoma.

METHODS AND MATERIALS

During the 15-year period, 1956-70, primary carcinoma of the pancreas was diagnosed in 90 of the autopsies in the ABCC autopsy files. All but four were pure adenocarcinomas showing various degrees of differentiation. Two cases contained, in addition to adenocarcinoma, definite foci of malignant squamous cells and two cases appeared to consist only of epidermoid carcinoma showing intercellular bridges as well as definite keratin pearls. The pancreases in these last two autopsies were re-examined and additional blocks were made.

Adenocarcinomatous elements were quickly found in one but in the other, a tumor measuring 7 by 4 cm, lying in the body of the pancreas, adenocarcinomatous elements were not found until approximately 80% of the tumor had been blocked

の1例、およびABCC剖検記録にあった別の1例に関して、その特徴を報告する予定であった。しかし、文献の考察と著作者の資料の再検討によって、著者の示する誤りであり、しかも、より重要なことに、比較的少数の文献に報告されている肺気腫の扁平上皮癌例にも同様の誤りがあるかもしれないことが明らかになった。なぜなら、著者たちは多数の切片を検索してはじめて、この二つの類表皮癌例において明白な悪性扁平上皮癌が認められたからである。ABCC剖検記録には、扁平上皮癌と腺癌との混合像を示した肺気腫2例があった。

本報告の中心をなすこの4例は、二つの細胞型の割合が異なるかに違うかを示したばかりでなく、徹底的な検索を行なえば、肺気腫の扁平上皮癌の少々の病巣がしばしば発見されるかもしれないことを示唆しているのである。さらにこの4例では、転移巣における類表皮癌の存在は必ずしも原発性肺腺癌を除外するものでもなく、また、腺癌を伴う転移巣および扁平上皮癌を伴う転移巣の存在が、悪性度原発性癌からの起源の一部の証拠ともならない。

腺癌癌、肺気腫上皮癌、粘膜上皮癌、および混合癌のごとき、扁平上皮癌および扁平上皮癌を含む癌に対しては、いくつかの名称が用いられているが、理由によると、著者は腺癌癌という名称を適確と考え、これを使用する。

方法および材料

1956-70年の15年間には、ABCC剖検例のうち90例に原発性肺腺癌が診断された。4例を除く全例が純然たる腺癌で、いわゆる度合いの分化を示していた。2例は、肺気腫に加えて悪性的扁平上皮癌の明確な病巣が認められ、2例は類表皮癌のみから成り、細胞間隔および明白な癌細胞を呈しているように思われた。後者の2例の肺気腫をあたかも検査し、新しい組織切片を作製した。結果、1例には腺癌成分がふつうに認められた。

他の1例には肺気腫部分で7×4 cmの腺癌があったが、腺癌の約80%について連続的に15ヵ所から切片を作製しはじめた場合の腺癌成分が発見された。4例の肺気腫の腺癌
RESULTS

Table 1 lists the clinical features of the four cases. Two of the patients were men and two were women. The duration of life from onset of symptoms to death ranged from 4 to 13 months, with a mean of 9 months. The age range for the four patients was 76 to 86 years with a mean of 82 years. The average age for the 90 patients with primary pancreatic carcinoma of all histologic types was 66 years.

<table>
<thead>
<tr>
<th>Case</th>
<th>Autopsy No.</th>
<th>Age</th>
<th>Sex</th>
<th>Onset of Symptoms to Death</th>
<th>Initial Clinical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>86</td>
<td>Male</td>
<td>4 months</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>76</td>
<td>Female</td>
<td>9 months</td>
<td>Fullness of lower abdomen, Loss of appetite</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>83</td>
<td>Male</td>
<td>11 months</td>
<td>Jaundice, malaise</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>84</td>
<td>Female</td>
<td>13 months</td>
<td>Jaundice, emaciation, &amp; general weakness</td>
</tr>
</tbody>
</table>

Two patients died of widespread metastases, one died of myocardial infarction associated with nonbacterial thrombocendocarditis of the aortic valve, and one died of bilateral acute bronchopneumonia.

Table 2 lists pertinent anatomic data. In each of the four cases, two or more benign tumors were found at autopsy. One patient had a coexistent adenocarcinoma of the stomach.

