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ENDOMETRIAL MANIFESTATIONS OF OVARIAN FEMINIZING MESENCHYMOMAS

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Female sex hormones produced by ovarian feminizing (granulosa-cell and theca-cell) tumours of mesenchymal origin can be demonstrated in the experimental animal by biological means, chemical methods, and on the basis of their effect on the host organism. This last possibility is important insofar as the hormonal effect is studied in the very organism in which the tumour has developed. Two methods of this kind are known, analysis of vaginal smears, and the histological examination of the endometrium. Endometrial biopsy is the more reliable of these two methods, an intervention which beside being a diagnostic aid is frequently performed for therapeutical purposes as well. Feminizing tumours give often rise to abnormal uterine bleeding which necessitate curettage. It frequently happens that the histological analysis of the curettings furnishes the clue which leads to the discovery of a hormone-producing tumour.

Led by such considerations, we have examined the endometrium of 53 patients with feminizing mesenchymoma (Table I). As far as we could observe, the hormonal action of feminizing mesenchymomas may have five forms of endometrial manifestation.

1. The so-called glandular-cystic hyperplasia represents the most marked manifestation. It may occur at any age. The endometrium is hypertrophic and

Table I

Distribution of endometrial changes

Glandular-cystic hyperplasia	26
Glandular hyperplasia	7
Endometrial activity	10
Atrophic endometrium	3
Adenocarcinoma	3
Regressive hyperplasia	2
Endometrial secretion	2
Total	53 cases

* A part of this work was carried out in the Department of Obstetrics and Gynaecology of the Humboldt University, Berlin, Germany and in the Department of Pathology of the Medical University, Szeged, Hungary.

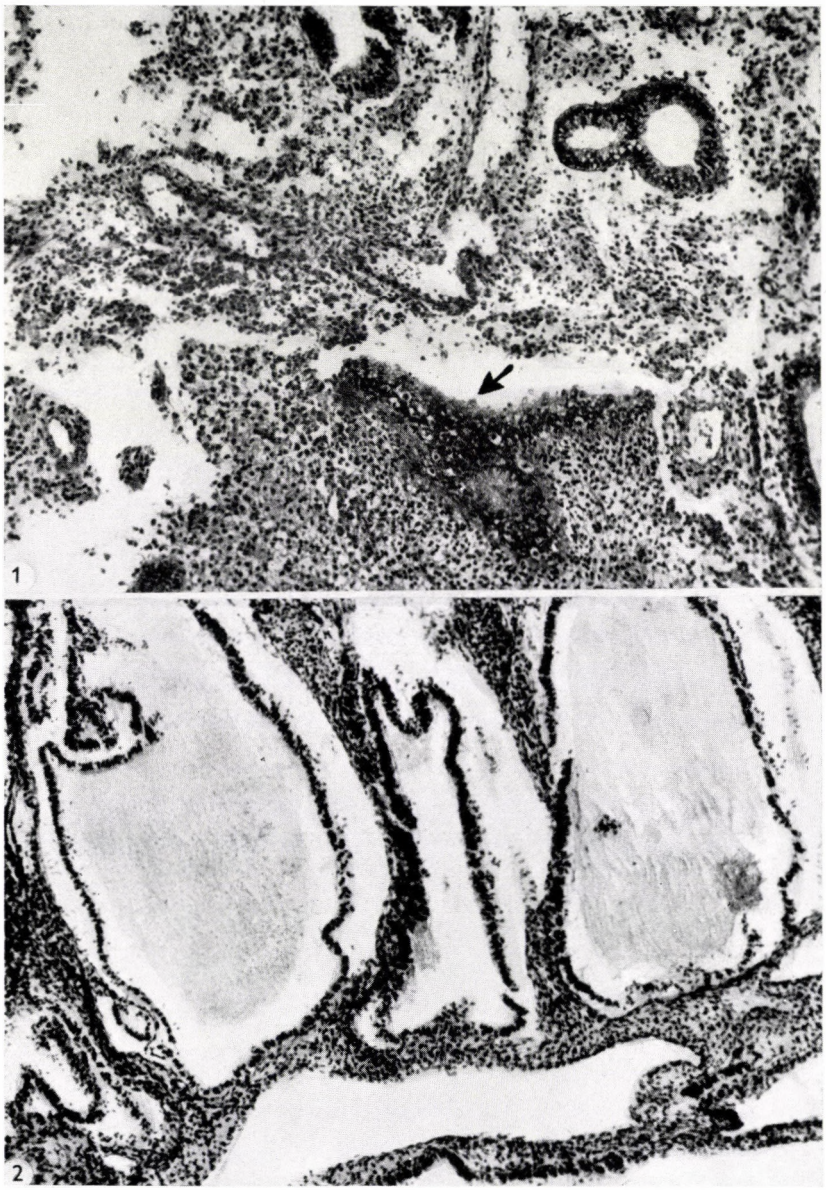

Fig. 1. L. U., 44 years of age. Uterine bleeding five years after the last menstruation, provoked by feminizing mesenchymoma (granulosa-cell tumour). The glands of the endometrium contain clear cells; they are especially abundant at the point indicated by arrow

