PAPILLO-ENDOTHELIOMA OVARIU

REPORT OF THREE CASES AND A DISCUSSION OF SCHILLER’S
“MESONEPHROMA OVARIU”

TEVFIK REMZI KAZANCIGIL, M.D., WERNER LAQUEUR, M.D.,
AND PETER LADEWIG, M.D.

(From the Department of Gynecology and the Cancer Research Institute,
University of Istanbul, Turkey)

In a recent paper Schiller described a group of papillomatous cystic tumors of the ovary which differ widely from those usually encountered. He pointed out the close similarity of the greater part of the tumor elements to endothelium with “an approach to an epithelial form” only when proliferation is particularly active. In agreement with the majority of pathologists, he denies the occurrence of true endotheliomas in the ovary.

Having raised the question where, in the region concerned, structures consisting of “endothelial-like cells” and “endothelial-like epithelium” are to be found, he comes to the conclusion that “there is but one answer—the glomerulus of the kidney.” Moreover, in all his cases he was able to demonstrate “glomerulus-like” formations, resembling closely the primitive glomeruli of the mesonephros (wolffian body). In accordance with his findings, he concludes that the neoplasms originate from remnants of mesonephric tissue and suggests the name “mesonephroma ovarii.”

We have had the opportunity of studying three similar tumors.

CASE I (G166/36): An encapsulated tumor, weighing 3 kg., was removed from a girl of seventeen. It arose from the right ovary and was partly cystic and partly solid. A cross-section showed numerous relatively large cysts in a soft yellowish-gray tumor tissue, with extensive areas of necrosis.

On microscopic examination the tumor is found to consist of several types of tissue, no one of which appears to predominate. Large areas are made up of rather loose collections of completely undifferentiated sarcoma-like cells separated by occasional strands of connective tissue (Figs. 2–4). The individual cells have large, dark, polymorphic nuclei. Mitoses are frequent. Such areas bear a close resemblance to the so-called dysgerminomas. The stroma consists largely of a network of fine capillaries; the tumor cells are united by argentaffine fibers. Practically no large vessels are to be seen.

Interrupting these dysgerminoma-like parts are interlacing strands of closely packed cells in regular arrangement, showing some similarity to ovarian stroma. The cells are uniform with faintly staining vesicular nuclei. Connective-tissue fibers are demonstrable by the usual methods.

Between these two component tissues the line of demarcation is not always sharply drawn. One often forms islets within the other (Fig. 2).

More or less abundantly distributed throughout the areas described above are nests of epithelium-like cells (Figs. 3–5). These are generally to be seen close to or even within the stroma-like cell strands. The cells are cylindrical or cuboid with vesicular nuclei and usually surround small cavities filled with an acidophil colloid material. At the periphery and adjacent to the cavity a palisade arrangement is evident. These formations resemble fully developed granulosa tissue. They are sharply demarcated from the neighboring tissue and are frequently bordered by strands of hyaline connective tissue. The shrinking incident to preparation of the sections causes the granulosa structures, or “pseudo-follicles,” to stand
out from the surrounding tissue, and here and there the transition from the adjacent stroma-like tissue can be distinguished (Fig. 3). From their points of origin they extend into the neighborhood without evidence of destructive infiltration. Both the granulosa and the neighboring tissues have a tendency to undergo progressive hyaline degeneration.

There are, in addition, considerable areas of the tumor characterized by perivascular formations. In a few such places the capillaries and small veins are enclosed in masses of sarcoma-like cells entirely undifferentiated and sometimes with a slightly radiating arrangement. For the most part, however, the picture closely resembles that upon which Schiller based his diagnosis of "mesonephroma ovarii" (Figs. 8–12), with collars or star-like haloes of cells in the adventitia of the vessels (Schiller's glomerular structures). From these perivascular formations papillary processes arise, extending to form a labyrinth of communicating channels.

The less differentiated areas show short cell chains and no stroma (Figs. 6–7). The cells are highly polymorphous, mitoses are abundant, and there is at the same time necrosis, beginning with the formation of intracellular hyaline droplets and eventuating in complete calcification. Where a higher degree of differentiation has taken place, the tumor cells appear to be strung on connective-tissue fibers, which form the frame-work of the communicating channels. They show a high degree of regularity and a button-like arrangement unlike that of epithelial lining cells. They are usually not in direct contact with one another but rather widely separated (Figs. 9–11).

