CUMSTON (C.G.)

With the writer's compliments.

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MALIGNANT TRANSFORMATION OF DERMOID CYSTS OF THE OVARY.[1]

BY CHARLES GREENE CUMSTON, B.M.S., M.D.,

of Boston.

Assistant Professor of Surgical Pathology, Faculty of Medicine, Tufts' College.

I AM to begin to-day the lectures on surgical pathology, the knowledge of which is so important for everyone who intends to practise surgery. I have explained the plan of these lectures to you, and, as has been my custom in previous years, I shall devote the inaugural lecture to the study of some point in surgical pathology, and I have selected the subject of malignant transformation of dermoid cysts of the ovary for the present occasion.

Before taking up the study of malignant transformation arising in ovarian dermoids, it appears to me that it is quite essential to first consider in a few words the histology of these cysts before they have undergone any pathologic change. From the study of their structure we will be able to deduce a number of conclusions that will permit us to understand how and why such cysts undergo malignant transformation.

In the study of their pathologic anatomy, dermoid cysts may be divided into two groups. The first comprises *simple dermoid cysts*, also termed fetal neoplasms of the epithelium or epidermoids, while the second includes the *compound dermoid cysts*, or fetal meso-epidermic formations.

Simple dermoid cysts are usually small, unilocular

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or bilocular productions, of varying contents, being sometimes composed of sebaceous matter, while at others they consist of a serous or oily fluid. In some few instances the fluid is perfectly transparent, or the contents may form a calcareous mass. The structure of the walls of these cysts is most important. In thickness they vary from 1 to 3 mm., but they may attain as much as 5 or 6 mm. in some cases. They are composed of several distinct layers, which, passing from the outside to the interior of the cyst, are as follows: A strong fibrous layer; an adipose layer, which will be found more or less well developed in various cases; a dermic layer, in every way analogous to that of the cutis; and, lastly, an epidermic layer, which undergoes keratogenic evolution. This last only differs from the same structure in the skin by the relatively small size of its cell-elements and the slight development of the keratogenic layer. The dermis is separated from the epidermis by a straight or somewhat undulating basement-membrane. No papillæ are present, or if by chance there are a few, they are large and covered by tufts of hair. This want of papillæ, as well as the presence of a straitly outlined basement-membrane, is not a different structure from the external integuments, as in many parts of the cutis the basement-membrane is quite flat.

Like any cutaneous layer, dermoid cysts present hair-follicles, which are usually supported by a single large papilla, as well as numerous well-developed sebaceous glands and sudoriparous glands in smaller number. Simple dermoid cysts, such as those just described, are usually seated in the subcutaneous cellular tissue and, so far as I am aware, malignant transformation does not occur in them.

Dermoid cysts of the ovary belong in most instances to the second group, namely compound dermoids. They present all the histologic elements found in simple

cysts, but in the former we find teeth, either free in the cavity of the production, or implanted in its fibrous walls, or even in a plaque of bone. The shape of the teeth varies, simulating at times the incisors, they may at others be more like molars. They may be present in great numbers, as many as 300 having been found in one cyst.

Besides teeth, shapeless bits of bone may be found, or on the contrary, bones shaped like those of the skeleton may be present, as well as cartilage, unstriped muscle-fibers, nerve-cells and fibers, etc.; but all these structures are simply accessory and do not have the same vitality as the dermoid and epidermoid tissues forming the cyst itself.

Many are the theories that have been put forth to explain the presence of these cysts within the body. It was formerly thought that they were the result of an extrauterine pregnancy, but as dermoids are found in children and in virgins, this opinion cannot be upheld. Lefert explained their presence by his well-known theory of *plastic heterotopia* as follows: Simple or compound cysts may be found in the most complex organs or any part of the body that normally does not contain any of the histologic elements composing the cyst. It is needless for me say that this theory, as well as the preceding one, is only of historic interest.

Duval and Répin explained the genesis of dermoids by a partly enogenic development of the ovum. They contended that there is a special type of degeneration of the ovum, which, when the cyst is a muco-dermoid, is associated with consecutive proliferation of the epithelium of the ovisac. This theory does not, however, explain the presence of these cysts in other regions of the body or exterior to the ovary. Some authorities believe that dermoids are due to diplogenesis from fetal inclusion, but the number of teeth sometimes present in the cyst weakens this theory.

