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Reprinted from The Journal of Pathology and Bacteriology.
Vol. XV. (1911).

Journal of Pathology and Bacteriology, Vol. XV.

PRIMARY SARCOMA ARISING IN A CIRRHOTIC LIVER.[1]

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PLATE XXVIII.

ABSTRACT OF CLINICAL NOTES.

A MAN, æt. 46, was admitted to St. George's Hospital, on 1st July 1910, with nausea, vomiting, and progressive weakness and swelling of the abdomen. There was an alcoholic history, but none of syphilis or of hæmatemesis.

The patient was somewhat wasted, and had a florid complexion due to extremely extensive dilatation of the facial capillaries. The veins of the skin over the abdomen were dilated. There was œdema of the lumbar region, but none elsewhere. The skin was slightly jaundiced. There was tenderness over the liver, and the margin could be felt below the costal arch in the nipple line. The spleen was not palpable. The urine (acid, sp. gr. 1024) was free from albumin and sugar. The abdomen measured 37 inches and contained free fluid.

As the ascitic distension was considerable, the abdomen was tapped and a little fluid having a pressure of 5 mm. Hg and resembling blood rather than blood-stained ascitic fluid was obtained. The trocar and cannula were withdrawn and then introduced in two other places, but the fluid obtained was the same in character. In all 30 oz. were removed. Two days later the abdomen was again tapped and 6 pints of fluid with exactly the same appearances were withdrawn. Mr. W. E. Waller found the specific gravity was 1018, and that the red blood corpuscles formed 97 per cent. of the cellular elements; of the other cells, 48 per cent. were polymorphonuclear leucocytes, 34 per cent. swollen epithelial cells, and 18 per cent. lymphocytes. Three days later the abdomen was again tapped and 24 oz. removed. The fluid looked more watery than previously, but had the appearance of dilute blood. Bacteriologically, it contained groups of large Gram-negative diplococci. Though relieved by the tappings the patient steadily lost ground, and had rather persistent abdominal pain which necessitated his being kept under morphine. He passed into a condition of toxæmic delirium and died on 20th July, the temperature having shot up to 104° F. The diagnosis in life was hepatic cirrhosis.

[1] Received October 20, 1910.

NECROPSY PERFORMED SEVENTEEN AND A QUARTER HOURS AFTER DEATH.

The body is emaciated and jaundiced. A definite lump is visible and palpable through the abdominal wall in the region of the gall bladder. The big-toe joints are free from uratic deposit.

Thorax.—There are adhesions, but not of long standing, over each lung.

The *lungs* (right, 28 oz.; left, 20 oz.) are both very œdematous. On section there is hypostatic congestion, and both show small areas of consolidation due to aspiration pneumonia. There is not any evidence of tuberculosis, neither are there any new growths. In both lungs there is acute bronchitis.

Pericardium normal. *Heart* (9 oz.) is small and atrophied, the muscle being soft and fatty. The valves are healthy. The *aorta* shows a few spots of atheroma and bile-staining of the intima.

Abdomen.—The peritoneal cavity contains 28 oz. of fluid mixed with blood. There are some scattered, easily-torn adhesions here and there between the intestines, but no active peritonitis. There are several small nodules of growth, the larger being of the size of a haricot bean, on the parietal peritoneum. One of these, situated almost in the middle line above the urinary bladder, is very hæmorrhagic. The omentum is shrunken along the tranverse colon, and on the left side is studded with small nodules of growth. The lump seen and felt before opening the abdomen is a projection from the edge of the liver, to which a mass of omentum is adherent.

The *liver* weighs 5 lb. 5 oz. The surface is irregularly hobnailed as in portal cirrhosis, and in addition presents many large projecting white nodules which are not umbilicated. These nodules are more numerous and more obvious on the under than on the upper surface, and are practically confined to the right lobe. Two of them on the diaphragmatic surface have burst through the liver capsule. On section the right lobe contains a large mass of new growth, roughly pyriform in shape, with the broad base at the diaphragmatic surface and the narrower end downwards. The long and the short diameters of the cut surface of the tumour measure 14 and 12 cms. respectively. The long axis of the growth makes an angle of 22 degrees with a vertical tangent drawn to the anterior surface of the liver. The tumour is sharply circumscribed, as are also the secondary nodules mentioned above. It is very soft and buttery in consistence and colour, being at the same time mottled by numerous hæmorrhages. The main mass is divided by strands of glistening fibrous tissue, which run radially to the centre of the growth. Large areas are obviously necrotic. Some of the secondary nodules seem to lie in branches of the portal vein. The rest of the liver tissue shows a mosaic-like section, suggesting coarse portal cirrhosis. It is very tough and creaks when cut.