Fig. 2. I. T., 58 years of age. Regressive endometrial hyperplasia, associated with combined feminizing mesenchymoma (granulosa-theca-cell tumour). The uterine mucosa is lined by thin, atrophic epithelium. The dilated cystic glands are lined similarly

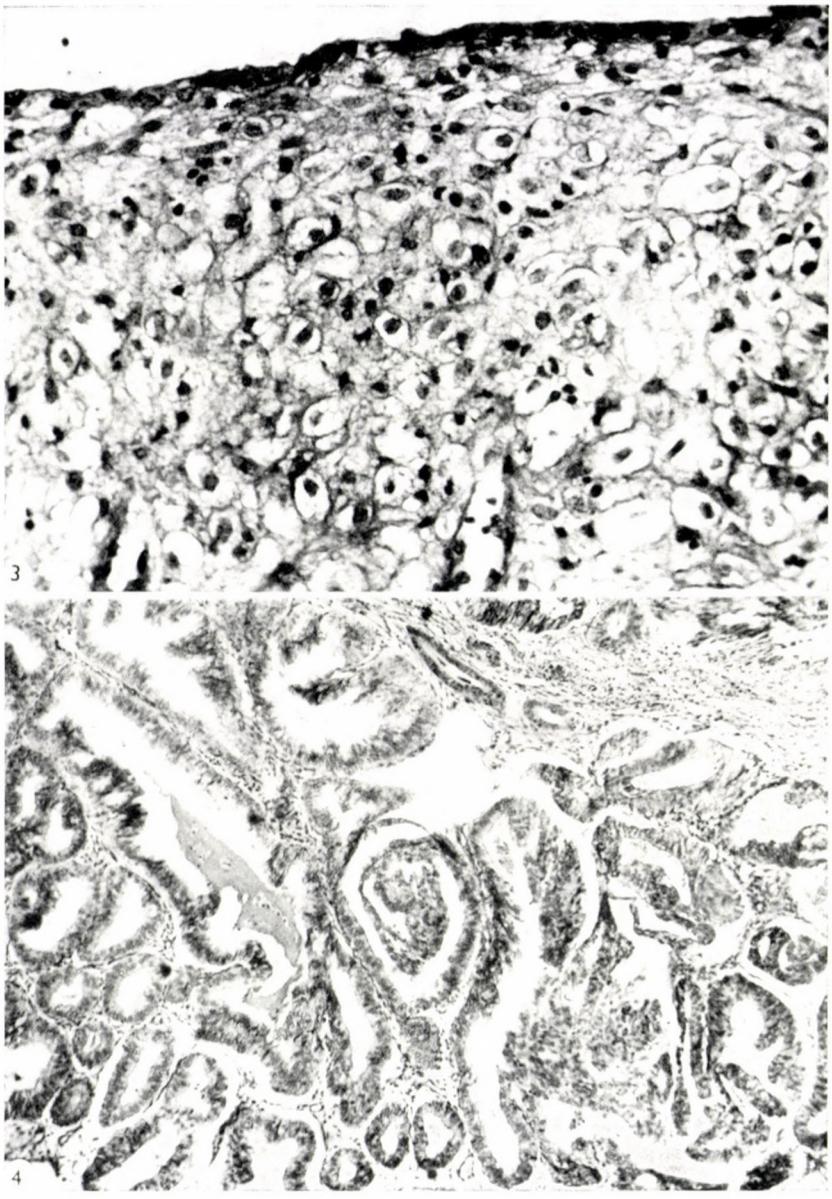

Fig. 3. I. T., 61 years of age. Feminizing mesenchymoma (androblastoma) showing signs of luteinization which provoked bleedings 16 years after the menopause. Secretory endometrium, with decidual transformation of stroma cells