This brings me to the more scientific theories of inclusion. Some writers believe that the external integument becomes pinched in during embryonal life, and the part thus caught can be compared to a glove-finger turned inside out; the external aspect becomes internal, and we know that it is in the inside of the cyst that the cells undergo their evolution and desquamation. Verneuil attributed the formation of some dermoid cysts to a faulty closing of the bronchial arches.

The nodal-cell theory of Bard has the great advantage over the others that it explains not only the presence of cysts situated in any part of the body, but also their compound structure. According to this well-known pathologist of Lyons, embryonal cells, or, as he terms them, nodal-cells, are always present in the midst of our tissues, and they can split up and give rise to the various types of tissue, the germs of which they contain, such as muscle, epithelium, etc.

Cohnheim believes that there are numerous embryonal tissues contained within the structures of the body that were not utilized at the time of development, and that these can give rise to all types of neoplasms, both simple and compound. If we state, however, the actual knowledge that we possess regarding ovarian dermoids, I would say that they are *congenital neoplasms having an uncertain pathogenesis*, and that *the theory of inclusion is probably the correct one;* these cysts are more or less aged embryonal debris, according to the complexity of the tissues entering into their structure.

From what has been said it will now be possible to better understand the pathology of dermoid cysts. I said "the pathology" because in reality a dermoid may be properly considered as an *abnormal organ*, made up of *perfectly normal tissues*, identical with the skin, capable of giving rise to all pathologic productions that the cutaneous surface may be the site of. For example,

the internal lining of a dermoid may be the seat of cysts, keratogenic productions, such as horns or nails, verruca, etc., sometimes presenting a high degree of development.

Like the skin, the walls of dermoids may undergo malignant transformation in the form of carcinoma, epithelioma or sarcoma, and I might even say that these cysts have a greater tendency to malignant changes than the cutis itself. Now, in all the theories that have been given regarding dermoids, there is the belief that they arise from embryonal debris, and general pathology teaches that any change in position or normal structure of an organ or part of an organ creates a tendency to neoplastic formation, and that any kind of embryonal debris is a most excellent nidus for the development and growth of a tumor. A dermoid cyst is generally considered a benign neoplasm, and it is a well-known fact that a benign growth often takes on a malignant transformation.

The appearance of a malignant neoplasm in a non-malignant growth is perhaps more frequent in occurrence than in normal structures, but nevertheless such a condition is not common. A tissue that is the seat of great physiologic proliferation is more prone to the development of a malignant growth than is a less active tissue. There is always a more intense renewal of cells in a nonmalignant neoplasm than in its corresponding normal tissue, and for this reason alone a benign growth should be often the starting-point of malignant transformation.

Now in point of fact malignant transformation in dermoid cysts of the ovary is not a common occurrence, although it would appear that this should be so; and when it does take place only a few vegetations are present on the internal lining of the cyst at the beginning, or only a simple thickening of the cyst-wall will

be present, so that if the interior of a cyst is not carefully examined after removal, a malignant change may easily pass unnoticed.

As I have before remarked, I am not aware that any case of malignant transformation has been reported in other dermoid cysts than those arising in the ovary, and the only manner by which we can perhaps explain this change in them particularly, is that the ovary is the seat of a hyperemia due to menstruation, the puerperal state, or an inflammatory process, be it chronic or acute, and thus involves the cyst. The extra amount of blood present results in an active physiologic proliferation and a rapid renewal of the cells, so that the tissues of the tumor are quite likely to undergo considerable cell-development.

Dermoid cysts in other parts of the body are usually small, hardly ever larger than a good-sized walnut, while their evolution is slow and latent, and the entire process is far from active. All these circumstances detract from any tendency that they may have to malignant change.

When one or several carcinomatous nodules are joined in the wall of a dermoid, the question arises as to whether the cyst has undergone malignant transformation. Now, as has already been said, a dermoid cyst is an abnormal organ, and, strictly speaking, the malignant neoplasm is not a transformation of the cyst, but is *a new growth occurring in a tumor*. The malignant transformation is always epitheliomatous or sarcomatous.

During the first part of the evolution of the malignant growth, which we shall call the period of generalization, the neoplasm develops from Malphigi's epithelium, and then extends to the other layers composing the walls of the cyst. In other words a carcinomatous nodule arises in the internal layers and is similar to a cancroid of the cutis. The nodule has great difficulty in developing

toward the external layers of the cyst-wall, because the fibrous envelop acts as a barrier for some time; but, finally, this also becomes infiltrated by the malignant cell-proliferation, and then carcinomatous vegetations appear on the outer surface of the cyst.