The *gall bladder* is not distended and is free from stones. The main trunk of the portal vein is full of ante-mortem clot, which is firm, laminated, and partly organised at the hepatic end and soft and crumbly at the other.

The *portal lymphatic glands* appear to contain growth.

The *spleen* weighs 18 oz. The capsule is much thickened by chronic perisplenitis, with the result that it forms an "icing" to the organ, which on section is very firm.

The *pancreas* is firm and free from growth.

The *kidneys* (8 oz. each) are both large and congested and show uratic deposits in their papillæ.

The *adrenals* are normal, but in a small venule close to the right one there is a small nodule of growth.

Bladder normal. *Prostate* normal.

Alimentary canal.—The stomach is deeply pigmented from chronic

gastritis. The intestines are free from growth. The gastric glands are enlarged, and appear to contain growth.

MICROSCOPICAL PREPARATIONS were made from portions of the main growth, the secondary hepatic nodules, the growths on the peritoneum, the small nodule in the venule from the neighbourhood of the right adrenal, the thrombosed portal vein, and of the liver tissue unaffected by growth. All the tissue was treated with 10 per cent. formalin solution and stained with Ehrlich's acid hæmatoxylin and van Gieson's mixture.

The growths are seen to be alveolar, and consist of cell clusters embedded in a meshwork of well-formed fibrous tissue, continuous with that of the portal spaces, which is here in the excess seen in portal cirrhosis. The cells forming the growth are remarkably polymorphic, and undergo a distinct alteration in type according to their situation in the liver, peritoneal nodules, or the vascular growth near the right adrenal. Even in the liver growth itself the cells are remarkably variable. In the main they are rounded and polygonal with deeply staining rounded or oval nuclei, which are rich in chromatin (Plate XXVIII. Fig. 1). Their protoplasm stains pink with van Gieson's mixture as opposed to the brown colour of the liver cells. The size of the cells is very variable, from that of a red blood cell to four or five times that size. Many of the cells contain two nuclei, and in places they seem to fuse together to form large multinucleated protoplasmic masses or giant cells (Plate XXVIII. Fig. 2). At the periphery of the alveoli the cells in many places are indistinguishable from endothelial cells. Every transition from these to the rounded and polygonal cells from the main body of the cell clusters can be seen, and this gradation of change can be followed out, not only in the lining cells of spaces which are not obviously vascular spaces, but also in the endothelial cells of definite venous channels plugged with the growth. With high powers it is possible in some places to trace a fine intercellular fibrillar network. In most of the cell groups there are blood spaces lined by a single layer of endothelial cells, to the outer surface of which the cells of the tumour are closely attached (Plate XXVIII. Fig. 1). In the larger cell masses there are areas of necrosis, and in some of these, in fortunate sections, blood spaces can be seen cut across, surrounded by mantles of well staining cells, separated by intervening necrotic débris, the resulting picture being much like that of a perithelioma. Hæmorrhage has occurred into some of the cell groups.

The pressure exerted on the liver substance by the expanding tumour nodules has in places produced a most remarkable flattening and lengthening of the liver cells in their immediate neighbourhood. In isolated spots, invasion of the tissue proper by a bud-like process of growth can be seen. In some of the smaller cell groups the cells have a rather more definite cubical shape, suggesting the condition described by Marchand cited by Borst (1902 [2]) under the name of "angio-epithelioma."

In the nodule from the venule near the right adrenal the cells are arranged in closely packed, branching columns, separated by a fine vascular network, containing blood, and the polygonal character of the cells gives place to that of definite round and spindle cells, seen in sarcoma (Plate XXVIII. Fig. 4).

