A case of primary melanotic sarcoma of the liver / by Sheridan Delépine.

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By Sheridan Delépine, M.B.Edin.

Preliminary Remarks.—I am indebted to Dr. Burnet for the specimen on which the present paper is based. After showing it to me he exhibited the liver to the Pathological Society as a card specimen, and it may be well to quote here the remarks which were made on that occasion.[1]

"The specimen was removed from the body of a man, aged 63, who was admitted into the B— County Asylum on July 20th, 1881, and died there April 3rd, 1885. When admitted he was in feeble health and melancholic. During his stay in the asylum he was always in the Infirmary ward, and was given extra diet, tonics, &c. It was not until a fortnight before his death that attention was called to the peculiar shape of the abdomen. On being examined by Dr. Barron (to whom I am indebted for the notes and specimen), the right half of the abdominal cavity was found occupied by a solid tumour, rough to the touch and bulging out the lower ribs, but not showing much projection beyond the ordinary outline of the abdomen. He complained of no pain, but from this time he rapidly emaciated and sank. His weight on July 20th, 1881, was 9 st. 2½ lbs.; on October 16th, 1884, 9 st. 6 lbs.; on January 23rd, 1885, 9 st. 9 lbs.

"*Post-mortem.*—All organs except liver fairly healthy and free from any extraneous deposit. Liver enormously enlarged (weight 16 lbs. 11 oz.), but enlarged uniformly, so as to retain its normal

[1] 'Transactions of the Pathological Society,' vol. xxxvi, p. 252, No. 48, "Primary Melanotic Sarcoma of Liver" (card specimen).

shape. Surface covered with small flattened knots, like buttons. On section it looked very like a slice of brawn. Numerous small masses of deposit were scattered through whole liver, varying in colour from black to dirty white."

I. *Macroscopical appearances of the liver.*

The surface was nodulated, and presented an appearance not unlike that of a hobnail liver, with the difference that the nodules did not project much, had almost all of them a perfectly circular outline, and were separated not by narrow and deep furrows, but by more or less even areas, little or not depressed.

Some of the nodules could be seen through the capsule to have a whitish colour, contrasting in many places with the congested substance of the liver. In some regions dark brown, almost black nodules were very conspicuous. The organ felt firm, and even the nodules did not give to the touch an impression very different from that given by the ordinary substance of the liver.

The surface of section presented a large number of more or less regularly rounded pinkish-white nodules, varying in diameter from 1 mm. to 10 or 15 mm., but many of them formed by aggregation larger and more irregular masses. Several nodules, instead of being pale, were, on the contrary, of a very dark brown colour.

Some of the white nodules were partly pigmented, the pigmentation in these cases being often in the form of the peripheral network.

The intervening liver substance was evidently much altered, being in some places pale and fibrous, elsewhere granular and degenerated-looking, whilst in other places it was evidently congested and pigmented as in passive congestion. Many vessels of small size and quite patent (about 1 mm. in diameter), and evidently branches of the hepatic veins, penetrated into nodules, pigmented or not.

II. *Microscopical examination.*

The *capsule* of the organ is thickened in some places, chiefly in parts corresponding to some large interlobular veins. The serous surface is generally smooth, but here and there a small patch of false membrane projects from the surface.

The *fibrous tissue* of Glisson's capsule can be followed along a

number of interlobular veins; it is much increased in amount, and penetrates between the peripheral cells of the lobules. It is very cellular, and masses of embryonic-looking cells are found in its midst. These cells in some cases occupy the lumen of a small vessel; this is well seen in several parts of the deep layer of the capsule. This cirrhosis is far from being universal.

The *vessels* are remarkably altered; many of them, chiefly in the subserous coat of the organ, are distended with masses of rather large micrococci; these masses are either homogeneous or mixed with blood-corpuscles. Similar masses are found also in the deeper parts of the liver, but not so abundantly.

The *portal vessels* are much altered by increase of fibrous tissue around them, by the pressure of tumour nodules, causing obliteration of some and distension of others, and by proliferation of cells in their walls; but in the last respect they are little altered in comparison with the *intra-* and *sub-lobular* veins.