Microscopically, each primary tumor was characterized by the coexistence of two distinct histologic patterns, one being well to poorly differentiated adenocarcinoma and the other well to poorly differentiated adenocarcinoma and the other well to poorly differentiated adenocarcinoma. The adenocarcinomatous portions of all four pancreatic cancers were positive when stained with mucicarmine. All four adenocanthomas were in patients from Hiroshima. Only one patient had been irradiated at the time of the A-bomb (Case 2, 34 rad) and there was no suggestion in these four cases or in the entire series of 90 primary carcinomas of the pancreas that there was a relation between the development of these cancers and irradiation.

結果

表1に4例の臨床的所見を示した。その2例は男であり、2例は女であった。症状の発現から死亡までの期間は4～13か月、平均9か月であった。この4例の年齢は76～86歳、平均82歳であった。各組織型から生発の原発性腺癌90例の平均年齢は66歳であった。

死亡原因については、2例は広範な転移、1例は大動脈弁の非細菌性血栓性心内膜炎を伴う心筋障害、1例は急性下痢細気管支肺炎であった。

検体では、原発性腫瘍には共存する2つの特徴的組織像が認められた。すなわち、一つは炭化の像であり他の一つは扁平上皮癌の像であり、いずれも分化の良好なものと不良
<table>
<thead>
<tr>
<th>Case</th>
<th>Location in Pancreas</th>
<th>Metastases</th>
<th>Other Tumors Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Head</td>
<td>Liver, Gallbladder, Lungs, Lymph nodes, Peritoneum</td>
<td>Hamartoma, lung; Leiomyoma, stomach</td>
</tr>
<tr>
<td></td>
<td>頭部</td>
<td>肝臓、膀胱、肺、リンパ節、腹膜</td>
<td>腫瘍の形態異常；胃の平滑筋肉</td>
</tr>
<tr>
<td>2</td>
<td>Body &amp; Tail</td>
<td>Liver, Lymph nodes</td>
<td>Chromophobe adenoma, pituitary gland; Leiomyoma, uterus</td>
</tr>
<tr>
<td></td>
<td>体部および尾部</td>
<td>肝臓、リンパ節</td>
<td>下垂体の卵巣細胞腫；子宮の平滑筋肉</td>
</tr>
<tr>
<td>3</td>
<td>Body</td>
<td>Liver, Peritoneum, lymph nodes</td>
<td>Adenocarcinoma, stomach; Leiomyoma, stomach; Hemangioma, liver; Polyp, ileum</td>
</tr>
<tr>
<td></td>
<td>腹部</td>
<td>肝臓、腹膜、リンパ節</td>
<td>腫瘍の形態異常；胃の平滑筋肉；肝臓の血管腫；回腸のポリープ</td>
</tr>
<tr>
<td>4</td>
<td>Head</td>
<td>Liver, Lungs, Lymph nodes</td>
<td>Oxyphilic cell adenoma, parathyroid gland; Ganglioneuroma, neck</td>
</tr>
<tr>
<td></td>
<td>頭部</td>
<td>肝臓、肺、リンパ節</td>
<td>上皮小体の好酸性細胞腫；頚部の神経性神経腫</td>
</tr>
</tbody>
</table>

differentiated squamous cell carcinoma. There was variation in the amount of tumor represented by either the squamous or adenocarcinomatous element. Up to 80% of one primary tumor had to be blocked before the adenocarcinomatous element could be identified. Transitional zones between these two patterns were readily observed in those sections demonstrating both patterns. In the majority of instances, there was an intermediate zone in which the tumor showed both squamous and adenocarcinomatous elements. An example of this type is shown in Figure 1 in which a gland-like structure is lined in part by squamous-appearing cells. In the central portion a small amount of wispy, mucicarmine-staining material is present suggesting mucin production by at least some of the squamous cells. In another pattern seen only in some areas in Case 3, there was an abrupt change from squamous to adenocarcinomatous structure (Figure 2). Perineural invasion, a common feature of pancreatic adenocarcinoma, was seen with both the adenocarcinomatous and squamous carcinoma elements of the four adenoacanthomas (Figure 3).

