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Hepatoid adenocarcinoma: A distinctive histological subtype of alpha-fetoprotein-producing lung carcinoma

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Summary. Seven cases of alpha-fetoprotein (AFP)-producing lung carcinoma were studied histologically to determine whether they fell into any previously described category. The patients were all males from 40 to 73 years of age and their serum AFP levels ranged from 1039 to 320000 ng/ml. Five cases of hepatoid adenocarcinoma, one case of endodermal sinus tumour, and one case of papillary adenocarcinoma were found. The possible origins of the tumours and their differential diagnosis are discussed. Hepatoid adenocarcinoma is a major histological category among AFP-producing lung carcinoma; other types are less frequent. The occurrence of hepatoid adenocarcinoma in both the stomach and the lung suggests that this neoplasm may also be seen in other organs of endodermal origin. It may be a major histological subtype of AFP-producing endodermal neoplasms of non-germ cell origin.

Key words: Alpha-fetoprotein – Lung carcinoma – Hepatoid adenocarcinoma – Endodermal sinus tumour

Introduction

Rare lung carcinomas that produce alpha-fetoprotein (AFP) have been reported (Miyake et al. 1986; Yokoyama et al. 1981; Hayatsu et al. 1983; Takizawa et al. 1984; Yasunami et al. 1981; Miyake et al. 1987; Tamura et al. 1986; Koizumi et al. 1979; Yoshimoto et al. 1987), but their clinicopathological features have not been well elucidated. It has recently been shown that gastric adenocarcinomas associated with high serum AFP levels often contain cells with hepatocellular features, and those tumours have been designated hepatoid adenocarcinomas (Ishikura et al. 1985, 1986). The histology of these tumours is a mixture of tubular or papillary adenocarcinoma and sheets of neoplastic cells resembling hepatocellular carcinoma cells. Since the lung is derived from a ventral outpouching of the primitive fore-gut, it is not surprising that some AFP-producing lung carcinomas have features in common with AFP-producing gastric carcinomas. In accordance with this view is the report by Kodama et al. (1980) that an AFP-producing lung carcinoma composed of poorly differentiated glandular cells with eosinophilic or water-clear cytoplasm had a histological resemblance to an AFP-producing gastric carcinoma that these authors had previously examined.

Hepatocellular differentiation of neoplastic cells has been described in two types of AFP-producing ovarian neoplasm: heptoid yolk sac tumour (Prat et al. 1982) and hepatoid carcinoma (Ishikura and Scully 1987). Hepatic features have also been described in minor (histological) foci in two other types of ovarian AFP-producing neoplasms; endodermal sinus tumours (EST) (Prat et al. 1982; Salazar et al. 1974) and the endometrioid-like variant of yolk sac tumour (Clemnt et al. 1987). All of the seven tumours to be described here have been reported in the literature under various names (Miyake et al. 1986; Yokoyama et al. 1981; Hayatsu et al. 1983; Takizawa et al. 1984; Yasunami et al. 1981; Miyake et al. 1987) but a consideration of their differential diagnosis from hepatoid adenocarcinoma has not been made. For these reasons we investigated the pathological features of seven lung carcinomas associated with high serum levels of AFP to determine whether these tumours had any of the features of previously described AFP-producing neoplasms, especially those of hepatoid adenocarcinoma.

Materials and methods

All seven lung carcinomas have been reported in the literature, five in Japanese (Cases 3–7), (Miyake et al. 1986; Yokoyama et al. 1981; Hayatsu et al. 1983; Takizawa et al. 1984) and two in English (Cases 1 and 2) (Yasunami et al. 1981; Miyake et al. 1987). The clinical and gross features of the seven cases are summarized in Table 1. The seven AFP-producing carcinomas of the lung were

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Table 1. Clinical and gross features of AFP-producing lung carcinomas

Case (Age/Sex)	Serum AFP (ng/ml)	Con A binding of serum AFP (%)	Symptom	Size (Primary site)	Metastasis (Detected by)	Prognosis (Duration)
1 (67/M)	19,000–160,000	ND	Back pain	8 cm-mass (right upper lobe)	Duodenum (autopsy)	Died (1.5 years)
2 (73/M)	1,039	18.7	Bloody sputum	$5 \times 6 \times 5$ cm (left S^{1+2})	Brain (CT scan)	Died (1.5 years)
3 (40/M)	3,090	52.1	Bloody sputum, cough	$8 \times 9 \times 7$ cm (right S^1 and S^2)	Peritoneum (CT scan)	Died (14 months)
4 (55/M)	2,123	80.7	Cough, back pain	5 cm-mass (right S^1)	Pericardium (operation)	Died (4 days)
5 (69/M)	5,050– 88,000	ND	Bloody sputum, fever, cough	$11 \times 11 \times 7$ cm (right lower lobe)	Kidney, brain (autopsy)	Died (2 months)
6 (68/M)	320,000	ND	Hemiplegia	5 cm-mass (right lower lobe)	Lungs, liver, esophagus, brain, kidney, thymus, lymph nodes (autopsy)	Died (6 months)
7 (45/M)	15,000–102,000	ND	Cough, fever bloody sputum, chest pain	Filling pleural cavity (primary undecided)	Liver (3 cm), lung, spleen, kidney, lymph nodes (autopsy)	Died (3 months)