Some of the *intra-lobular veins* are apparently almost normal, but with these few exceptions these vessels are much altered. Generally their *endothelium* and that of the adjacent capillaries has proliferated to such an extent that in a great number of places the lumen is entirely occluded. The changes seem to take the following course.

At first there is a swelling of the endothelial cells, which very soon begin to proliferate. By this the lumen of the vessel is diminished, but blood can still flow on. The cells then go on proliferating, and many of them separating from the walls get mixed with the blood. (In places where the vessels are surrounded by an appreciable amount of fibrous tissue proliferation of the same kind is observed in the connective-tissue corpuscles outside the vessel.)

Finally, the cells accumulate within the lumen of the vessels to such an extent that they occlude them entirely; the proliferation continuing, the occluded vessels become considerably distended with cylindrical or more or less irregular masses of cells. These masses are at first entirely surrounded by hepatic cells more or less altered by pressure.

Some of the vessels which are almost occluded contain still a few small groups of red blood-corpuscles undergoing disintegration, and golden-brown pigment granules are found either within the vessel or absorbed by the cells surrounding them.

In a number of capillaries spherical masses of a peculiar oily-

looking greyish-brown or blackish substance are found; some of these masses are granular, many of them are apparently homogeneous. They are generally found in unoccluded vessels, and I have seen some of them at the opening of intra-lobular veins into sub-lobular veins. These are probably fluid pigment globules, passing into the blood to be finally excreted by the kidney; it is well known that in such cases the urine has been found to contain a very dark pigment, at any rate after standing some time or being treated by strong acids (melanuria).

The tissue proper of the organ, that is the *hepatic epithelium*, is, as may be surmised from the previous description, much altered. A few lobules seem to have escaped destruction and even distortion, but most of them are either replaced by the new tissue, to be described more fully later on, or are in a state of atrophy or necrosis, either owing to pressure or to stoppage of blood supply. In some parts also the intra-lobular vessels are considerably distended with blood, and the cells deeply pigmented, as in very advanced passive congestion. More than nine tenths of the epithelium of the organ seems to be destroyed by pressure.

This atrophy takes place in two ways: either the cells remain enclosed between the nodules of the tumours, and as the nodules increase in size the cells are at the same time compressed and separated one from the other; or else they are pushed at the periphery of groups of nodules, and being pressed one against the other they form a kind of laminated false capsule, in which the individual cells may become so flattened that they may be hardly recognisable.

Many of the liver-cells are pigmented. These infiltrated cells are found either in the neighbourhood of pigmented or non-pigmented nodules; in fact, this accumulation of blood-pigments seems to take place in the regions where the congestion is excessive and the epithelial cells atrophied—as, for instance, in those places where the vessels have just become occluded by accumulation of endothelial cells in their lumen.

The *bile-ducts* show much the same changes as those generally observed in cases of biliary cirrhosis, but this is not the case all over the organ. They are best seen where the interstitial tissue is increased. Here and there they penetrate deeply into the substance of the lobule. Some of these ducts are dilated and more or less convoluted, evidently through accumulation of retained secretion.

As to the *neoplastic nodules* themselves, their mode of formation has been already described in relation to the vessels. The origin of small nodules is comparatively easy to trace, but the structure of the large ones is at first sight very perplexing. Some of them are pigmented, others are not; most of the pigmented ones are evidently composed of tolerably large spindle-cells, showing a very fine fasciculated arrangement. These masses have all the characters of large spindle-celled sarcomata.

But there are many nodules, and some of them among the largest where the structure is more difficult to understand. In such nodules the cells are tightly packed together, being altered by mutual pressure; they form small masses, filling up alveoli separated by network of apparently fibrous trabeculæ. The cells are of a moderate size with large nuclei, and it is difficult to see any intercellular substance between them. Here and there a small duct lined with cubical epithelium can be seen penetrating between these small masses.

Blood-vessels are very scarce in almost all the nodules, but, in a few, small groups of red blood-corpuscles can be seen between the cells. At the periphery of the tumours, where the liver-cells are not too much altered by pressure, the nature of these nodules becomes again clear.