The histologic pattern of the metastases varied widely in the extent of the tumor represented by adenocarcinoma and squamous carcinoma. Thus, some metastases were either predominantly glandular or epidermoid, while other metastatic foci consisted of these histologic patterns in more equivalent proportions. In no case did a metastatic focus consist entirely of squamous carcinoma, but in two cases, metastatic foci could be found which consisted only of adenocarcinoma. Special stains confirmed the presence of mucicarmine positive material within cytoplasmic vacuoles within adeno-
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Author</th>
<th>Cases</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Type of Study</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td>Herxheimer</td>
<td>1</td>
<td>1907</td>
<td>65</td>
<td>F</td>
<td>Case Report</td>
<td>Used term &quot;adenocarcinoid&quot;</td>
</tr>
<tr>
<td>47</td>
<td>Plenge</td>
<td>1</td>
<td>1927</td>
<td>No data</td>
<td>Case Report</td>
<td>Two patterns not seen together in metastases</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Lawrence</td>
<td>2</td>
<td>1934</td>
<td>66</td>
<td>M</td>
<td>Collected 2</td>
<td>Also reported one case squamous ca. of pancreas &amp; collected two case reports squamous cell ca.</td>
</tr>
<tr>
<td>48</td>
<td>Case Record, MGH</td>
<td>1</td>
<td>1945</td>
<td>55</td>
<td>M</td>
<td>Case Record</td>
<td>攝治記録の報告</td>
</tr>
<tr>
<td>45</td>
<td>Lowry &amp; Whitaker</td>
<td>2</td>
<td>1949</td>
<td>57</td>
<td>M</td>
<td>Case Reports</td>
<td>Also reported one squamous ca. of pancreas</td>
</tr>
<tr>
<td>1</td>
<td>Sommers &amp; Meissner</td>
<td>5</td>
<td>1954</td>
<td>57</td>
<td>M</td>
<td>Autopsy survey, 142 cases pancreatic</td>
<td>さらに胃癌の治瘄後之例を報告</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td></td>
<td>65</td>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
<td></td>
<td>77</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Cook &amp; Klickstein</td>
<td>2</td>
<td>1958</td>
<td>No data</td>
<td>Survey of 10,041 autopsies</td>
<td>Used term &quot;adenocarcinoid&quot;</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Halpert et al</td>
<td>5</td>
<td>1965</td>
<td>No data</td>
<td>Autopsy survey, 120 cases pancreatic</td>
<td>Also found 6 squamous carcinomas</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Klintrup</td>
<td>2</td>
<td>1966</td>
<td>No data</td>
<td>Survey of 94 autopsies</td>
<td>Called &quot;Indeterminate carcinoma with squamous metaplasia&quot;</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Elias</td>
<td>3</td>
<td>1969</td>
<td>No data</td>
<td>Autopsy survey of 58 cases pancreatic</td>
<td>Also found 6 squamous carcinomas</td>
<td></td>
</tr>
</tbody>
</table>

Carcinomatous metastases of each case. In several metastases, a pleomorphic histologic pattern was evident (Figure 4). Pleomorphic carcinoma of this type has been described in literature with differentiated adenocarcinoma in cases without squamous elements and apparently represents an undifferentiated phase of pancreatic adenocarcinoma.

Table 3 lists pancreatic adenocarcinomas which have been reported in the literature. A slight male predominance is noted in the reported cases which list these data. This predominance is similar to that shown in pancreatic carcinoma in general.
FIGURE 1. Transition zone between unequivocal squamous and adenocarcinomatous areas (not shown). Figure shows glandular structure lined by squamous-appearing cells. The wispy material in the central portion was mucicarmine positive suggesting the squamous-appearing cells were the source for this material (Case 4).

FIGURE 2. Adenoacanthoma showing abrupt transition from squamous carcinoma (lower left) to adenocarcinoma (upper right). This was seen in only one case (Case 3).