Con A, Concanavalin A; ND, Not Detected; M, Male; CT, Computed Tomography. References for the above cases are Yasunami et al. 1981 (Case 1); Miyake et al. 1987 (Case 2); Miyake et al. 1986 (Case 3, 4); Yokoyama et al. 1981 (Case 5); Hayatsu et al. 1983 (Case 6); and Takizawa et al. 1984 (Case 7)

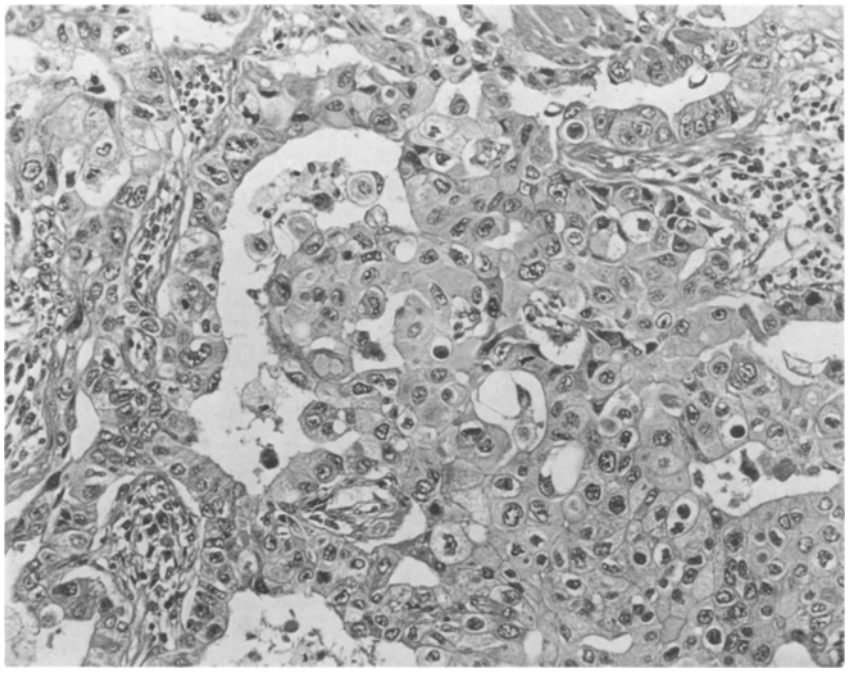


Fig. 1. Hepatoid adenocarcinoma of the lung (Case 1). Papillary/tubular adenocarcinoma cells merge almost imperceptably into sheets of neoplastic cells with abundant, eosinophilic cytoplasm. (H&E, ×200)

collected for examination without knowledge of their histological appearance.

Hepatoid adenocarcinomas have been defined as AFP-producing adenocarcinomas with foci of hepatic differentiation (Ishikura et al. 1985, 1986). We have adopted two criteria for a diagnosis of hepatoid adenocarcinoma: (1) a mixture of tubular or papillary adenocarcinoma with sheet-like or trabecular proliferation of neoplastic cells within an AFP-producing carcinoma, and (2) the presence of cells with abundant, eosinophilic cytoplasm and centrally located nuclei in sheet-like or trabecular portions, resembling those of hepatocellular carcinoma cells.

Hyaline globules (HGs) will be described as type I or II according to a previous description (Ishikura et al. 1986). Briefly, type I HGs are membrane-bound and consistently seen in intracytoplasmic lumina, and have a target-like appearance. Type II HGs are not membrane-bound and seen both intracellularly and extracellularly, and are round and homogeneous.

Paraffin blocks from each of the seven cases were recut and

stained with haematoxylin and eosin (H&E), mucicarmine, alcian blue, periodic acid-Schiff (PAS) with and without diastase digestion, and Hall's bile stain. For immunohistochemical reactions, the peroxidase-antiperoxidase method was employed on formalin-fixed, paraffin-embedded material. Rabbit antibodies employed included anti-human AFP, albumin (ALB, Cases 1 and 5), alpha 1-antitrypsin (AAT), alpha 1-antichymotrypsin (ACT), and carcinoembryonic antigen (CEA). These rabbit antibodies, as well as goat anti-rabbit immunoglobulin and the peroxidase-antiperoxidase complex, were purchased from Dako, Copenhagen, Denmark. The activity of endogeneous peroxidase was blocked by a preincubation of slides with 0.01% H_2O_2.

