PRIMARY CARCINOMA OF THE LIVER

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INTRODUCTION

Primary carcinoma of the liver occurs in 0.028 to 0.03 percent of all necropsies according to the statistics collected by Winternitz. A number of cases have been reported in the literature but this form of cancer occurs very rarely in the experience of any one pathologist.

It is the purpose of the present investigation to compare two cases of carcinoma of the liver, the first case being that of apparently primary growth in the liver while the second case had its primary focus in the gall bladder, from which the growth directly invaded the liver. These cases occurred at successive necropsies.

The following questions concerning the case of primary carcinoma will be considered: (1) whether the cancer is derived from liver cells or from cells of the smaller bile ducts; (2) whether there is any relation of the malignant growth to cirrhosis; (3) whether the growth takes place by a gradual metamorphosis of liver cells into cancer cells, or by autocellular proliferation; and (4) whether the cancer is multicentric or unicentric in origin.

According to Wegelin the most important and reliable differential feature between cancers derived from liver cells and those derived from the cells of the small bile ducts is the nature of the stroma, liver cell cancers having a capillary stroma, while the bile-duct-cell cancers have a predominantly connective tissue stroma.

The majority of investigators believe that cirrhosis precedes primary malignancy and is the causative factor. Cirrhosis is thought to be preceded by injury and followed by hyperplasia.
of the liver cells. The hyperplasia continues and takes on malignant character.

v. Heukelom and other investigators have found in cases of primary carcinoma of the liver what appeared to be transitions from the liver cells to cancer cells and have interpreted such findings as appositional growth in which a gradual metamorphosis from liver cell to cancer cell took place. This hypothesis has been attacked chiefly by Ribbert, who claims that the growth of primary liver cancer is from one focus.

Because of the demonstration of the so-called transitions in multiple small cancerous nodules in the liver, v. Heukelom, Travis, and others considered that primary liver cancer was multicentric in origin. Ribbert and Winternitz, on the other hand, deny the multicentricity of origin, and their investigations tend to show that the neoplasm arises from a primary focus and that the growth develops by extension and metastases through the portal system.

I find in the cases here to be reported that there is a close similarity between some of the microscopic pictures presented by the primary cancer and those presented by the cancer arising in the gall bladder and secondarily invading the liver. In the case of primary carcinoma the neoplasm apparently arises from the liver cells. Cirrhosis is not marked and is secondary to the neoplasm. The mode of growth is autogenous, and the origin is unicentric.

REPORT OF CASES

1. A case of primary carcinoma of the liver.

Clinical Note. The patient, a white woman sixty-three years old, was admitted to the University of Virginia Hospital, March 26, 1920, complaining of weakness, nausea, and rather vague pains in the abdomen. The patient began to lose strength and weight about two months prior to admission. About three weeks before admission her abdomen became distended and a little later she became jaundiced. On physical examination the margin of the liver could be palpated below the costal margin. A diagnosis of carcinoma of the liver was made. Three days after admission the patient died.
Necropsy note. The body is that of a rather well nourished old woman, with an intense yellow color. The abdomen is prominent and rather tense.

Upon opening the peritoneal cavity a large amount of bile stained fluid escapes. The liver extends about 5 cm. below the costal margins. The omentum is adherent to the liver and gall bladder by easily separated adhesions. There are enlarged and very hard nodules in the gastrohepatic omentum. The lymph nodes of the mesentery and small intestine are not enlarged. The intestines show subserous ecchymoses.

Upon opening the pleural cavity there is no free fluid found. There are a few old fibrous adhesions between the lungs and the chest wall. The pericardial cavity shows a normal amount of bile stained fluid. The lungs show a recent process of bronchopneumonia in the right upper lobe. The heart, spleen, stomach, intestines, pancreas, adrenals, ureters, bladder, uterus, ovaries, and the thyroid show nothing of special interest and no evidence of neoplastic change. The kidneys present the picture of chronic interstitial nephritis. The retroperitoneal tissue presents no evidence of malignancy. The wall of the gall bladder is thickened and upon opening it there is found a dark almost tarry bile, and several brown rather hard stones. There is no tumorous growth of the gall bladder. The cystic and common duct traced into the intestine show no obstruction. The brain and spinal cord are not examined.