In the peritoneal metastases the growth resembles an ordinary small-celled sarcoma composed of round and oval cells. Here the cells are much smaller than in the liver, the nuclei being even more darkly staining and the protoplasm very scanty. These metastases are remarkably vascular and full of wide blood vessels with walls composed of a single layer of endothelial cells (Fig. 3).

In the sections through the portal vein, where it is filled with laminated clot, a channel is seen on one side, bounded by the wall of the vein and by the clot here clothed with endothelial cells. Into this channel has grown a piece of the tumour, which now consists of a mass of small round cells clumped around a small blood space, and infiltrated with blood.

The liver tissue which is free from growth shows a typical coarse-meshed

portal or multilobular cirrhosis. The meshes are of very variable size, in some places single lobules being enclosed. Here and there areas are met with in which the fibrous tissue has penetrated the lobule-surrounding groups of liver cells and even individual cells as in pericellular cirrhosis. The fibrous tissue is well formed, not very cellular, and in places contains numerous "pseudo-bile-canaliculi."

The liver cells for the most part are well preserved, though some contain fatty globules. In places the intercellular bile canaliculi are loaded with bile.

Remarks.

In attempting to classify this growth we are met at the outset by the common difficulty that the size of the parent tumour is such as to veil its actual starting-point completely. From a study of the material available, several points stand out: (1) The polymorphism of the cells of the tumour; (2) the undoubtedly sarcomatous character of the metastases; (3) the great vascularity of the growth, and especially of its peritoneal offshoots from which the hæmorrhage into the peritoneal cavity is in part due. Leaving aside for a moment the definition of what is meant by the term "angio-sarcoma," several observers (*vide* Marx, 1904[7]) agree that cellular polymorphism is a characteristic of "angio-sarcoma" of the liver.

In a case of primary sarcoma of the liver described by Marx,[7] which he regards as derived from a cavernoma, this polymorphism was so prominent as to resemble chorion-epithelioma. On the other hand, polymorphism is a marked characteristic of both hæmangio- and lymph-angio-endotheliomas, and in this case the prominent endothelial proliferation in the tumour alveoli within the liver certainly lends support to the view that the tumour arose from some hepatic blood vessel—possibly a branch of the portal vein—in view of the curious selection of the portal spaces for the formation of secondary growths.

The presence of large delicate-walled blood spaces in *all* the different parts of the tumour examined and the cellular polymorphism are not compatible with the view that its angio-sarcomatous appearance is fictitious and due to mechanical causes. For, as Ribbert (1904[9]) points out, in ordinary sarcomas, simulating angio-sarcomas, the tumour cells are all of the same type.

We are of opinion that the vascularity in this tumour is in itself a part—an integral part—of the tumour growth, and that, with the endothelial proliferation seen in the hepatic nodules, it further supports the view as to the origin suggested above. Given that the tumour originated in a blood vessel, it would be only right from the hepatic growth alone to call it a malignant hæmangio-endothelioma, and such a growth we consider it to be. In view of the definite sarcomatous metastases, however, it seems preferable to retain for it the old title of "angio-sarcoma."

Quite recently Rénon, Géraudel, and Monier-Vinard (1910[8]) have described, under the new name of hepatoma, a primary tumour of the

liver in connection with cirrhosis, which originates in a proliferation of the liver cells and of the endothelium of the adjacent capillaries. The resulting growth is a "tissue" tumour possessing the attributes of embryonic liver tissue. It is never met with except in association with cirrhosis, and never gives rise to metastases. The authors state that some of the described cases of carcinoma with cirrhosis and of multiple adenoma in cirrhosis belong to this class of "hepatoma" and have been wrongly named. In our case the absence of any demonstrable participation in the formation of the growth by the liver cells, and also the presence of metastases, place it in a different category, in spite of some resemblance of portions of the neoplasm to Fig. 5 in Rénon, Géraudel and Monier-Vinard's paper (1910 [8]).

Primary sarcoma of the liver is far from common, and when associated with cirrhosis is distinctly rare.