Case reports. Brief clinical details are shown in Table 1.

Results

Histologic findings

Case 1. The pulmonary tumour is a papillary and tubular adenocarcinoma merging almost imperceptably with foci of compact sheets of cells (Fig. 1). The adenocarcinoma portion is conspicuous as shown by Yasunami (1981), and is composed of columnar to cuboidal cells. In some areas with a well-differentiated tubular adenocarcinoma, columnar neoplastic cells have striated borders (Fig. 2), and have many intracytoplasmic lumina. In the sheet-like portions, the neoplastic cells have abundant, eosinophilic cytoplasm, with some foci being associated with PAS-positive, diastase-resistant HGs of type I and II. In the sheet-like areas, neoplastic cells form solid nests of various size packed together. Mucin is sometimes observed in the intracytoplasmic lumina. Glycogen is demonstrated in a small number of neoplastic cells. Keratinization is not seen. No teratomatous or germ cell components were observed. These features are consistent with a diagnosis of hepatoid adenocarcinoma.

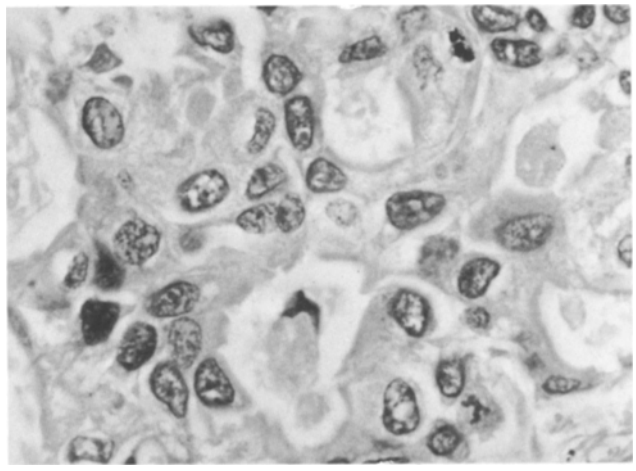


Fig. 2. Hepatoid adenocarcinoma of the lung (Case 1). Many neoplastic cells have a striated border at their luminal surfaces. (H&E, ×788)

Case 2. The neoplastic cells in the sheet-like areas resemble hepatocellular carcinoma cells in that they have abundant, eosinophilic cytoplasm and central nuclei (Fig. 3 and 5B in Miyake et al. 1987). In some areas, the tumour cells have clear cytoplasm. PAS-positive, diastase-resistant HGs of type I and II are numerous. Small amounts of glycogen are demonstrated in many neoplastic cells. Extensive necrosis, as well as lymphocytic and polymorphonuclear infiltration, is seen. No teratomatous or germ cell components were observed. The tumour in the lung was diagnosed as hepatoid adenocarcinoma.

Case 3. The tumour is composed of sheets of large, polygonal cells, and occasional papillae with central, thin fibrovascular cores. The neoplastic cells have abundant,

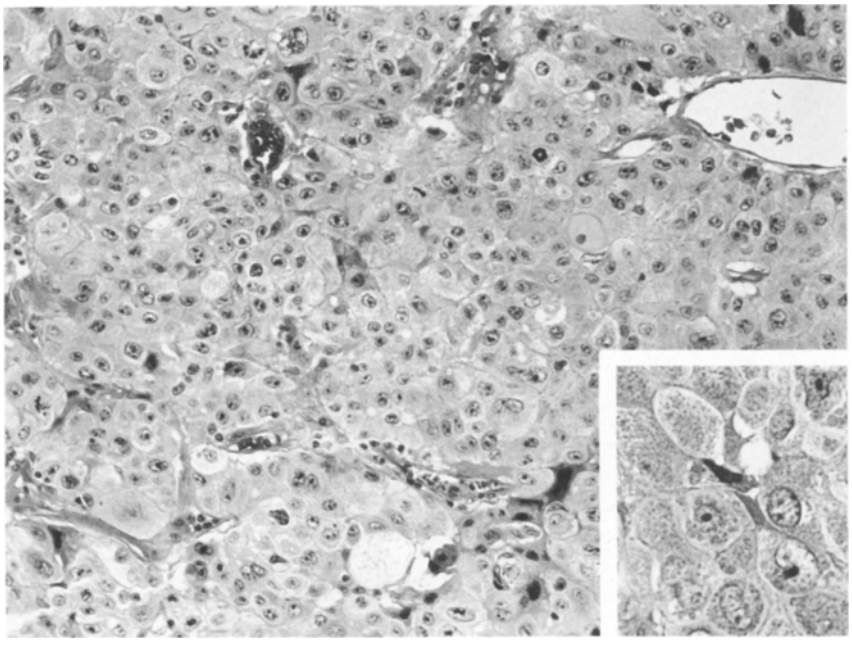
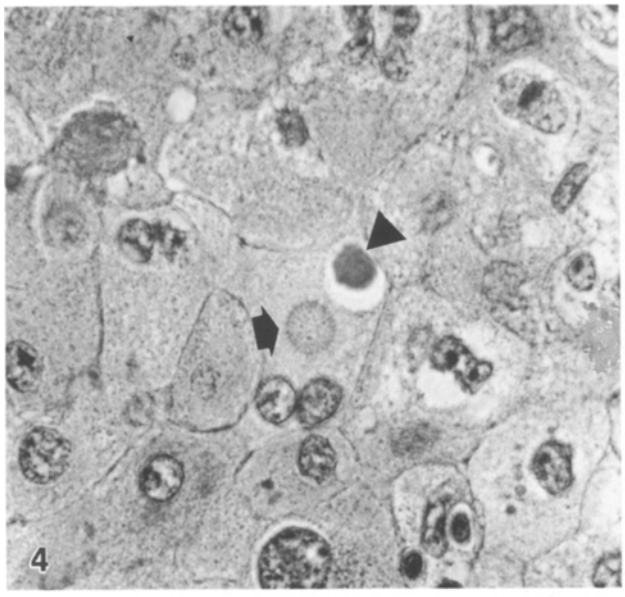