It is true that the typical arrangement in these areas resembles in cross-section the primitive or embryonic glomerulus of the kidney with a single capillary loop (Fig. 11), as described by Schiller. Outside the perivascular collar of cells is a free circular or crescent-shaped space with an outer border of tumor cells belonging to the papillary system described above, reproducing the picture of a glomerular loop with both the parietal and visceral layers.

**Fig. 1. Case II: Plastic Reconstruction of Perivascular Structures**
Fig. 2. Undifferentiated tumor tissue, rich in cells, in part resembling dysgerminoma; adjacent to it closely woven strands of connective tissue, somewhat hyalinized, with large fusiform cells, bearing some resemblance to ovarian stroma. \( \times c. 70 \)

Fig. 3. Irregularly formed inclusions of "granulosa," narrow bands of which extend into the surrounding connective tissue. The structure is typical: polygonal cells, with large nuclei, surrounding colloid-filled cavities; lining cells in palisade formation. \( \times c. 70 \)

Fig. 4. Area of tumor showing numbers of "granulosa" inclusions (pseudo-follicles), dysgerminoma-like tissue, and stroma. The spaces about the pseudo-follicles are due to shrinkage in preparation. \( \times c. 20 \)

Fig. 5. High-power photograph of one of the pseudo-follicles in Fig. 4, showing palisade arrangement of bordering cells, follicle cavities, and close relation to adjacent stroma. \( \times c. 100 \)

of Bowman's capsule. On closer examination, however, these structures show no evidence of a glomerular form, especially as concerns their plastic aspect. The capillaries do not form loops nor do there exist the well defined morphological constituents of glomeruli as seen in serial sections. In longitudinal sections of the tumor (Fig. 12), in which the capillaries with their surrounding cell mantles are clearly shown, there is no resemblance to glomeruli (cf. the plastic reconstruction from Case II, Fig. 1).

Finally, throughout the entire tumor are small foci of hematopoiesis (Fig. 13).

CASE II (128/39): A married woman of twenty-seven years with a lower abdominal tumor of three months' duration was found at laparotomy to have a large growth arising
Two different stages of differentiation of the papillary channel system are shown. Fig. 6 shows a completely undifferentiated system of cavities, lined with polymorphous cells, and little stroma (cf. Figs. 22 and 28A). Fig. 7, from an adjacent area, in the neighborhood of a small blood-vessel, shows short cell chains in papillary arrangement, but there is still practically no stroma. The cells are large and polymorphous. × 90

from the left ovary and adherent to the sigmoid and greater omentum. It was removed in its entirety but the patient died in shock twenty-four hours later. At autopsy necrotic tumor fragments were found in the pouch of Douglas and metastatic nodules in the para-aortic lymph nodes. The abdomen contained 750 c.c. of hemorrhagic fluid.

The tumor, which measured 25 × 18 × 11 cm., was partly solid and partly cystic; no remnant of the ovary could be found. Except for the areas adherent to the sigmoid, the mass was enclosed in a thin yellow-gray capsule. The surface was irregular due to numerous small nodules protruding from the main body of the tumor. On cross-section only a few areas of well preserved solid tumor tissue were to be seen. They were yellowish-white and of soft consistence. Numerous cystic cavities were present, filled for the most part with soft masses of a dirty reddish yellow color. On the right side was a hydrosalpinx of moderate size.

Structurally this tumor shows a tendency to the formation of channels or cavities (Figs. 14–18) with papillary ramifications, lined by a single layer of cells. Here and there are solid areas, with dark compact cell strands in a cell-poor stroma (Fig. 16), but even the cell columns in the neighborhood are canalized. Otherwise the histologic aspects are due to variations in the proportion and mutual relations of the two main tumor elements—the channel system and the stroma.

In large areas the tumor closely resembles that in Case I—a complicated labyrinth of fine papillary processes arising from perivascular structures (Fig. 15). Schiller's glomerular structures are thus to be seen in large numbers. The tumor cells in these areas appear to be strung on fine fibers, mostly in a single, but not always uninterrupted, layer. The cells nearest the vessel walls commonly show a more compact arrangement and stain intensely (Fig. 14).