The second stage consists in the generalization of the neoplasm, and follows the same laws that govern a cutaneous cancroid. Carcinoma gives rise to metastasis in distant organs, while a cancroid remains localized in the lymphatics, distant metastasis only playing a secondary part. Extension and dissemination of the neoplasm take place by grafting; the peritoneum becoming the seat of the disease by a direct graft of the neoplasm at the point of contact, the parietal peritoneum, occasionally the intestine, being the first involved.

Extension of the growth is consequently entirely local, and takes place only by direct contact, while distant metastases by the lymphatics or bloodvessels are indeed quite rare. Malignant transformation of an ovarian cyst that has given rise to a generalized metastasis will not be diagnosticated during life, because, in a subject presenting numerous carcinomatous foci, it is most difficult to discover their starting-point.

Sarcoma arises in the connective-tissue elements that make up the dermic layer and capsule of a dermoid cyst. Now, a cancroid at its beginning will have a tendency to invade the interior of the cyst, while a sarcomatous deposit that is undergoing its evolution will rapidly invade the fibrous layer of the cyst and extend outside of it. When a sarcoma has arrived at this point, it may give rise to local generalization by continuity, or it may produce metastasis throughout the entire organism. You must not confound foci of generalization of dermoid cysts, as has been pointed out by Bard. The carcinomatous tissue forming the foci of malignant metastasis only presents a single type of

cell identical with those composing the primary growth grafted on the dermoids, while the foci of generalization of simple dermoid cysts are made up of multiple tissues, the same as those composing the primary neoplasm; in other words their structure is a compound one. The foci are not the result of a true metastasis, for the primary cyst does not give rise to the others by rupture, and cases are recorded in which the necropsy demonstrated that the primary ovarian cyst was absolutely intact, its walls being perfectly solid and showing no trace of fissure or rupture.

The initial cell comes from a single nodule cell, which multiplies before it divides in two, and it may happen that the cells, born from this multiplication, are carried through the economy in the form of emboli to various parts. In most instances the symmetric organs of the adult are derived from the division of a primarily single focus, and, consequently, if we find cysts of the peritoneum or other abdominal organs having the same structure as that of a dermoid cyst present in the ovary of the subject, they should be considered as being derived from the same origin, that is to say from the same nodule cell; but, as the agglomeration of cells becomes divided and separated into masses from the growth and development of the organs and tissues in which they are implanted, we may have a number present in one individual, but this fact does not in any way detract from their benign nature.

Theoretically, it is quite evident that in a case of a compound dermoid cyst any one of its tissues may undergo malignant transformation, but in reality the epidermic and the dermic structures alone take on this change in the form of carcinoma or sarcoma. These two tissues only produce this pathologic change, because they alone are possessed of a real vitality, the others being simply accessory and associated with the funda-

mental tissue of the cyst, and pathology teaches us that it is only those tissues having a vitality that are usually subject to these monstrosities of cell-development constituting neoplasms in general. Atrophied tissues have a low degree of vitality, and are consequently little adapted for the development of malignant changes.

A dermoid cyst being alone capable of giving rise to a pavement-cell epithelioma, if the malignant neoplasm found is such, it may be concluded that it has arisen in a dermoid cyst. On the other hand, when in the course of a celiotomy you find a growth composed of a dermoid and a mucoid cyst, along with sarcomatous tissue, as has occurred, it is only by the site of the sarcomatous foci that it can be stated without being affirmative, which is the starting-point of the neoplasm, because both mucoid and dermoid cysts can give rise to sarcomatous transformation.

There is another variety of growth that is quite interesting that I would add to the list of primary malignant transformation, and that is endothelioma. Histologically this type of neoplasm is an intermediary of epithelioma and sarcoma. It arises from either the lymphatic capillaries or the bloodvessels, and in the cases thus far reported the starting-point of this neoplasm was from the lymphatic vessels or the bloodvessels entering into the cyst; but, as the latter form an integral part of a dermoid, it is probable that the tumor developed from them.

As to the prognosis of a dermoid that has undergone malignant transformation, it naturally differs with the extent of development of the process at the time of the operation, as well as the type of tissue.

If a dermoid is removed while the epithelioma is still at its first period, that is to say when the malignant transformation is as yet confined to the internal aspect

of the cyst, or even with a few secondary nodules in its walls that have not come in contact with the peritoneum, the prognosis is not very serious, because the malignant elements are still encapsulated and separated from the rest of the peritoneal cavity. The small size of the pedicle is also a good point in the prognosis. By removal of the entire cyst, all danger is practically done away with, and the patient will most likely never have a recurrence.