Fig. 3. Hepatoid adenocarcinoma of the lung (Case 3). The neoplastic cells have abundant, eosinophilic cytoplasm, resembling those of a hepatocellular carcinoma. (H&E, ×200). *Inset*: In some areas, neoplastic cells are packed with eosinophilic, tiny globules. (H&E, ×500)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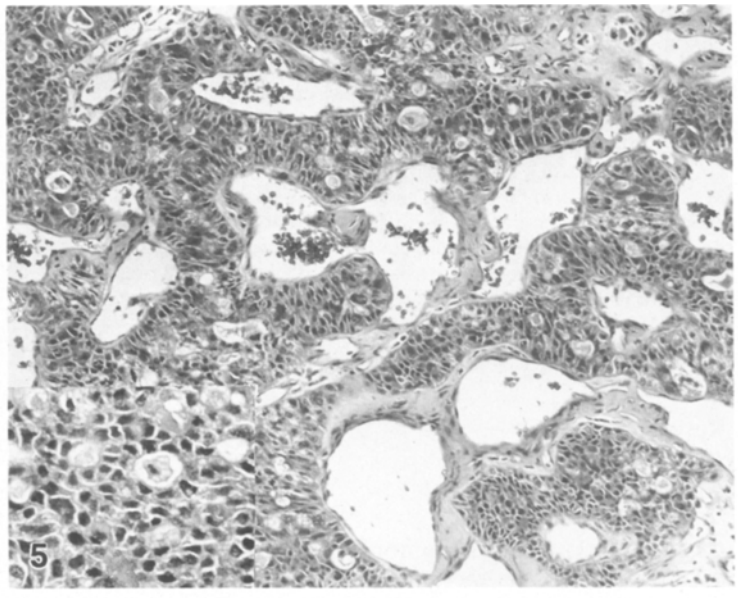
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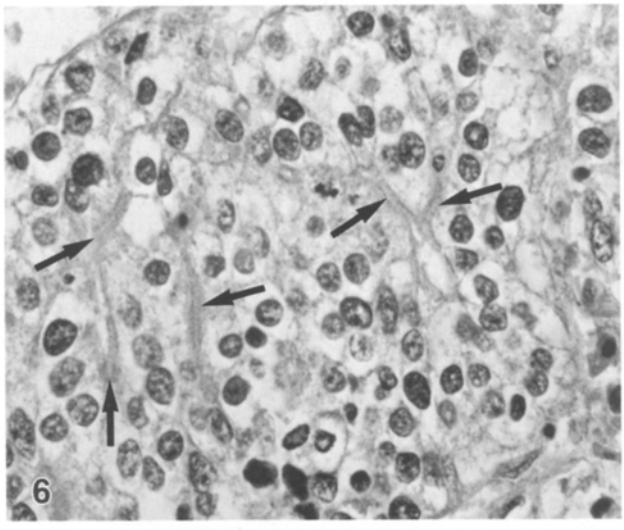
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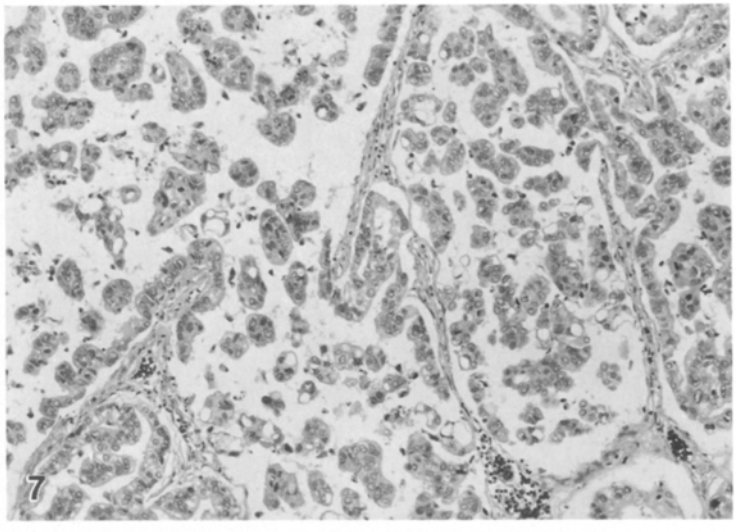
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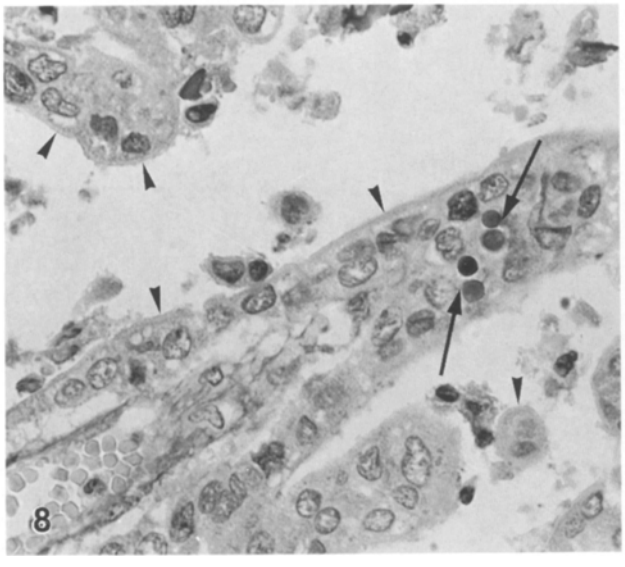
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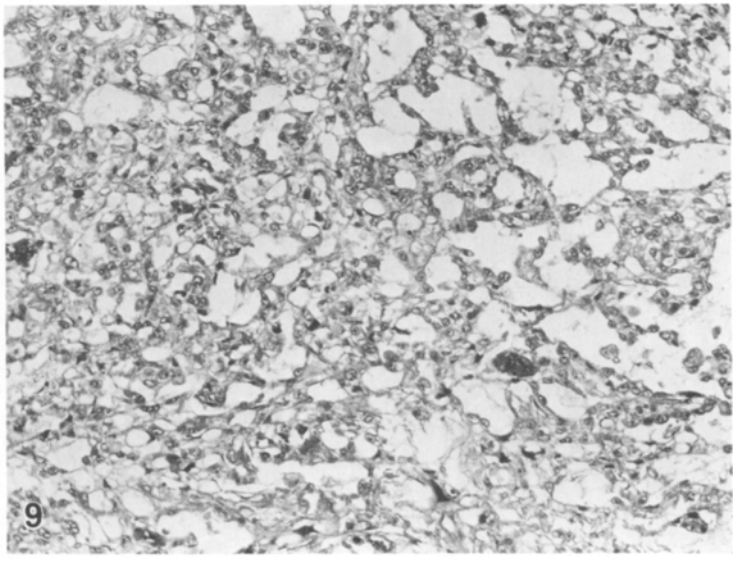
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eosinophilic cytoplasm (Fig. 3), resembling hepatocellular carcinoma cells. In some foci, the neoplastic cells are filled with eosinophilic globules of various size. Some of them are uniformly small (Fig. 3, inset), and are negative for PAS. There are foci of large cells with many HGs of type I and II. Several typical examples of intracytoplasmic lumina with peripheral halo and spikes (spicular bodies) are seen (Fig. 4). A large amount of glycogen is demonstrated in many tumour cells. No teratomatous or germ cell components were observed. Although well-differentiated tubular/papillary adenocarcinoma portions were not observed, the tumor was diagnosed as hepatoid adenocarcinoma.