Microscopic study of the above-mentioned tissues fails to demonstrate any malignant neoplasm. There are metastases to the lymph nodes of the gastrohepatic omentum.

The liver is slightly enlarged and presents a very peculiar appearance. There is a background of grass-green tissue with yellow tracings. Splotched about on the surface are areas, roughly circular in shape, of a grayish yellow color with a depressed center and a slightly raised border, and with a suggestion of radial striations. In some cases these areas have a pinkish tinge due to congestion. The average size of these areas is about 2 cm., and they cover about half the surface area of the liver. The liver borders are sharp. The whole liver is rather firm and the above-mentioned spots seem firmer than the surrounding tissue.

On gross section, again there is discernible a grass-green background traced with yellow and punctuated with the above-
described roughly circular spots which appear more granular than the liver tissue (fig. 1). The centers of these spots retract promptly after section. The greater portion of the neoplasm is situated in the right lobe and here was probably the primary focus. The veins do not seem to be involved in the cancerous growth and are patent.

Microscopically a variety of pictures are seen. These may be divided into three general types: (1) fields in which only liver tissue is seen; (2) fields containing both liver tissue and malignant tissue, and (3) fields exclusively cancerous.

Type 1. The liver tissue shows all stages of degeneration. The more normal cells show cloudy swelling, while in the areas of greatest degeneration fatty changes are marked. Degeneration seems to be more marked at the periphery of the lobules. There is no evidence of regeneration or hyperplasia. No mitotic figures are seen, but occasionally cells with double nuclei are present. There is no increase in the stroma. In some areas the capillary sinusoids are congested. The bile ducts appear normal and there are no cancer cells in the portal veins.

Type 2. The picture presented by this type of field gives the impression that the liver tissue is melting away before the invading cancer cells. First, there is a zone of liver cells which are in a fair state of preservation. From this zone there is a gradual transition into a second zone in which degenerative changes of the liver tissue are marked, and become more marked as the zone formed by the cancer cells is approached.

In the first zone, with the exception of cloudy swelling of the liver cells, there is nothing abnormal. In the second zone degeneration becomes marked, and the cytoplasm of the cells is filled with vacuoles (figs. 3 and 4), probably due to fatty changes. The nuclei are small and stain deeply. There is no evidence of regeneration of the liver cells. There is no increase in the stroma and the arrangement of the cells is normal. The cancer cells of the third zone are arranged in trabeculae (figs. 3 and 4). The predominant cell is polyhedral and somewhat larger than the liver cell. The cytoplasm is granular and stains a bright pink with eosin. The nucleus is large and hyperchromatic.
Mitotic figures are numerous in this region and occasionally an atypical figure can be observed (fig. 3). In some cases there is direct continuity between the column of cancer cells and the liver trabecula, but the cancer cell and the liver cell in apposition with it are sharply differentiated (figs. 3 and 4). There is no evidence of a transition from liver to cancer cells; the liver cells next to the cancer cells are necrotic. The stroma is composed of capillaries. The invading cancer cells make use of and grow between the pre-existing parallel capillaries of the liver trabeculae (figs. 3 and 4).

Type 3. Passing from the newer regions of the cancerous growth above-described into the more mature areas, the picture is somewhat altered. The stroma is increased, and while it is still made up largely of capillaries the connective tissue elements are also multiplied. The cancer cells are divided into islands by the stroma, and the trabecular formation is lost. The cells are somewhat smaller than the newly formed cells, and the nuclei take a deeper stain. There is no mitosis but some of the cells have double nuclei. The central portion of a large cancer nodule often shows necrosis.

2. A case of primary carcinoma of the gall-bladder, with invasion and metastases in the liver.

Clinical note. The patient, a white woman, sixty-three years old, was admitted to the University of Virginia Hospital March 23, 1920, complaining of loss of weight and progressive weakness. Two months prior to admission a mass was noted in the abdomen. The patient died eight days after admission.

As the present interest in this case centers about the liver, the details of the necropsy will be omitted.