図1 明かな扁平上皮癌と腺癌（写真にない）との移行部、図は扁平上皮癌細胞に包まれた腺様構造を示す。中央部の細かい物質は、ムシカリミン陽性で、扁平上皮癌細胞はこの物質の起源であることを示唆する（症例4）。

図2 腺様癌で、扁平上皮癌（左下）から腺癌（右上）への突然移行を示す。これは1例にのみ認められた（症例3）。
FIGURE 3 Perineural invasion by squamous elements of adenoacanthoma of the pancreas (Case 3).
図3 検査機の喉頭上皮成分による神経周囲への侵襲（症例3）。

FIGURE 4 Pleomorphic pattern seen in portions of several metastases as well as in foci of primary pancreatic adenoacanthomas (Case 3).
図4 いくつかの転移癌と原発性腺腺癌細胞に認められる多形細胞像（症例3）。

7
DISCUSSION

Cancers containing both squamous and glandular elements are found in many organs and are the source for considerable confusion. There is disagreement concerning nomenclature, pathogenesis, clinical significance, and epidemiologic features of these tumors. Although this situation applies to many cancers as witness the work of the Classification Centers of the World Health Organization and the Nomenclature Committee of the International Union Against Cancer, there appears to be a developing consensus for the names to be used for these tumors containing both glandular and epidermoid elements and thus implying agreement on other problems. However, it appears that it is the need for a uniform diagnostic code in the face of disagreement among authorities which is leading to compromise rather than the solution of the problems and difficulties.

The tumors are usually described in sites where adenocarcinomas are generally found (i.e., stomach, colon, pancreas, gallbladder, uterus, ovary, and endocervix) but they are also reported in the esophagus, anus, and vagina where epidermoid carcinomas predominate, and in the lung where a variety of cancers occur.

Theories to account for the presence of squamous elements where only adenocarcinoma is expected include:

Origin of the two cell types from separate but neighboring foci one of which had previously undergone squamous metaplasia in reaction to chronic inflammation.

Merging of two separate tumors, a collision tumor.

Squamous metaplasia in the peripheral portions of an adenocarcinoma, the squamous elements being well differentiated and histologically not malignant.

Squamous metaplasia of portions of a proliferating adenocarcinoma, the squamous elements having malignant potential similar to the entire tumor.

Squamous metaplasia of cancer cells which have the potential of differentiating into any of a variety of cell types including columnar, cuboidal, spindle, squamous, giant cell, signet ring, and mucus producing cells.
The essential conflicts raised by these theories revolve about the question of metaplasia and malignancy. We have no new evidence to present but believe that the variation in cell type so often seen within the same tumor and the presence of squamous elements in the metastases of these combined tumors support the theory that the cancer cells have the potential to undergo metaplasia and that the frequency of discovery of such metaplastic changes is directly proportional to the diligence of the search.

A different explanation is offered when adenomatous elements are found in tumors ordinarily squamous in type. It is usually suggested that submucosal glands in the proximal portion of the esophagus and in the anus are the source for the adenomatous elements of combined tumors in these sites and invasion by gastric mucosa as the source for combined tumors in the distal esophagus.

There is little support for the possibility of metaplasia of squamous carcinoma cells into adenomatous cell types. However, it has been suggested that adenocanthomas of the cardia could arise from esophageal epithelium capable of differentiation into both epidermoid and glandular cell types. Although mucin granules have been described in the cytoplasm of squamous carcinomas in various locations, there is disagreement on the "interpretation of some of the mucin-like substances." A varied terminology has been used for designating malignancies consisting of both adenocarcinoma and epidermoid carcinoma. Frantz in referring to these tumors used the terms mucoceloid and adenocanthoma interchangeably. Mucoceloid carcinoma has been applied rather consistently to locally invasive, slowly metastasizing tumors predominantly epidermoid in character but with unequivocal mucus production. Mucoceloid tumors of salivary glands and pulmonary bronchi are well known examples which differ histologically and clinically from the highly malignant tumors under discussion.

The terms mixed carcinoma and mixed squamous cell and adenocarcinoma as used by Dougherty and Cotten and Glücksman and Cherry in reporting tumors of the cervix are confusing and evidently were not intended to imply a relation to the mixed tumors of skin and salivary glands.