Case 4. The tumour is composed of cells with both sheet-like growth and tubule formation, with the former predominating. In many areas, the neoplastic cells are small, with high nuclear/cytoplasmic ratios. In such areas, the nuclei are hyperchromatic and irregular in shape, resulting in a primitive appearance. In other areas, the neoplastic cells have large amounts of eosinophilic cytoplasm. Canaliculi are seen among neoplastic cells. Even in the sheet-like areas, tubular lumens and intracytoplasmic lumina with or without HGs or mucin are found. Mucin is secreted extensively into tubular lumens. In many areas, anastomosing trabeculae reminiscent of those of a hepatocellular carcinoma are seen (Fig. 5). A network of dilated capillaries is obvious between trabecular-like nests. A large amount of glycogen is demonstrated in many tumour cells. No teratomatous or germ cell components were observed. A diagnosis of hepatoid adenocarcinoma was made.

Fig. 4. Hepatoid adenocarcinoma of the lung (Case 3). A typical intracytoplasmic lumen with peripheral halo and spikes is shown (*arrow*). Intracytoplasmic lumina with peripheral halo and spikes vary in size. A peripheral halo is not conspicuous in this particular example of spicular body. *Arrowhead*: type II hyaline globule. (H&E, ×788)

Fig. 5. Hepatoid adenocarcinoma of the lung (Case 4). The neoplastic cells from anastomosing trabeculae separated by dilated vessles (H&E, ×125). *Inset*: Note tubular lumens filled with mucinous substance and the primitive appearance of tumour cells with high nuclear/cytoplasmic ratio. (H&E, ×313)

Fig. 6. Hepatoid adenocarcinoma of the lung (Case 5). In this sheet-like area, the neoplastic cells have clear cytoplasm, in which glycogen was demonstrated. Branching intercellular canaliculi are seen (*arrows*). (H&E, ×500)

Fig. 7. Papillary adenocarcinoma, resembling a serous ovarian tumour (Case 6). (H&E, ×125)

Fig. 8. Papillary adenocarcinoma, resembling a serous tumour (Case 6). The neoplastic cells are columnar to cuboidal, and have eosinophilic cytoplasm. Note conspicuous striated apical borders of neoplastic cells (*arrowheads*) and type II hyaline globules (*arrows*). (H&E, ×500)

Fig. 9. Endodermal sinus tumour of the lung (Case 7), with predominant reticular pattern. (H&E, ×125)

Case 5. The lung tumour is composed of cells with abundant, eosinophilic cytoplasm. Occasional cells have water-clear cytoplasm. The tumour cells are arranged predominantly in a sheet-like fashion, and tubular or papillary adenocarcinoma areas are rare (Fig. 6). However, even in the sheet-like areas, numerous small lumina are seen. There are many intracellular lumina with peripheral halo and spikes (spicular bodies), often containing mucin. Intercellular canaliculi with peripheral halo and spikes (spicular bodies) and eosinophilic material in the lumens are occasionally observed (Fig. 6). A very large amount of glycogen is found in the cytoplasm of most of the tumor cells. Extensive necrosis is present, and the tissue surrounding the tumor is fibrotic with scattered lymphocytic infiltration. No teratomatous or germ cell components were observed. A diagnosis of hepatoid adenocarcinoma is made.

Case 6. It showed fine papillae lined by columnar to cuboidal cells, resembling a serous adenocarcinoma (Fig. 7). The cytoplasm of the neoplastic cells is usually eosinophilic, but in some areas, water-clear. Glycogen is demonstrated in many tumour cells. Most of the columnar cells have striated borders (Fig. 8). Groups of cells have vacuolated cytoplasm. Sheets of neoplastic cells are seen only in several tiny foci, in which type I and II HGs/intracytoplasmic lumina with peripheral halo and spikes (spicular bodies) are seen. Type II HGs are observed in columnar cells lining the fine papillae (Fig. 8). There are foci with calcification, some of them similar to psammona bodies. Extensive necrosis is seen, especially at the center of neoplastic nests. No teratomatous or germ cell components were observed.

Case 7. The tumour is composed of cells arranged in a reticular pattern or forming small, indifferent glands, associated with many PAS-positive, diastase-resistant HGs. The findings are consistent with a diagnosis of endodermal sinus tumour (Fig. 9). Schiller-Duval bodies are not found. In a small area, the cytoplasm of the neoplastic cells is abundant and eosinophilic, and these cells form sheet-like nests, representing hepatic differentiation. In another small area, tumour cells form fine papillae, with a high nuclear to cytoplasmic ratio. Necrosis is a prominent finding. The nuclei of neoplastic cells are hyperchromatic, and contain one or more nucleoli. A large amount of glycogen is demonstrated in most of the neoplastic cells, including cells in the hepatoid, serous-like, and reticular portions. A polyvesicular vitelline pattern, or other teratomatous elements, are not seen.

Immunohistochemical findings

AFP was demonstrated in varying numbers of neoplastic cells in all the cases except for Case 4. Immunoreactive AFP was found in the cytoplasm and in intracytoplasmic and extracellular lumina in sheet-like areas of Cases 1–3,

and 5. Some cells lining glands were also positive for AFP. In Case 6, many columnar to cuboidal cells lining fine papillae were stained for AFP. In Case 7, many anti-AFP-reactive cells were dispersed throughout the tumour, including areas with a fine papillary architecture. AAT and ACT were demonstrated in a small number of cells in the cytoplasms and intracytoplasmic and extracellular lumina in Case 1–3, and 5. In Case 6, many columnar cells were positive for AAT and ACT. In Case 7, AAT and ACT were demonstrated in numerous tumour cells in a pattern similar to that of AFP. ALB was demonstrated predominantly in intracytoplasmic and extracellular lumina in Cases 1 and 5. Staining for CEA was predominant in intracytoplasmic lumina and along the surfaces of glandular epithelial cells in Cases 1–3, and 5, and along the surfaces of columnar epithelial cells in Case 6. In Case 7, CEA was intensely stained in glands lined by cuboidal cells. In Case 4, no cells stained for AFP, AAT, ACT, or CEA.