The liver is about one and a half times its normal size, and the right lobe shows the most enlargement. The enlargement in the right lobe is accompanied by numerous nodular, irregular protuberances with discolored areas looking like venous blood. These nodular protuberances remind one very much of bunches of varicose veins just beneath the liver surface. In other areas,
notably in the left lobe, there are also enlargements which, however, do not show the blood color but appear as nodular pale white lumps beneath the surface. Between these two extremes are various stages. The liver tissue between these raised areas is pale, mottled, and yellow. The organ is rather soft in consistency, the varicose areas above-mentioned give a semi-fluctuating sensation.

On gross section a confusing array of appearances is seen, and as the liver is cut a quantity of dark bloody grumous material escapes as if under pressure. Very little liver tissue can be seen on section through the right lobe. The varicose nodules appear as dirty, grayish, soft, granular tissue, interspersed with numerous spaces containing dark, semi-fluid blood. These areas vary in size and seem to be well circumscribed. The liver in places shows a great excess of fibrous tissue. There are some areas which appear as dirty whitish growths that do not show much hemorrhage (fig. 2). These correspond to the nodular growths seen from the surface.

The surface of the gall-bladder is roughened, due to the separation of adhesions between it and the transverse colon. The wall of the organ is thickened, and upon being opened a mass of fungoid, pale, rather soft tissue is found nearly obliterating the cavity. The cancerous wall is thick and cartilaginous (fig. 2). In the fundus is a solitary oval stone. The growth in the gall-bladder bears a close resemblance to the cancerous extensions in the liver.

Under the microscope a great portion of the tissue from the liver shows hemorrhage and necrosis. In the less affected areas the pictures differ according to the age of the malignant invasion of that region. In the more mature regions the nodules of cancer cells are surrounded by dense bands of connective tissue. The cancer cells are cuboidal. They have a granular cytoplasm and large hyperchromatic nuclei. Some of the cells contain double nuclei, but mitotic figures in these areas are rare. In some places the cancer cells have invaded the surrounding connective tissue and entered the blood vessels. There is a round cell infiltration of the connective tissue stroma and in places groups
of hyperplastic liver cells are seen. These groups of cells have an irregular arrangement which bears no relation to the normal arrangement of liver cells. The cytoplasm of these cells takes a bluish tint with hematoxylin and eosin staining, and the nuclei are hyperchromatic. These cells are easily distinguished from carcinoma cells (fig. 5).

In the younger regions the picture is one of invasion of the liver tissue by cancer cells, with degeneration and disappearance of the liver tissue before the advancing cancer cells. The liver cells proximal to the cancer cells show the greatest amount of vacuolar degeneration. In these areas there is no evidence of hyperplasia of the liver cells. The cells have a normal arrangement and the stroma is not increased. The cancer cells are arranged in trabeculae. The cells are polyhedral, somewhat larger than the liver cells, and contain large hyperchromatic nuclei. Mitotic figures are frequent. In some cases the columns of cancer cells are in direct continuity with the columns of the liver cells and grow by advancing between parallel capillaries of the pre-existing liver tissue, destroying and replacing the liver cells in their advance. Thus, in this region of invasion, the cancer cells have a capillary stroma (fig. 6). In the older regions this capillary stroma is supplemented by the growth of connective tissue which becomes the predominating element. In some instances the cells of this cancer show a tendency to the formation of duct-like structures.

**REVIEW OF LITERATURE**

The rarity of primary carcinoma of the liver is shown in the following table:

<table>
<thead>
<tr>
<th>INVESTIGATOR</th>
<th>NEUROPSIES</th>
<th>CASES</th>
<th>PER CENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldzieher and v. Bokay (7)</td>
<td>6,000</td>
<td>18</td>
<td>0.03</td>
</tr>
<tr>
<td>Wheeler (28)</td>
<td>5,233</td>
<td>15</td>
<td>0.028</td>
</tr>
<tr>
<td>Winternitz (30)</td>
<td>3,700</td>
<td>6</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>14,933</strong></td>
<td><strong>39</strong></td>
<td><strong>0.024</strong></td>
</tr>
</tbody>
</table>

*Average per cent.*
The condition occurs at all ages, but according to statistics given by Yamagiwa (31) about 50 per cent of cases occur between the ages of forty and sixty years. Statistics by the same author show a slight preponderance in males.