In the trabeculæ separating the small nests of cells, atrophied hepatic cells can be easily discovered, whilst many of the small alveoli are directly continuous with some distended vessels; it is therefore evident that the large compound nodules have exactly the same origin as the small ones.

III. *Summing up of the description.*

We are therefore led by a careful examination to say that, notwithstanding their alveolated structure, all these tumours are sarcomatous. The walls of the alveoli are the more or less altered remains of the vascular walls and liver-cells, whilst the contents of the alveoli are chiefly composed of the products of the proliferation of the endothelium of these vessels. Some of the sarcomatous cells seem, however, to have sprung from the interstitial connective tissue of the organ, which in some places is seen to penetrate deeply into the lobules, separating columns of hepatic cells. It is these

liver-cells which, proliferating within a space gradually diminishing, become more numerous and smaller, and assume the characters of bile-ducts.

[The appearance of the tumour suggested to me that in some places the irritation of the epithelium might have led to the formation of adenomatous nodules, but all the masses which I examined carefully were undoubtedly of sarcomatous nature.]

The tumour is therefore essentially a sarcoma of vascular origin, distinctly alveolated; it is pigmented in various parts; it might, therefore, be called a *melanotic, alveolated, spindle-celled angio-sarcoma;* it might also be called an *endothelioma.*

IV. *Discussion of the case.*

Anatomical and physiological remarks.—A. We have, therefore, to deal with a primary sarcoma of the liver, originating in and growing along a certain set of vessels. Owing to this the sarcoma has acquired a peculiar alveolated structure; the vessels have become gradually obstructed, the obstruction leading to changes in the liver analogous to those produced by extensive *endophlebitis.*

B. The most remarkable anatomical feature of the case is undoubtedly the gradual *replacement of the contents of the vessels* by an embryonic tissue similar to that from which both blood and blood-vessels originated. The accumulation of these new products has led to the same changes as those resulting from accumulation of blood in the vessels, as can easily be seen by comparing the changes observed in this case and in cases of *cavernous angioma.*

C. Another anatomical feature worth noticing is the *rapid destruction of the liver-cells* surrounded by the sarcomatous cells, for in places where this destruction is going on it cannot be said that the products of the degeneration of the atrophied cells are removed by blood-vessels, since these are often entirely obstructed; it is therefore probable that the newly formed cells absorb the old cells they have surrounded.

D. The *excessive proliferation of endothelial cells* is of great interest, for it demonstrates on a large scale what takes place in various degrees, either in health or disease, within the vessels. I have often demonstrated that in clots formed within vessels of internal organs during life, or even in clots formed in the vessels

after death, endothelial cells can be found at a distance from the walls of the vessels, and that in order to occupy such a place it is necessary that they should have been separated from the walls whilst the blood was circulating. These cells, as their reactions show, were not dead when they separated from the walls, and a study of the formation of blood-vessels and of blood itself would lead one to expect that endothelial cells so separated might have some further use, and be transformed into some form of blood-corpuscles. These considerations, which I reserve for some further communication, are confirmed by some very interesting observations made by the late Dr. Handfield Jones on "Morbid changes taking place in the cerebral arterioles in inflammatory and other states."[1]

In this case the activity of the growth of the embryonic tissue within the vessels can be easily estimated, for we find that during the four years the patient was under observation his weight increased steadily by about 6½ lbs. Now that increase was taking place notwithstanding general emaciation, and was entirely due to the increase in weight of the liver, more than counterbalancing not only the loss of weight of its own atrophied substance, but that of all the other organs together. Admitting that only half of the liver tissue had been destroyed, we find that more than 15 lbs. of new tissue had been added to the organ.

Pathogenetic remarks.—E. Another very interesting feature of the case is the evident *relation of the tumour to the vessels.* This indicates evidently a source of irritation connected with the blood, and therefore we have here an instance of a tumour originating very much in the same way as specific inflammation. The problem which this case places before us is, however, more complicated than it seems at first. It would be difficult to support the view that the irritant was brought to the liver by the hepatic artery only, for even admitting that, owing to its slow circulation, the liver might have been at first singled out of all the other organs as the seat of disease, it would be almost impossible to conceive that it should have remained the only organ involved.