Certain general features of hepatoid cells were identified. They have abundant, eosinophilic cytoplasm with centrally located nuclei. The nuclei are usually round, but occasionally elongated. PAS-positive, diastase-resistent hyaline globules are sometimes seen. Spicular bodies are found after an extensive review of slides.

Discussion

Among the seven cases of AFP-producing lung carcinomas, five tumours (Cases 1–5) were diagnosed as hepatoid adenocarcinoma. The adenocarcinoma component usually predominates in hepatoid adenocarcinomas of the stomach, while, although this component was also substantial in the lung cases, it was less prominent. In Case 1, striated borders, a characteristic of intestinal absorptive cells, were observed in most of the neoplastic cells in a tubular adenocarcinoma area (Fig. 2). Intracytoplasmic lumina with peripheral halo and spikes (spicular bodies) shown in Fig. 4 have been claimed to represent the neoplastic cells intestinal absorptive or biliary tract characteristics (Ishikura 1990). Moreover, many neoplastic cells in a hepatoid adenocarcinoma of the stomach have been shown to have microvilli with actin cores (Ishikura et al. 1985). These findings imply that hepatoid adenocarcinoma cells have features of intestinal absorptive cells.

Bile pigment was not found in any of the five cases of hepatoid adenocarcinoma of the lung but failure to find it does not necessarily indicate a lack of hepatic differentiation. Only a fraction of hepatocellular carcinomas produce bile (Anthony 1979). It should be emphasized, however, that, although the neoplastic cells in the hepatoid components of stomach tumours resemble hepatocellular carcinoma cells, and even produce bile in a few cases, cells with intestinal characteristics are also a substantial component of hepatoid adenocarcinomas.

The Con A-binding property of serum AFP from two cases of hepatoid adenocarcinoma of the stomach was of the hepatic type; about 90% of the AFP bound with Con A (Ishikura et al. 1986). In the other gastric cases, the Con A-binding property was not examined. In the hepatoid adenocarcinoma of the lung, the Con A-binding properties of patients' serum AFP in Cases 2, 3, and 4 were 18.7, 52.1, and 80.7%, respectively. The figure in Case 4 is consistent with a hepatic differentiation of neoplastic cells, but, in Case 2, the serum AFP was not of hepatic type. In Case 3, the figure, 52.1%, fell between those of Cases 4 and 2, and was not conclusive for a hepatic differentiation. Therefore, it appears obvious that further accumulations of cases are necessary regarding the presumptive relation between the histological manifestations of an AFP-producing tumour and the Con A-binding property of serum AFP produced by the tumour.

The possibility that a hepatoid adenocarcinoma of the lung originates from ectopic liver should be considered; a neoplasm arising from ectopic liver in the lung has been reported (Shah et al. 1987). However, supradiaphragmatic ectopic livers have generally been reported to be in the vicinity of the diaphragm, (Mendoza et al. 1986; Le Roux 1961) and it seems likely that neoplasms arising from them should be located in the lower lobes. Four of the five hepatoid adenocarcinomas of the lung in the present study, however, originated in the upper lobes of the lungs (Table 1). We suggest it is unlikely that the hepatoid adenocarcinoma of the lung originates from ectopic liver.

A germ cell-origin of the hepatoid adenocarcinoma of the lung may also be considered since AFP-producing germ cell tumours with hepatoid features (hepatoid yolk sac tumours (HYST) Prat et al. 1982) have been reported. In addition, hepatocellular differentiation can be seen focally in a variety of germ cell tumours (Nakashima et al. 1987). A HYST has hepatoid features but other histological patterns of germ cell tumours may also be associated with HYST (Prat et al. 1982). The ages of the patients with hepatoid adenocarcinoma of the lung (average 61 years) differ from those of HYSTs (average 22 years) (Ishikura and Scully 1987). Intrathoracic ectopic germ cell tumours have mostly been found in the mediastinum, and intrapulmonary germ cell tumours have been reported in infants and young adults very rarely (Ali and Wong 1964; Collier et al. 1959; Gautam 1969; Trivedi et al. 1966). Origin of hepatoid adenocarcinoma of the lung from ectopic germ cells thus also appears unlikely.