Heredity, as in other malignant conditions, may play a part in primary liver cancer, but in the majority of cases the family history is negative. Hedinger (9) reports primary carcinoma occurring in two sisters. By breeding with selected strains of mice, Maude Slye (23) was able to produce a strain in which the incidence of primary malignancy of the liver was high.

Clinically there is no definite picture produced by the disease. Karsner (13) states that in the majority of cases the symptoms are those of cirrhosis. The earliest symptoms are vague gastrointestinal disturbances. After the tumor develops there is a loss of flesh, cachexia, and digestive disturbances. Icterus is present in 63 per cent of cases; ascites in 58.5 per cent; edema in 41 per cent; splenic tumor in 32 per cent; and fever in 14 per cent of cases. The condition is not very often diagnosed.

A number of cases have been reported in which primary carcinoma of the liver has been associated with some other disease in the liver. Syphilis has been reported by DeMassary (16). Modena (18) has described cancer associated with echinococcus cysts. In a case reported by Cleland (3) leprosy bacilli were demonstrated.

Primary carcinoma of the liver is a rapidly fatal condition. The duration of the disease seldom exceeds three months. Castle (2) reports a case which died fourteen days after the onset of symptoms, while Ribadeau (19) reports a case which lasted for four years.

Although a very malignant disease, surgical intervention has met with some success. Schlimpert (22), Keen (14), Williams (29) and Freeman (6) have reported operations for this condition in which the tumor was removed and the cavity curetted or in which the whole affected lobe was successfully removed. Yoe-mans (32) reports an operation for a recurrence seven years after the removal of the primary growth.
Since Hanot and Gilbert (8) divided primary carcinoma of the liver into three groups, cancer massif, cancer nodulaire, and cancer avec cirrose, there have been a number of classifications advanced. Goldzieher and v. Bokay (7) divide primary liver cancers into two main groups: (1) those derived from the small bile ducts or "carcinoma cholangiocellulare," and (2) those derived from the liver cells or "carcinoma hepatocellulare." Yamagiwa (31) simplifies this terminology, calling the two types "cholangioma" and "hepatoma" respectively. This is probably the most logical basis for classification. Ewing (5) accepts these terms but classifies under them both benign and malignant epithelial neoplasms arising from the cells of the small bile ducts and from the liver cells.

A number of criteria have been advanced for the differentiation of hepatomata and cholangiomata. Ribbert (20) says that the malignant adenomata which he considers derived from liver cells are usually colored by bile pigment within the cells. Eggel (4) lays great stress upon the morphology of the cancer cell itself, but because of the similarity between the cells of the two classes in certain cases this criterion is limited, for while cancer in many cases conforms to the structure from which it is derived, in other cases this does not hold true.

Wegelin (27) concluded that the liver cell cancer has a stroma composed only of a network of capillaries. The bile-duct-cell cancer has a stroma of relatively abundant connective tissue.

Adelheim (1) agreed with Wegelin (27), and by using preparations stained with silver nitrate showed that the supporting framework in liver cell carcinoma possessed striking similarities to that of normal liver tissue.

The combined statistics of Eggel (4), Yamagiwa (31), and Goldzieher and v. Bokay (7) show that 87 per cent of the cases of hepatoma are associated with cirrhosis, while cirrhosis is found in 50.6 per cent of cases of cholangioma. Every possible hypothesis regarding the relationship of tumor formation to cirrhosis has been advanced. Because the most cirrhotic areas in their material were free from cancer, Kelsch and Keiner (15) concluded that the two processes were entirely independent.
The finding of some other morbid condition in the liver associated with cancer led some investigators to suggest that a disease such as syphilis might be the cause of both the malignancy and the cirrhosis. Wegelin (27) pointed out the possibility of the cirrhosis being secondary to the tumor formation. His view was that, due to its toxic effect, the cancer caused the degeneration of the liver cells with the subsequent formation of scar tissue. The theory that cirrhosis precedes the cancer in the vast majority of cases and is the direct cause of the neoplastic growth was first advanced by Sabourin (21). Schmeiden (24) regarded the hyperplastic liver cell islands which occur in cirrhosis as pre-cancerous stages. The view of Ribbert (20) that cancer arises from liver cells which have become displaced and surrounded by cirrhotic connective tissue, although particularly applicable in this case, is not adhered to by the majority of investigators. The more popular view is that, on account of injury, there is a destruction of liver tissue and that this is followed by fibrotic changes and regeneration. Regeneration leads to the production of hyperplastic nodules of liver cells. These hyperplasias are to be regarded as an expression of repair such as occurs in cirrhosis. The blastomatous degeneration expresses itself in an excess of growth beyond the margin of the processes of overgrowth and regeneration.