Fig. 4. I. M., 60 years of age. Endometrial adenocarcinoma associated with feminizing mesenchymoma (theca-cell tumour). Besides glands lined with a single layer of regular columnar epithelium, there are glands lined with several layers of cancerous epithelium displaying signs of papillary anaplasia

thick, a pattern particularly striking in the menopause because one expects to find atrophy at this period. The glands are cystic and their epithelium is high, NOVAK [12] compared them to Swiss cheese. There are, as a consequence of increased oestrogenic influence, many clear cells in the epithelium (Fig. 1), especially in sexually mature individuals and at the onset of the menopause, when the epithelium is not yet too senile. Such clear cells seem to be the result of degenerative processes, and their accumulation goes parallel with the rise of the oestrogens level [3, 7]. Mitoses are frequent in the endometrial stroma in cases of glandular-cystic hyperplasia. Such hyperplasia of the endometrium has been observed in 26 of our patients. The age distribution was similar to that of the women with feminizing mesenchymomas. The mucosa sometimes contains polypous structures, and vessels with thick walls are found in the endometrium in such cases. Again, it sometimes happens that cystic hyperplasia is present, the endometrium is thick the number of glands high, but cystic dilatations are absent. Our material contained 7 cases corresponding to this description.

2. Activity of the endometrium in the menopausal woman points to a moderate hormonal action of feminizing mesenchymomas. The mucosa is not atrophic but presents the normal pattern of sexual maturity or is even thicker. The glands, too, are such as befit the age of sexual maturity, their lumen is not narrow, and their epithelium is high. The number of clear cells increases with the approach of the menopause. We have observed 10 cases of this so-called "active" endometrium.

3. An atrophic endometrium means a weak hormonal effect or even the total absence of hormones. There are two varieties. In the first the endometrium is thick, the glands are still numerous, and may even be cystic, but they are lined by a low inactive columnar epithelium. These symptoms point to a regression so that the term regressive hyperplasia has been coined to denote the pattern of which we have observed 2 cases. In second the endometrium is thin, glands are scarce, their lumen is narrow and their epithelium low. No, or only few, clear cells are seen. Our material contained 3 cases of atrophic endometrium.

Endometrial types of the first two categories are, as a rule, associated with bleedings. These may be protracted, especially in cases of glandular cystic hyperplasia. The hyperplastic mucosa undergoes necrosis and is gradually cast off amidst the discharge of coagulated blood. On the other hand, some feminizing mesenchymomas are associated with amenorrhoea in spite of endometrial hyperplasia (hyperoestrogenic amenorrhoea). It is worthy of note that irregular bleeding may occur even if the endometrium is atrophic, a phenomenon difficult to explain. It was in two of our three cases of endometrial atrophy that irregular bleedings were observed.

The above mentioned endometrial changes are constant as far as none of the three conditions is disturbed by cyclic changes. This uninterrupted

oestrogenic effect may be the very reason why feminizing mesenchymomas are relatively frequently associated with endometrial adenocarcinoma.

4. Feminizing mesenchymomas may exceptionally be accompanied by secretory changes of the endometrium, the decidual transformation of the endometrial stroma (Fig. 3). Our material included 2 such cases. The phenomenon in question was particularly surprising in the case of a 61-year old patient. The unusual endometrial picture was due to the fact that the tumour had become luteinized and was producing progesterone. Endometrial secretion in the other case occurred just prior to the onset of the menopause, in connection with a cherry-sized feminizing mesenchymoma. The amount of oestrogen produced by this tumour was obviously not enough to inhibit ovulation and the subsequent development of the secretory stage.

5. While all endometrial disorders mentioned so far are benign, feminizing mesenchymomas may also be associated with endometrial adenocarcinoma. Our material comprised 3 such cases. Theca cells were predominant in all of them. The endometrium in one of the cases showed glandular-cystic hyperplasia and adenocarcinoma (Fig. 4). The cancer must have developed from the hyperplastic substrate. All the three patients were in the menopause, two were 57, the third 60, years of age.

Discussion

SCHRÖDER [14] was the first to observe endometrial hyperplasia associated with feminizing mesenchymoma (granulosa-cell tumour), SZATHMÁRY [16] in 1933 considered it the most characteristic phenomenon in connection with granulosa-cell tumours.

Likewise SCHRÖDER [15] was the first to report on a feminizing mesenchymoma accompanied by an endometrial change which pointed to malignancy or was actually an incipient adenocarcinoma, a diagnosis confirmed by MEYER. There was glandular hyperplasia in the other parts of the endometrium. SZATHMÁRY [16] observed a similar case.