Pepere (1904 [6]), in a collection of forty-five cases,—he gives forty-six, but Burnet's case (No. 15) was more fully described by Delépine (No. 26),—mentions three in which cirrhosis was regarded as antecedent to the development of a primary sarcoma (but omits to mention the presence of cirrhosis in another of his collected cases which on reference to the original should be included). These cases were two of Arnold's (1890 [1]) (a round-celled sarcoma and a large spindle-celled sarcoma), von Kahlden's (1897 [5]) (a large round-celled sarcoma), and de Vecchi and Guerrini's (1901 [10]) (small round-celled sarcoma with large cells in the centre). In Marx's (1904 [7]) collection of sixty-seven cases of primary sarcoma of the liver, two only were associated with true cirrhosis. One of these was de Vecchi and Guerrini's, already mentioned, and the other Ford's (1900 [4]) case (a round- and spindle-celled growth with many capillaries). Marx mentions another case described by Karl Fischer, in which there was much hepatic fibrosis, but this was thought to be of syphilitic origin. To these must be added a remarkable case described by Dominici and Merle (1909 [3]) of carcinoma and sarcoma occurring in a cirrhotic liver.

In our case and in the other six cases of primary sarcoma occurring in a cirrhotic liver (K. Fischer's case is not included) the patients were males, the youngest being fifteen years old and the oldest sixty-six. This corresponds with the sex-incidence of primary carcinoma arising in a cirrhotic liver; in thirty-seven cases of this form of primary carcinoma of the liver, collected by us, thirty-five were males. In five of the cases there was ascites, blood-stained or containing blood in three and not blood-stained in two. In all except three cases—von Kahlden, de Vecchi and Guerrini (1901 [10]), and one of Arnold's (1890 [1])—there were metastases, which in Dominici and Merle's case were sarcomatous and were present in the pancreas, adrenal, and lung. In Ford's case and the other case of Arnold's, as in ours, metastases were present in the peritoneum and omentum. In all except Dominici and Merle's (1909 [3]) and von Kahlden's (1897 [5]) cases the right lobe was the seat

of the primary growth, and in these the tumour was more or less encapsuled.

In the majority of the cases which we have collected the starting-point of the sarcoma has been considered to be the walls of the smaller blood vessels. In five of the cases multi-nucleated giant cells are described, but were not present in such numbers as to constitute an essential feature of the tumour. The common occurrence of cirrhosis, as compared with the rarity of primary sarcoma of the liver, does not favour the view that there is any causal relation between the conditions, and more particularly militates against the natural assumption that the proliferation of fibrous tissue present in cirrhosis would favour the growth of a primary sarcoma. On the other hand, von Kahlden admits that in his case the microscopical sections do not show that the two conditions are quite independent, and his case is open to the suspicion that the fibrous increase is in part secondary to the growth of the tumour.

For the illustrations we are much indebted to Mr. W. E. Waller, B.A. Oxon.

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DESCRIPTION OF PLATE.

Plate XXVIII.

Fig. 1.—Portion of the main growth. The section includes portions of several alveoli of the tumour, divided by a branching fibrous network. To the left of the figure there are two thin-walled blood spaces surrounded by tumour cells. Several areas of necrosis are indicated. (×55.)

Fig. 2.—Portion of a blood space seen in Fig. 1. The polymorphism of the cells and their direct relationship with those bounding the blood space are well shown. At the lower end of the blood space is a large multinucleated cell. (×340.)

FIG. 3.—From a peritoneal metastasis. The cells are smaller. Numerous blood vessels lined by a single layer of endothelium and surrounded by tumour cells are shown. (×55.)

FIG. 4.—Portion of secondary growth in the venule near the right adrenal. The branching columns of closely packed round and oval cells are separated by a fine capillary network. In the figure most of the cells appear round owing to the plane of section. (×340.)