As early as 1878 Schuppel (25) described transitions of liver cells to cancer cells at the periphery of the innumerable tumor nodules, and it was generally conceded that each nodule arose in the place where it occurred from the pre-existing liver cells of that area. v. Heukelom (11) showed not only that the columns of liver cells were in many instances directly continuous with columns of tumor cells, but that in many cases the liver capillaries were in direct continuity with the tumor capillaries. From his observations v. Heukelom (11) concluded that primary liver cancer is multicentric in origin, and that there is a progressive metamorphosis of liver cells to tumor cells at the periphery of the growth. These observations have been repeatedly confirmed. v. Heukelom's (11) interpretation has been adopted by Milne (17), Adelheim (1), Travis (26), Goldzieher and v. Bokay (7), and numerous other investigators.
Heussi (12) observed the same pictures as v. Heukelom (11), but by staining with Orange G. the cancer cells and the liver cells were sharply differentiated, and from this he concluded that the apparent connection between tumor and liver cell was an artefact. This view is supported by Ribbert (20) and Herxheimer (10). Ribbert (20) and others have described pictures, similar to the apparent transitions, occurring in metastatic growths where the secondary nature of the cancer was unquestionable.

Regarding the metamorphosis of liver cells to cancer cells, there also is disagreement. Eggel (4) denies the possibility and considers the growth autogenous. Goldzieher and v. Bokay (7) state also that appositional growth does not occur. Wegelin (27), while he admits the possibility of appositional growth, thinks that it seldom occurs.

Adelheim (1), Milne (17), v. Heukelom (11), Goldzieher and v. Bokay (7), and other investigators, who emphasize the above-described transitions, adhere also to the theory that primary liver cancer is multicentric in origin.

The principal advocates for the theory of unicentricity of origin have been Ribbert (20) and Heussi (12). Ribbert (20) says that primary cancer is not necessarily multiple. Small metastases may form very late from the primary nodule. Secondary nodules occur through the invasion of the portal veins by the primary growth. According to this investigator most of the tumor nodules are sections of tumor cords which represent the portal vein dilated and filled with tumor thrombi. In a number of cases he was able to strip the tumor mass from out of the vein in a cast-like form. In other cases there is invasion of the portal vein by the cancer cells followed by embolus formation, and in this way metastases occur to other portions of the liver.

**DISCUSSION**

Because of the trabecular arrangement of the parenchyma, the occurrence of a stroma composed of capillaries, and the absence of any evidence of proliferative changes of the bile-duct epithelium, this example of primary carcinoma of the liver belongs to
the class of hepatoma, according to the classification of Goldzieher and v. Bokay, as modified by Yamagiwa.

The picture presented is one of invasion by the cancer cells, and not that of a gradual metamorphosis at the periphery of the cancer nodules from liver cells to cancer cells, as was said to be the case by v. Heukelom. In many instances there is direct continuity between the columns of liver cells and the columns of cancer, the cancer cells growing between parallel pre-existing liver capillaries with the same general arrangement as the liver cells. At the line of apposition, however, there is a sharp demarcation between cancer cells and liver cells. The liver cell in each case shows marked degenerative and necrotic changes. Nowhere is there hyperplasia of liver cells. This observation can only be interpreted as proving that the so-called transitions of v. Heukelom do not occur in this case and leads to the adoption of the view held by Ribbert, Heussi, and Winternitz, that this growth is autogenous and not appositional. Moreover, in the case of secondary carcinoma of the liver studied, where there was no possibility of transition from liver to cancer cells, pictures identical with those seen in the case of primary carcinoma were observed. It would seem, therefore, that the pre-emption of the liver capillaries by the cancer cells with the degeneration of the liver cells before the advancing cancer, is not restricted to primary liver carcinomas.