That great constitutional changes had taken place can be well shown by the fact that for four years before his death the patient was melancholic, so ill that he had to be kept all that time in the ward of an infirmary, and that he became at last very weak and

[1] 'Trans. Path. Soc. Lond.,' 1885, p. 158.

emaciated, notwithstanding good diet, tonics, &c. The slight gain in weight also, as I will point out, rather supports than invalidates this statement.

The fact that, notwithstanding the general distribution of the disease all over the organ, a great number of portal vessels have escaped, and that the morbid changes in most instances begin in the lobular capillaries or intra-lobular veins, is against the view that the irritant was brought to the organ through the portal vessels; whilst it would be almost preposterous to hold the view that mere passive congestion might be sufficient to lead to such changes as those above described. We are therefore driven to the conclusion that the irritant must have been elaborated by the liver itself.

The proofs of this are not wanting, but the most striking is found in the fact that the most altered of the three vessels is evidently the hepatic vein at its origin. Now the hepatic vein (as well as most other veins) must be considered to be not only a vessel carrying blood away from the organ, but also a channel collecting products which have been added to the blood during its circulation through the capillaries of the organ. It therefore seems probable that if any abnormal product happened to be manufactured by the hepatic cells, the first vessels to suffer would be the intra-lobular capillaries, and that the disease would have a tendency to extend more rapidly in the direction of the blood-flow than in any other direction. But as the blood-current is soon retarded or stopped, the extension backwards of the process would, of course, be possible also very early (this explains how a number of branches of the portal vein and hepatic artery have become affected).

Against this view one can set the fact that all the lobules of the organ are not affected; but, on the other hand, it can be said that the same difficulty would arise in a number of cases where inflammatory changes take place, whilst the remarkably even distribution of the disease all through the organ is very much more striking than the escape of a few parts. It must be remembered that although the organ had reached the enormous weight of 16 lbs. 11 oz. (*i. e.* nearly five times its normal weight), yet it had not lost its original shape.

F. It will be noticed that I have attached little importance to the *Staphylococcus* found so abundantly in the vessels. My reasons for doing so are the following:

1st. The micro-organisms are found in the most superficial parts

of the organ in very much greater numbers than in the deep parts, and their distribution does not correspond to the distribution of the disease, nor are they found in regions presenting any definite relations to the centres of invasion.

2nd. If they had been brought to the liver by the hepatic artery, and *had been the real cause* of the disease in the liver, other organs should have been affected too.

3rd. If they had been brought by the portal vein, and been the *actual irritant*, the branches of that vessel would have been more affected than the others, or at any rate as much.

4th. They are (the micrococci) found in vessels showing very little trace of proliferation in their elements, and although distending them in some places their appearance suggests the probability of their having grown there after the death of the patient, or perhaps after the partial death of the part, local death, which may have taken place a long time before the actual somatic death. In this last case the germs might have found their way into the blood, and owing to the debilitated state of the organism reached further than they would have done under less favorable circumstances, and finding a suitable "nidus" in the half-dead tissues of the liver, formed there a number of colonies. These of course would have to be considered in the light of complicating elements and nothing more.

5th. To all these arguments we may add the negative results obtained by C. A. Ballance and S. G. Shattock,[1] who in their numerous cultivation experiments have been unable to discover any form of micro-organism connected with any of the new growths which they have investigated.

6. The cause of the pigmentation of certain sarcomata is very obscure. *Melanotic sarcomata* do not always originate in parts previously pigmented, and when they begin in such parts the production of pigment is generally quite out of proportion with that of the part from which the sarcomatous cells have originated. It would therefore appear that in such cases the sarcomatous cells have the power to make melanin, or else to abstract that pigment from surrounding tissues or fluids. Many observers have tried to prove that all the pigments of the body were derived from hæmoglobin, but they have not succeeded in proving their point satisfactorily. On the other hand, there is strong evidence of the

[1] 'Trans. Path. Soc.,' 1887, p. 413.