In places the channels are more regularly arranged; they are also wider, with a lining consisting of an uninterrupted layer of flat endothelium-like cells. Surrounding them are
Fig. 8. Papillary system of minute channels with characteristic collar-like structures about the blood-vessels (Schiller's glomerular structures). × 40

Figs. 9 and 10. Breaking up and transition of the perivascular collars into a system of papillary channels with a single layer of endothelium-like lining cells and a framework of fine connective-tissue fibers. × 80

Fig. 11. Schiller's "glomerular structure." The picture looks, indeed, like a primitive glomerulus with a single capillary loop and both layers of Bowman's capsule. The resemblance is increased by the capillary ramifications of the vessels. Compare with Fig. 9, where the relation of the "glomerular" structure to the adjacent tissues is clearly shown. × 115

more or less narrow strands of connective tissue, generally poor in cells (Figs. 17 and 18). In some areas this stroma is of especially loose texture and includes large, star-like, ameboid cells, producing a picture closely resembling Wharton's jelly. The whole appearance is typically angiomatous. Differentiation sometimes reaches such a degree as to present the histologic aspect of a cavernous body.

Scattered throughout the tumor are small glandular, ring-like structures. In the shrinkage incident to fixation these are frequently detached and are seen to consist of narrow, high-cylindrical elements with vesicular nuclei and a somewhat vacuolized protoplasm. Sometimes they contain a homogeneous mucoid secretion. In a very few places there are what appear to be communications between these glandular structures and the cavities described above. At such points the epithelium seems to be continuous with the endothelium-like cells lining the angiomatous channels.
CASE III (P24): The clinical details of this case are scanty. The patient was an unmarried woman of twenty with a right ovarian tumor. The left ovary had been removed previously for unknown reasons. Metastatic nodules were present in the peritoneum.

The description of the tumor is based on sections from four paraffin blocks. Only two components were recognized, which appeared to be closely related. One consisted of a network of finely branched papillary structures, especially around the vessels of different caliber, forming the glomerulus-like structures mentioned above (Fig. 23). The other, closely associated with the first, resembled a cavernous angioma (Fig. 21), the tubes lined by a single layer of endothelial cells. A more detailed histologic study showed features closely corresponding to those described in Cases I and II. The main picture was one of irregular channels and surfaces covered with a single layer of cells, but solid areas were present made up of small angular cells with dark nuclei. Beginning canalization was observed in these areas (Fig. 22). Here even the large blood vessels show an extremely simple structure.

Histologically there can be no doubt as to the close resemblance—if not actual identity—of the three tumors described here to one another and to those described by Schiller. We are in full accord with Schiller as to the endothelium-like character and arrangement of the tumor cells. We agree with him, also, and with Meyer, Kermnauer and Sternberg, that cell similarity alone does not suffice for the diagnosis of an endothelial tumor. According to these authors, a diagnosis of angio-endothelioma is justified only
when there exists a structural relationship between the tumor and the essential elements of the blood or lymph vessels. That any such a relationship exists in the tumor which he describes Schiller denies. He therefore refuses a diagnosis of endothelioma and seeks to link the endothelium-like cells and the glomerulus-like formations to the primitive glomerulus of the mesonephros, the more so in view of the close topical relationship of the ovarian and mesonephric anlage.

In the light of this conception the glomerulus-like formations take on a special significance both for classification and diagnosis. A plastic reconstruction was undertaken by Schiller in one of his cases and we decided to repeat this procedure, choosing Case II because of the frequent occurrence of the formations in question. The course of these structures was followed through 48 serial sections and drawings were made (enlarged 65 times) of the peculiar collar-like formations as they appeared in each section. These drawings were then superimposed upon one another and the plastic reconstruction was made on this basis. Fig. 1, showing the reconstruction, fails to demonstrate any circumscribed structures resembling glomeruli, however primitive. The picture is rather one of a close system of irregularly communicating channels, and the collar-like formations are to be regarded merely as cross-sections of the cell mantles surrounding the vessels in the tumor.

The findings are similar in Cases I and III, for apart from the characteristic picture in cross-sections, the appearance in longitudinal sections cannot be easily explained if well limited glomeruli are assumed (Figs. 12 and 14). There exist, however, other pictures which give the impression of true capsular spaces surrounding the glomerulus-like structures, apparently lined by visceral and parietal cell layers (Figs. 9 and 11).