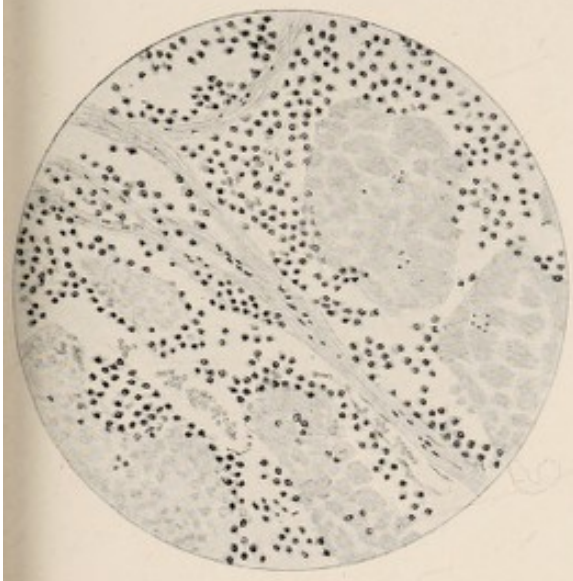

FIG. 1.

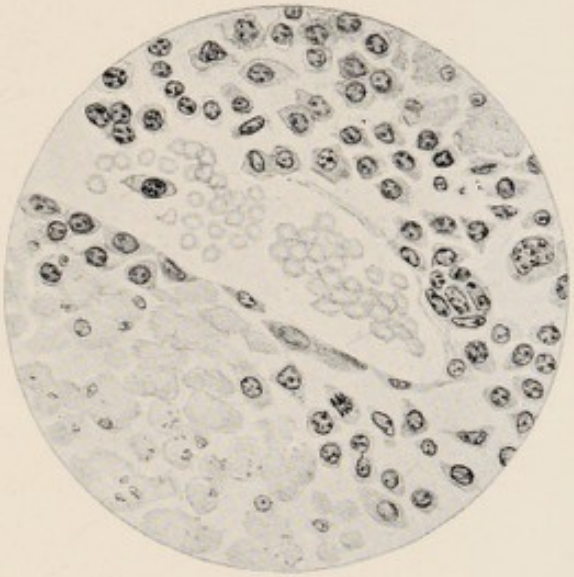

FIG. 2.

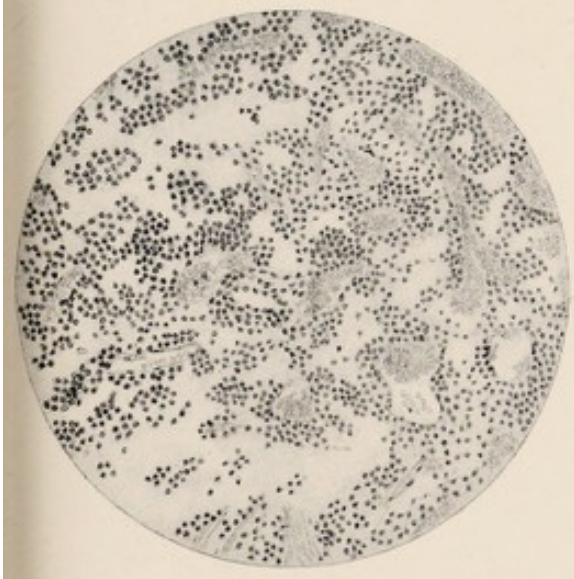

FIG. 3.

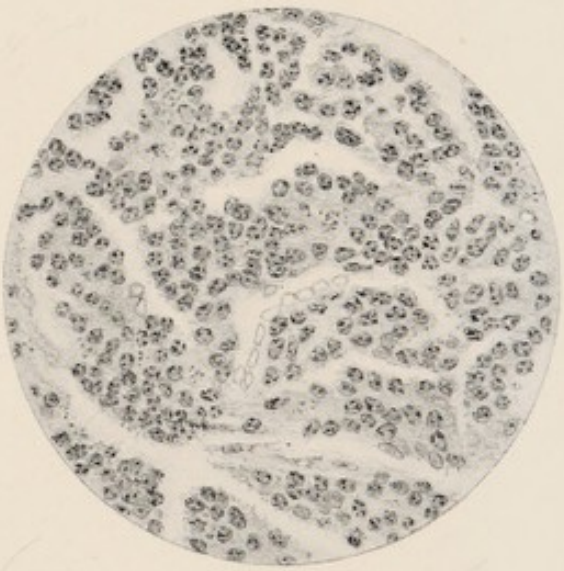

FIG. 4.