Hepatoid adenocarcinoma may arise from the respiratory epithelium and neoplastic epithelial cells thus have the potential to express the characteristics of cells in digestive organs in tumours. Intestinal-type adenocarcinomas have been reported in the respiratory epithelium (Barnes 1986; Marcus et al. 1982). Recently, hepatocytes were identified in carcinogen-induced or copper-deletion-induced regeneration of the pancreas of the hamster and rat (Rao et al. 1982, 1986).

The differential diagnosis of hepatoid adenocarcinoma of the lung include primary large cell carcinoma, adenocarcinoma, and metastatic carcinoma, especially from the liver, stomach and ovary. The original diagnoses of the five cases of hepatoid adenocarcinoma of

the lung were large cell carcinoma (Cases 3 and 5) (Miyake et al. 1986; Yokoyama et al. 1981), poorly differentiated adenocarcinoma (Cases 2 and 4) (Miyake et al. 1986, 1987) and moderately differentiated adenocarcinoma (Case 1) (Yasunami et al. 1981).

A large cell carcinoma can be differentiated from a hepatoid adenocarcinoma by the fact that these tumours generally do not produce AFP. Whenever a "large cell carcinoma" with or without mucin secretion is composed of large, eosinophilic cells, and produces AFP, a diagnosis of hepatoid adenocarcinoma should be suspected, and an association of tubular/papillary adenocarcinomatous portions, as well as the presence of spicular bodies, should be sought. Conversely, in cases of AFP-producing "adenocarcinomas" of the lung, a search for a sheet-like growth of neoplastic cells with abundant, eosinophilic cytoplasm should be performed.

A clinically important differentiation is from hepatocellular carcinoma metastatic to the lung. Association with hepatic cirrhosis may be helpful in the differential diagnosis. Gross findings, including the distribution of lymph node metastases, should also be helpful. The frequent presence of tubular/papillary adenocarcinomas favors a diagnosis of hepatoid adenocarcinoma.

Metastases from AFP-producing gastric and ovarian tumors should also be considered. The histologic appearances of hepatoid adenocarcinomas of the stomach and those of the lung are similar, and a metastatic lung mass was found in two of seven cases of hepatoid adenocarcinoma of the stomach (Ishikura et al. 1986). An endoscopic or x-ray examination of the stomach may be necessary to exclude a possible gastric origin. Possible origin of the tumor in the ovary should be excluded, in women. The reported examples of hepatoid carcinoma of the ovary, which occurs at an average age of 63 years (Ishikura and Scully 1987), have not had a papillary/tubular adenocarcinoma component. Carcinomas of the ovary are rarely associated with lung metastases except in late stages of the disease when extensive abdominal spread is typically present.

Other AFP-producing lung tumours found in this study include an EST (Case 7) and a tumour composed of columnar to cuboidal cells with fine papillae resembling a serous adenocarcinoma (Case 6). Although serous features have not been recognized in hepatoid adenocarcinoma of the stomach, they have been reported in an AFP-producing ovarian neoplasm (Higuchi et al. 1984). However, striated borders were demonstrated in most of the neoplastic cells, even in the areas with a serous appearance (Fig. 10). Moreover, in some tiny sheet-like foci, spicular bodies were frequently found. Therefore, Case 6 appears to be a papillary adenocarcinoma of intestinal epithelial type, and may be related to hepatoid adenocarcinoma.

An endodermal sinus tumour (EST) of the lung is extremely rare, although a similar tumour of the mediastinum has occasionally been reported (Mukai and Adams 1979; Friedman 1951). ESTs of the mediastinum are said to arise from ectopic germ cells (Mukai and Adams 1979). It is difficult, however, to postulate an origin of the EST in Case 7 from germ cells, because the lung is an unusual site for germ cell tumours, although teratomas have been found in the pulmonary parenchyma of infants and young adults (Ali and Wong 1964; Coller et al. 1959). An alternative explanation for the origin of EST in Case 7 is the somatic, respiratory epithelium. ESTs arising from the gastric epithelium and the prostate have been reported at ages of 65 and 51 years, respectively (Garcia and Ghali 1985; Benson et al. 1978). Transitional cell carcinomas with EST-like features have been reported in the nasopharynx and paranasal sinuses of 43- and 34-year old patients (Manivel et al. 1986). These tumours appear to be examples for ESTs originated from somatic epithelial cells.

In summary, hepatoid adenocarcinomas similar to those seen in the stomach are the predominant histological form of AFP-producing lung carcinoma, although a single EST and a single papillary adenocarcinoma similar to a serous carcinoma have also been found. The papillary tumour may be related to intestinal differentiation as in hepatoid adenocarcinomas. To find hepatoid adenocarcinomas in two organs of endodermal origin, raises the possibility that tumours with a similar histologic appearance and AFP production may be found in other endodermal organs, especially those derived from the endoderm adjacent to the embryonic liver bud (gallbladder, bile ducts, pancreas, and duodenum).

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