In this connection the picture in our Case III assumes special significance. Within the connective tissue forming the outer coat of certain small blood vessels are to be seen festoons of relatively wide cavities, similar to lymph spaces and lined with endothelial cells, so arranged that the perivascular area has a distinct papillomatous appearance (Fig. 24). The resemblance to the collar-like structures described above is evident. Here, as there, the papil-
Fig. 14. Labyrinth of narrow channels formed by minute ramifications of the perivascular cell structures. Endotheliomatous lining cells. \( \times 27 \)

Fig. 15. Small blood-vessels with characteristic perivascular structures (Schiller's "glomerular structures") sending out papillary processes into the tumor parenchyma. \( \times 88 \)

Fig. 16. Field showing solid tumor tissue with dark, compact cell columns imbedded in a relatively cell-poor stroma (left), and, adjacent to it, apparent canalization of these columns, producing a system of channels which constitute one of the most striking features of the growth. \( \times 76 \)

lomatous structures are limited by endothelial cells, represented in this instance by the lining cells of the cavities. The irregular papillomatous channels, therefore, are not unlike fully developed lymph spaces, and the change in their character is to be attributed to a higher degree of tissue differentiation. In Cases II and III, moreover, there occur areas which, according to all morphologic criteria, correspond to angiomatous formations—simple angioma
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Fig. 17. Case II: Narrow Channels Lined by Flat Endothelial Cells
The aspect is that of an angioma. The stroma is poor in cells. × 29

Fig. 18 and 19. Case II

Fig. 18. Channels with wide, rigid lumina, suggesting cavernoma; myxomatous stroma with star-like cells resembling embryonic connective tissue. × 79

Fig. 19. Glandular, ring-shaped structures consisting of narrow, high-cylindric epithelial cells; lumina partially filled with mucoid secretion. × 126

and cavernous angioma in Case II (Figs. 17 and 18) and capillary angioma or even angio-endothelioma in Case III (Figs. 21 and 22).

Finally mention may be made of the frequent occurrence of hemopoietic foci in Case I (Fig. 13), presumably pointing to the participation of a primitive angioblastic mesenchyme in the formation of the tumor matrix.
Fig. 20. Case III: General Aspect of Ovarian Tumor

Areas of small papillary channel systems (C) amalgamating with rather typical angiomatous or angio-endotheliomatous structures toward the center (A). M and N. Necrotic areas. × 20

All these findings seem to require a diagnosis of (angi0)endothelioma so far as the tumor components are concerned. But while we cannot accept Schiller's designation of mesonephroma, our own concept is difficult of absolute proof. The demonstration, in plastic reconstruction, of the absence of any well defined glomerulus-like formations cannot be regarded as an adequate basis for rejecting the diagnosis of mesonephroma; on the other hand, the presence of an irregular perivascular channel system is not of itself satisfactory proof of an angio-endothelioma. It is fully recognized that topical relationships between characteristic elements of any tumor matrix may be abolished in the corresponding autonomous growth.

Our interpretation of the tumors as endotheliomatous is based on the findings as a whole: the endothelium-like character and arrangement of the tumor cells, as acknowledged by Schiller; the angioma- and cavernoma-like pictures in Case II, and the rather typical angio-endotheliomatous appearances in Case III, in a strict continuity with perivascular structures and papillary arrangement of less differentiated areas; the occurrence, in Case I, of hemopoietic foci; a plastic reconstruction which failed to demonstrate any true glomerulus-like formations but showed instead a system of irregularly communicating perivascular channels.

In addition to the angio-endotheliomatous structures there were demonstrable in Case I frequent inclusions of rather typical ovarian granulosa areas (Figs. 3 and 5), with a stroma closely resembling the stroma of the ovary. Other areas of highly cellular, wholly undifferentiated tissue showed an histologic structure almost exactly similar to the so-called dysgerminomas (Figs. 2 and 4). In Case II gland-like tubules were observed, often containing a homogeneous, mucus-like secretion (Fig. 19).
Fig. 21. Minutely ramifying channels lined with endothelial cells; strong resemblance to capillary angiomia. \( \times 57 \)

Fig. 22. Small, rather solid tumor nodules, rich in cells and showing evidence of canalization. The larger channels, as seen in the center of the picture, are in contact with such areas as shown in Fig. 2. Cf. Figs. 6 and 28A. \( \times 126 \)

Fig. 23. Small vessels with Schiller's "glomerular structures." \( \times 57 \)

Fig. 24. Series of adjacent cavities in adventitious tissue of a small vessel. They are lined by endothelial cells and resemble lymphatic spaces. The perivascular area thus has a papillomatous aspect. Pictures such as this are to be regarded as more differentiated forms of the comparatively primitive collar-like structures shown in Fig. 23. Cf. Fig. 26. \( \times 88 \)