formation of melanin independently of the presence of hæmoglobin. I have shown elsewhere that melanin is constantly manufactured in the epithelia exposed to light and other stimuli, and that some colourless or pale soluble compound allied to it must pass from the skin into the deeper parts of the body, and by elaboration in hæmopoietic organs be one of the elements in the production of hæmoglobin ('Proceedings Physiological Society,' December, 1890; 'Journal of Phys.,' vol. xii). I have also elsewhere shown that iron is normally stored in the liver, and leaves that organ in some soluble form by the hepatic veins; and I have surmised that the iron thus saved from the products of degeneration of decayed red blood-corpuscles was used again in the production of fresh hæmoglobin ('Practitioner,' August, 1890). It is easy to understand how a disturbance or want of equilibrium between these two functions would lead on the one hand to anæmia, and on the other to melanosis.

Clinical remarks.—From a clinical point of view the case is of interest in showing the almost absolute *balance* existing between the loss of weight by the body generally and the increase of a single organ.

The weight of the body generally increased only by 6½ lbs. during four years, and therefore can be said to have remained nearly stationary. The weight of the liver increased by at least 13 lbs. It is important to keep in mind that the increase of weight during the first three and a quarter years was only 3½ lbs., *i. e.* about 1 lb. per annum. During three months of his last year of life the increase was 3 lbs., *i. e.* at the rate of nearly 12 lbs. in the year. Such a rapid increase of weight at a time when the patient was getting worse is extremely remarkable. It is all the more significant that it is soon after this rapid increase had been noticed that the large size of the liver began to attract attention, and that was only a fortnight before death. So that whilst the body (the liver being excluded) was losing 6½ lbs., the liver was gaining the same number of pounds and 6½ more.

There is, however, one fact which is of interest in relation to that part of the question, and it is this: the liver, being on the road taken by a large portion of the food absorbed by the intestine, might have *diverted part of the food* which usually is only stored up in its substance, or simply passes through it. This is rendered probable by the general increase of weight, increase which is evidently due to the growth of the parasitic tissue. This points

to the fallacy of some of the results obtained by simply weighing a patient in order to judge of the state of his metabolism.

I may indicate as points of special interest the following conclusions.

V. *Conclusions.*

1. A considerable overgrowth of the endothelial cells of the hepatic vessels may give rise to the rapid[1] production of tumours having all the characters of sarcomata distributed all over the organ, but entirely confined to the liver.

2. The proliferation seems to be due to the elaboration of some substance by the hepatic cells in a state of disordered activity.

3. A large amount of melanin may accumulate in some of the nodules thus produced. This melanin does not seem to be produced out of any of the ordinary blood-pigments, and seems to be elaborated by the sarcomatous cells themselves.

I venture to suggest that some pale or colourless material was brought to the organ by the vessels, and that it was out of this material that melanin was precipitated in the cells.

4. Some of the hepatic veins contained globules of a brownish substance, not so dark as melanin, and evidently fluid; and these globules, I think, indicate the circulation of some such substance as the one just alluded to. This would explain how the urine of patients suffering from melanotic tumours and certain other disorders may become loaded with some product which, when exposed to the air, becomes very dark in colour (melanuria).

Note.—This paper was originally prepared for the Pathological Section at the Annual Meeting of the B. M. A. held in Glasgow (1888); I was, however, unable to attend, and the paper was not published.

Dr. Rolleston has attracted my attention to a paper by Dr. Hale White, published in the 'Guy's Hospital Reports' for 1890, p. 59. Those who wish to study the subject from a clinical point of view will do well to read the paper, which contains much information and a good digest of a number of cases. It may be interesting to notice that Dr. Hale White does not attempt to settle the pathological side of the question, owing to the discrepancies of opinion

[1] Primary melanotic sarcomata of the liver have been remarked by several observers to have run equally rapidly to a fatal issue.

among pathologists. With reference to this point I may mention that the case here recorded was first shown to me as a case of melanotic cancer, and lately another case of the same nature was also at first supposed to be cancerous; I had, however, no difficulty in proving that in both cases the disease was essentially a connective-tissue growth, and therefore a sarcoma.

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