The absence of any transition from liver cell to cancer cell would not suggest that the growth had a multicentric origin. In the gross specimen on section, although discrete nodules of cancer tissue may be seen in one plane of section, other planes show that these apparent discrete nodules are cross sections of fingers of malignant tissue which evidently extend from the right lobe in a branching tree-like form. This would lead to the conclusion that the cancer is unicentric in origin, the primary focus being in the right lobe since the bulk of the growth is at that site.

The growth does not seem to have invaded the portal system to the extent of using the veins as a pathway of extension, as was demonstrated in the four cases reported by Winternitz.
In a few of the veins cancer cells are present, and there is a possibility that some of the nodules are metastatic, but from the gross appearance of the tumor it would seem that most of the cancer is formed by direct extension from the primary focus.

As little cirrhosis is present in this case, there could not possibly be any relation between cirrhosis and the causation of this cancer. The small increase of connective tissue occurred after the invasion of the cancer and is only found in the cancerous areas.

SUMMARY

1. On the basis of the arrangement of the cells, the presence of capillary stroma, and the absence of proliferation of the bile-duct epithelium, this carcinoma is classed as a hepatoma.

2. In the case in question, cirrhosis is not present in the liver tissue, and nowhere is there hyperplasia of the liver cells. Although there are numerous instances in which the cancer cells grow between parallel capillaries, and are in direct continuity with the liver cell trabeculae, there are no transitions between liver cells and cancer cells.

3. The growth is unicentric in origin, the primary focus being in the right lobe, from whence it grows by direct extension without using the portal system as a pathway.

4. In the case of secondary carcinoma of the liver studied, appearances very similar to those observed in the case of primary carcinoma are seen.

I am indebted to Dr. Harry T. Marshall for the privilege of using this material and for inspiration in the pursuit of this investigation.

REFERENCES

(7) Goldzieher and V. Bokay: Virchows Arch., 1911, cxxiii, 75.
Par., 1920, 3 S., xlii, 1191.

PLATE 1

Fig. 1. Gross section of left lobe of primary hepatic carcinoma. The lighter striated areas represent the cancerous nodule. The darker background is the relatively normal liver tissue. Two-thirds natural size.

Fig. 2. Gross section of left lobe of liver and attached gall-bladder. Cancerous liver tissue is shown above and to the left. The gall-bladder is shown below and to the right. The gall-bladder shows malignant degeneration. Two-thirds natural size.
PLATE 2

Fig. 3. Microscopic section of portion of liver showing two adjacent areas (at left, below) of proliferating cancer cells. The reticulated enveloping tissue is composed of necrotic liver cells. The connective tissue immediately surrounding the two cancerous nodules represents largely collapsed capillaries. This figure illustrates the advance of the hepatic cancer between parallel capillaries. Note the multiple mitotic spindle in the central cell of the lower nodule. Magnification 1000 diameters.

Fig. 4. Similar larger area of hepatic cancer cells (above, at left), showing the advance of the carcinoma between parallel capillaries, and the degeneration of the liver cells in the path of the encroaching tumor. Magnification 1000 diameters.
Fig. 5. Microscopic section from secondary hepatic cancer showing a very mature portion of the neoplasm. Above is a band of dense connective tissue. This band is infiltrated with round cells. To the left and above are groups of hyperplastic liver cells. Below is a nodule of cancer cells. Magnification 200 diameters.

Fig. 6. Area from younger portion of secondary cancer. Above and to the left is liver tissue. Below are trabeculae of invading cancer cells. Two mitotic figures are present in the field. Between the advancing malignant cells and the comparatively normal liver cells is an area of degenerated and necrotic liver cells. Magnification 400 diameters.