The possibility of an aetiological relationship between granulosa-cell tumour and endometrial carcinoma was raised by DOCKERTY and MACCARTY [2]. From the literature published between 1920 and 1949, INGRAM and NOVAK [6] collected 50 cases in which feminizing mesenchymoma had associated together with endometrial adenocarcinoma. To these, they added 4 cases of their own. GREENE [4] then found further 67 cases in the literature between 1949 and 1957. It is clear from these data that endometrial adenocarcinoma is more frequently associated with theca-cell than granulosa-cell tumours, a fact which is worthy of note if we remember that thecomas occur considerably less frequently than granulosa-cell tumours. For instance, among the first 500 cases

recorded in the American "Ovarian Tumor Registry" there were 6 cases of thecoma and 67 cases of granulosa-cell tumour; again, 289 cases of feminizing mesenchymoma had been diagnosed up to GREENE's survey in 1957. Among these, granulosa-cells were predominant in 179 tumours, theca-cells in 76, while 33 were mixed growth and one was a luteoma. Theca-cells seem to be more closely associated with endometrial adenocarcinoma than granulosa-cells. It is possible that thecomas are more carcinogenic, presumably because they produce more oestrogen. This assumption seems to be borne out by cases in which theca-cell tumours are associated with both endometrial and breast cancer [5, 13, etc.).

The relations between feminizing mesenchymomas and endometrial malignancies is still a battleground of controversies. Neither BÁRSONY [1] nor VÁCZY [17] regard oestrogens as directly carcinogenic. Uninterrupted production of oestrogens may, according to BÁRSONY, render the existing tendency of proliferation irreversible and become thus responsible for tumorous growths. According to WAARD [18], not only the presence of oestrogens but also the absence of progesterone is characteristic of all these combined tumours.

Like feminizing mesenchymomas, drugs introduced to the organism may also produce oestrogenic effect undisturbed by cyclic changes. That their administration over several years may lead to endometrial adenocarcinoma has been repeatedly observed [8, 9 11, etc.).

Endometrial adenocarcinoma, associated with feminizing mesenchymoma, is actually a spontaneous biological experiment taking place in the human organism, a process which points to the carcinogenic influence of oestrogens — at least in the endometrium and, sometimes, in the breast. Cancerous growths developing after the chronic administration of oestrogens seem to support this theory.

The fact that adenocarcinoma is more frequently associated with theca-cell tumours is presumable due to that they grow slowly, take a long time to reach palpable size, remain therefore concealed for a long time and do not exert pressure on their surroundings. They often remain latent for several years during which oestrogens are constantly produced; in the case of an existing predisposition and possibly other factors, they may then induce the formation of a neoplasm. Granulosa-cell tumours grow more rapidly, give soon rise to endocrine and abdominal complaints, and are then soon removed so that they cannot act long lasting effect upon the endometrium. Another explanation would be that feminizing mesenchymomas in which theca-cells are predominant (or combined theca-cell and granulosa-cell tumours) develop, as a rule, in or after the menopause, i.e. at a time when the organism (and the endometrium in particular) is more susceptible or apt to forming malignant growths.

Summary

Ovarian feminizing mesenchymomas may be accompanied by five forms of endometrial change: 1) glandular hyperplasia; 2) hormonal activity after the menopause; 3) endometrial atrophy; 4) endometrial secretion; 5) adenocarcinoma. Glandular hyperplasia occurred with the greatest frequency in the material on which the present study has been based. Endometrial cancer is, of course, of the greatest significance for the patients.

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DIE FEMINISIERENDEN MESENCHYMOME DER EIERSTÖCKE UND DIE GEBÄRMUTTERSCHLEIMHAUT

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Die feminisierenden Mesenchymome der Eierstöcke können mit 5 verschiedenen Veränderungen des Endometriums einhergehen und zwar mit 1. glandulärer Hyperplasie, 2. hormonaktivem Endometrium nach dem geschlechtsreifen Alter, 3. atrophischem, 4. sekretorischem Endometrium, und 5. Adenokarzinom. Im besprochenen Krankengut war die glanduläre Hyperplasie die am häufigsten beobachtete Endometriumveränderung. Hinsichtlich des weiteren Schicksals der Kranken hat aber der Gebärmutterschleimhautkrebs die größte Bedeutung.

ФЕМИНИЗИРУЮЩИЕ МЕЗЕНХИМОВЫ ЯИЧНИКОВ И СЛИЗИСТАЯ ОБОЛОЧКА МАТКИ

А. ЯКОБОВИЧ

Феминизирующие мезенхимомы яичников могут сочетаться с 5 различными изменениями в эндометрии: 1. железистой гиперплазией, 2. гормональной активностью эндометрия после половой зрелости, 3. атрофическим, 4. секреторным эндометрием и 5. аденокарциномами. В материале автора, наиболее частой картиной со стороны эндометрия была железистая гиперплазия. Однако, для дальнейшей судьбы больных наибольшее значение имеет рак слизистой оболочки матки.

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