The interpretation of the pseudo-follicular inclusions in Case I as an imperfectly developed ovarian component meets with no special difficulty. The origin of the epithelial tubules in Case II is less obvious. They would appear, however, to be closely related to scattered epithelial inclusions or embryonic remnants such as are to be found in the ovaries of young children and are
Fig. 25. Perivascular collar-like formations and papillary processes generally lined with a single layer of endothelial cells. Cf. Figs. 9, 11, 12, 15, 23. × 78

Fig. 26. Arrangements of tumor tissue about a blood-vessel obstructed by an old clot, resembling lymph spaces; inflammatory infiltration in the loose adventitia. Cf. Fig. 24. × 78

commonly regarded as the starting point of the pseudo-mucinous cysts frequently encountered in adult ovaries. These "accessory" components thus seem to arise from an imperfectly developed ovarian anlage.

Since it is obvious that angio-endotheliomatous tumors may arise in any organ, the presence of the "accessory"—or organ-specific—components may be regarded as pointing to an origin in a developmental disturbance in the gonads. It must finally be taken into consideration that the gonads are a frequent site of tissue malformations (hamartomas) and teratoid tumors—a phenomenon which is related to the diverse potentialities of the gonadal cells (Oberndorfer).

In this connection it may be said that, so far as we are aware, no similar tumor has been described as originating from the testicles. Nor were we able in our own collection of testicular tumors, in that of Oberndorfer (more than 50 examples), or in two cases (No. 40 and 41) recorded by Klossner, to find any identical neoplasm. A metastatic tumor of the liver in a man of sixty, presumably originating in the testicle, and showing a striking resemblance to the tumors described above, has however come to our attention. The patient's history mentioned the extirpation of the right testicle, seven years earlier, for a malignant tumor ("sarcoma"), but no details as to the nature of the growth could be obtained. He remained free of complaints, however, for only a short period. Chronic bronchitis, pleurisy, and gradually increasing cachexia, suggesting possible pulmonary metastases, developed. Hospital

1 Agaki, under Walthard's direction, has shown similar epithelial inclusions in the ovaries of 15 out of 80 newborn infants.

2 For the biopsy material from this case and for permission to publish it here, we are indebted to Dr. Omer Vasfi Aybar, Director of the Surgical Department of the Şişli Çocuk Hastanesi.
Irregular channel system, rather suggestive of angio-endothelioma. Note the presence of some lumina with the appearance of well developed blood or lymph capillaries. Cf. Figs. 17 and 18.

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admission was for an abscess of the liver but laparotomy revealed large numbers of tumor metastases in the liver and peritoneum. The patient died postoperatively, but autopsy was not permitted.

A biopsy specimen from one of the liver nodules showed the presence of perivascular collar-like structures with papillary processes lined by endothelial cells and forming cavities resembling lymph spaces; masses of large lightly staining cells with a network of narrow channels and a dense framework of argentaffine fibers; an irregular system of cavities, of which the most highly differentiated had the appearance of blood or lymph capillaries (Figs. 25–28).

In view of these findings and the history of a testicular tumor, presumably the primary lesion, it seems justifiable to mention this case in connection with those recorded above. Further observations are obviously necessary before the question of the occurrence of such tumors in the testicle can be settled.
The entire appearance of the group of tumors here described justifies their separate classification, as Schiller has pointed out. Our study leads us to suggest for them the descriptive designation "papillo-endothelioma ovarii."

CONCLUSIONS

Three examples of malignant ovarian tumors have been recorded, presenting the same general picture as Schiller's "mesonephroma ovarii." Our study of these growths, however, including a plastic reconstruction of one of them, failed to reveal evidence of a derivation from remnants of the primitive mesonephros. In view of the endotheliomatous character of the cells and the presence of angiomatous and angio-endotheliomatous structures, we believe they are rather to be regarded as angio-endotheliomatous neoplasms. The occurrence of accessory organ-specific components in two of the cases suggests an origin in a gonadal anlage.

A similar tumor, presumably metastatic from the testicle, was observed in the liver of a man of sixty years.

We propose for this group of tumors the name "papillo-endothelioma."

NOTE: We desire to express our gratitude to Prof. Dr. Oberndorfer for his unfailing interest and helpful advice.

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