If, on opening the abdomen, carcinomatous growths are found projecting from the cyst, without adhesions or foci of metastasis, the removal of the entire mass may still save the patient; but it is quite evident that the prognosis is far from being as good as in the preceding case, for it is more than possible that a few carcinomatous cells have become detached, and later on will give rise to a secondary growth, although at the time of operation the peritoneum may appear quite normal.

Of course it is hardly necessary to say that if at the operation numerous secondary deposits are present in the mesentery, intestine, or peritoneum, it is better to at once close the incision, as a fatal issue is not far distant.

What I have said of carcinoma applies equally well to sarcoma, the only difference being that in cases of the latter neoformation its elements are on the exterior of the cyst almost from the beginning and that consequently the prognosis depends upon the presence or absence of metastatic foci within the abdominal cavity.

Sarco-endothelioma are highly malignant; their development is rapid; cachexia appears at an early date; and recurrence is sure to soon appear. It is evident that the importance of a careful microscopic examination of every dermoid cyst is great, if we wish to be certain as to our prognosis, and this should never be neglected.

Let us now consider the diagnosis of malignant transformation of dermoid cysts, excluding those cases in which the entire economy has already become the seat of numerous metastatic foci. For that matter, it is quite useless and even impossible to make a diagnosis of the seat of the primary growth in such a case. What I wish to more particularly consider is whether or not an exact diagnosis is possible when the malignant transformation of the cyst is still in the first period of its evolution; and the first problem that comes up is whether a differential diagnosis between a mucoid and a dermoid cyst can be made, and in reply to this I would say that in many instances it can.

Dermoids may be differentiated from mucoid cysts by their size, which varies from that of a lemon to a grape-fruit, while mucoid cysts are generally large, although this is not so in every case. The evolution of dermoid cysts is slow and insidious, and they may be present for years without giving rise to any symptoms. One patient, a woman of about 45 years, upon whom I operated a short time ago for a dermoid the size of an orange, had given birth to 11 children at term without any trouble arising in consequence of the tumor. A dermoid remains in a latent state until puberty and then will probably begin to develop, on account of the greater activity of nutrition that takes place when the menses occur, pain being the first and usually the only symptom to attract attention.

Usually a mucoid cyst will give rise only to symptoms of compression, with nervous or vascular disturbances, such as abdominal or lumbar pain, hemorrhage, edema, constipation, intestinal occlusion or difficulty in respiration when they are of some size. Dermoids are painful in most instances, the pain being superficial and rather acute, extending toward the groin and thigh. Slight pressure over the growth will produce a disagreeable

sensation, similar to that found in hysteric coxalgia, and if the integument is pinched much pain will be complained of by the patient. This is due to a hyperesthesia of the skin.

Mucoid cysts fluctuate, dermoids only partially, giving the sensation of doughiness to the exploring finger. Some dermoids will be found to fluctuate in certain parts, while at other points the feel is that of a solid neoplasm, in correspondence with the thicker portions of the cyst.

Generally speaking, it is not the fact of finding the foregoing symptoms that will make the diagnosis of a dermoid, but their coexistence is the important point. When the following three symptoms are all present, viz., a small, round tumor of slow evolution and with the characteristic pain, a diagnosis of a dermoid of the ovary is pretty certain to be correct.

Now, when a dermoid undergoes malignant transformation, it rapidly increases in size, and at the same time severe pain appears, shooting down the thigh corresponding to the side in which the cyst is located.

The pain is caused by sudden compression of the rapidly growing cyst, but I would not venture to assert that a rapid and sudden increase in size of the cyst, accompanied by severe pain, is absolutely characteristic of malignant transformation of a dermoid. This should only lead one to *suspect* that such a change is taking place. The age of the patient is also an indication that should be taken seriously into consideration, but there are cases in which malignant transformation has occurred in subjects under 25 years of age. Ascites is infrequent.

The general health of the patient will not be troubled until the malignant neoplasm has extended beyond the cyst and has invaded the abdominal cavity and its viscera. When this has taken place we have all the

symptoms of a generalization, viz., anorexia, cachexia, and loss of flesh.

In closing I would say that when the diagnosis of a dermoid cyst has been made, removal of the growth by celiotomy is indicated, because its presence is always a danger to the patient, not only from the possibility of malignant transformation, but also from that of septic infection or rupture of the cyst, two important complications that may occur at any time.