The Nomenclature Committee of the UICC recommended three terms for these tumors; Adenocarcinoma with squamous metaplasia, Adenocan-
thoma, and Adenocarcinoid. The WHO publication on Histological Typing of Lung Tumors suggested the term Combined Epidermoid and Adenocarcinoma. Carcinoid is a rather obsolete term in English defined by Dorland as "resembling cancer" and, as "a skin cancer of a moderate degree of malignancy." Adenocarcinoma is not likely to be used widely. Adenocarcinoma with squamous metaplasia arbitrarily solves some of the problems of pathogenesis but logically suggests the introduction of the term squamous carcinoma with adenomatous metaplasia for similar tumors of the esophagus, anus, and vagina. Combined epidermoid and adenocarcinoma is descriptive and accurate but awkward and long. According to Dorland, an adenocanthoma is "an adenocarcinoma in which some of the constituent elements exhibit malignant metaplasia to cells of a squamous type." There are obvious difficulties but adenoacanthoma appears to be the most acceptable of the proposed names and has the benefit of wide usage. Among many others, Boswell and Helwig and Wood used it for these tumors in the stomach and Al-Doroubi et al. and Cook and Klickstein used it for colon tumors. Finally the term adenosquamous carcinoma suggested by Gerughty et al. and Straus et al. and Rabson which appears equally satisfactory apparently has not received wide acceptance.

In adenoacanthoma of the pancreas it is generally believed that the squamous elements arise by metaplasia in preexistent adenocarcinoma. Indeed, zones of transition from glandular to squamous carcinoma can usually be found (Figure 4). Although carcinoma of the pancreas is rare in patients in the pediatric age group foci of squamous metaplasia were found in two cases suggesting that some inherent quality of the tumor rather than long-standing inflammation was responsible for the change. Since squamous metaplasia occurs in pancreatic ducts, it is consistent that the malignant cells of a pancreatic adenocarcinoma might express the metaplastic potential of the histogenetic progenitor, the ductal epithelium.

There is considerable variation in the reported frequency of both adenoacanthoma and squamous cell carcinoma of the pancreas. In a study of unusual carcinomas of the pancreas, Sommers and Meissner described 5 adenoacanthomas but no squamous carcinomas in 142 autopsy cases of pancreatic carcinoma. Halpert et al. found 5 adenoacanthomas and 6 squamous cell carcinomas in a study of 120 pancreatic carcinomas. It is probable that adenoacanthoma of the pancreas is much more common than one would suspect from

学的分類に関する WHO の判分物 では、上皮癌と腺類癌との混合腫瘍という術語を提案している。しかし、腺様癌が上皮癌に含まれることが、 adenocarcinoid は上皮癌に含まれることが、 adenocarcinoma は上皮癌が包含されることがある。Dorland によれば、「腺癌」または「中等度に悪性である皮膚癌」と定義している。腺様癌は上皮癌に含まれることが、 adenocarcinoma は上皮癌が含まれることが、 adenocarcinoid は上皮癌が含まれることが、 adenocarcinoma は上皮癌が含まれることが、 adenocarcinoid は上皮癌が含まれることが、 adenocarcinoma は上皮癌が含まれることが、 adenocarcinoid は上皮癌が含まれることが、 adenocarcinoma は上皮癌が含まれることが、 adenocarcinoid は上皮癌が含まれることが、 adenocarcinoma は上皮癌が含まれることが、 adenocarcinoid は上皮癌が含まれることが、 adenocarcinoma は上皮癌が含まれることが、 adenocarcinoid は上皮癌が含まれることが、 adenocarcinoma は上皮癌が含まれることが、 adenocarcinoid は上皮癌が含まれることが、 adenocarcinoma は上皮癌が含まれことがある。
the number of cases published. Only 24 adenocanthomas were found in a review of the literature (Table 3).

In a number of surveys of pancreatic tumors which included histologic study\textsuperscript{32-40} no adenocanthomas were reported although some squamous cell carcinomas were described. Other case reports and surveys of pancreatic tumors\textsuperscript{41-45} brought the total number of squamous cell carcinomas reported in the literature to 21. There is no indication that the course of disease, response to treatment, occurrence of complication, or frequency or location of metastases is different in adenocanthoma of the pancreas as compared to adenocarcinoma of the pancreas. It is not known why some pancreatic carcinomas show squamous metaplasia but there is an intuitive belief that in some way the change is related etiologically to the development of the cancer. This suspicion alone is sufficient to warrant more aggressive study and reporting of such metaplastic changes.

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