Department of Obstetrics and Gynaecology, University Medical School, Szeged
(Director: Prof. F. Szontágh)

OVARIAN FEMINIZING MESENCHYMOMAS, ANDROBLASTOMAS

A. Jakobovits

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Teilum [25] was the first to call attention to morphologically congruent tumours occurring in the testis and the ovary. Homologous tumours mostly produce hormones and are functionally similar, a phenomenon presumably due to the common origin of testis and ovary. The gonad is undifferentiated up to the sixth week of intrauterine life.

Feminizing tumours usually contain two elements; while they show the structure of mesenchymomas (granulosa- and theca-cell tumours), they also exhibit androblastomatous structure. The present study has been undertaken to ascertain the incidence of androblastomatous elements in our material, and to elucidate possible interconnections between the microscopic and the clinical picture. Let us first briefly survey the literature on this subject.

The term "granulosa-cell tumour" was first applied by Werdt [26] in 1914, and it was Löffler and Priesel [11] who, in 1932, assigned a separate category for theca-cell tumours. Following the suggestion of Fischel [6] that both types of tumour derive from the ovarian mesenchyme, Novak [27] applied the collective term "feminizing mesenchymoma". This theory regarding the common origin of the tumours under review has been accepted by most authors. The common origin is supported by the identity of the clinical symptoms, by the fact that both types of cells produce the same hormones, and that often both types can be found in one and the same tumour.

By producing oestrogen, feminizing mesenchymomas induce sexual precocity in children (pseudopubertas isosexualis praecox); in sexually mature subjects and in those in the menopause, they give mostly rise to haemorrhagic disorders.

It occasionally occurs that part of the feminizing mesenchymoma is luteinized, so that progesterone is produced which may provoke endometrial secretion and even decidual transformation. It is of some interest that Páli [16] observed defeminization in a subject with a partly luteinized thecoma. Other

* 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.

authors [3, 12, 21, etc.) reported on hirsutism or virilism in association with feminizing mesenchymomas. These phenomena indicate a change of progesterone into androgen. It must be remembered in this respect that progesterone (hydroxyprogesterone) is known as the precursor of androgenic substances [8, 23].

The universally accepted term "androblastoma", first applied by TEILUM [25], is used for ovarian tumours which have a structure like mature testes without spermatogenesis, sex cords or testicular tumours. PICK [17] was the first to describe a tumour of this nature. It caused metrorrhage in his case. Later, MEYER [13] studied such tumours and found that they induced masculinization in many instances. Androblastomas belong to three structural types; there are tubular androblastomas, sarcomatoid androblastomas of a connective-tissue character, and, as a third category, there are transitional forms. A blending of the different types is frequent. Tumours of a predominantly tubular character induce, according to MILLER [14], masculinization in one third of the cases.

On gross inspection there is no difference between androblastomas and feminizing mesenchymomas.

It was in human testes that TEILUM [25] and in the testis of dogs that HUGGINS and MOULDER [7] encountered feminizing tumours of a similar structure. Observations of this kind led TEILUM to the conclusion that in the testis tumours may develop which have the same structure and functions as ovarian tumours. The production of oestrogen by androblastomas is attributed to the Sertoli cells; these or morphologically similar cells have been observed in ovarian androblastomas as well.

There exists a diffuse type of androblastoma, the hiluscell tumour. This originates from those large round or angular cells which occur in the hilus of the ovary under physiological conditions and resemble the interstitial or Leydig cells of the testis.

Most hilus-cell tumours, like the rest of virilizing tumours, induce first defeminization, then masculinization. Although they produce androgens, a number of authors [2, 5, 19, etc.] reported on feminization caused by such tumours. Since it is rather improbable that the same kind of cell should produce androgen in one and oestrogen in another case, the possibility of androgens changing into oestrogens [22, 24] has to be considered, a theory supported by the chemical affinity of these products.

The present report is based upon a study of 71 patients suffering from feminizing mesenchymoma and 4 patients with androblastoma.

The size of the tumours varied in our material from a diameter of a few mm to twice the size of a human head. The highest number of operated patients, i. e. 22 cases, were in the age group of 51 to 60 years; the next highest incidence of feminizing mesenchymoma was in the next (61—70) and the preceding

(41—50) age groups. The youngest patient was 3 1/2, the oldest 81, years of age (Table 1).

Different forms of uterine bleeding constituted the complaints in two thirds of the cases; they were frequently associated with other complaints such as pain, tenderness, palpable tumour, etc.

Table 1

Age distribution
(Number of tumours containing androblastomatous elements is shown in brackets)

Age	0—10	11—20	21—30	31—40	41—50	51—60	61—70	71—80	81—90	Total
Number of cases	1 (1)	—	3 (2)	8 (1)	11 (4)	22 (5)	19 (7)	6 (1)	1 (1)	71 (22)

Various types of feminizing mesenchymoma were represented in our material (Table 2). Granulosa-cell tumours of the diffuse type were encountered in 37 cases, but these tumours contained, in most instances, parts with a different pattern. Parts with a theca-cell structure were found in 33 tumours, in 20 cases these were dominating the picture. Folliculoid structure, the otherwise most typical form, was fourth in the order of frequency. Table 2 presents the frequency of the observed types.

Table 2

Type distribution

Diffuse granulosa-cell	37
Theca-cell	33
Androblastomatous	22
Folliculoid	18
Cylindromatous	11
Trabecular	10
Moiré-like	9
Pseudoadenoma-like	7
Luteinized	3

Two of the tumours of definitely androblastomatous structure were of the tubular and two of the diffuse type (hilus-cell tumours). Three of these tumours induced feminization while two gave rise to bleedings during menopause (Figs. 1, 2) and the third induced hyperoestrogenic amenorrhoea interrupted by bleedings at intervals of 4 to 6 months (Fig. 3). The fourth androblastoma provoked virilism.

It was in 22 cases that androblastomatous parts were encountered in feminizing mesenchymomas; these parts imitated the structure of developing or adult testes or testicular tumours (Fig. 4). The incidence of androblastoma-

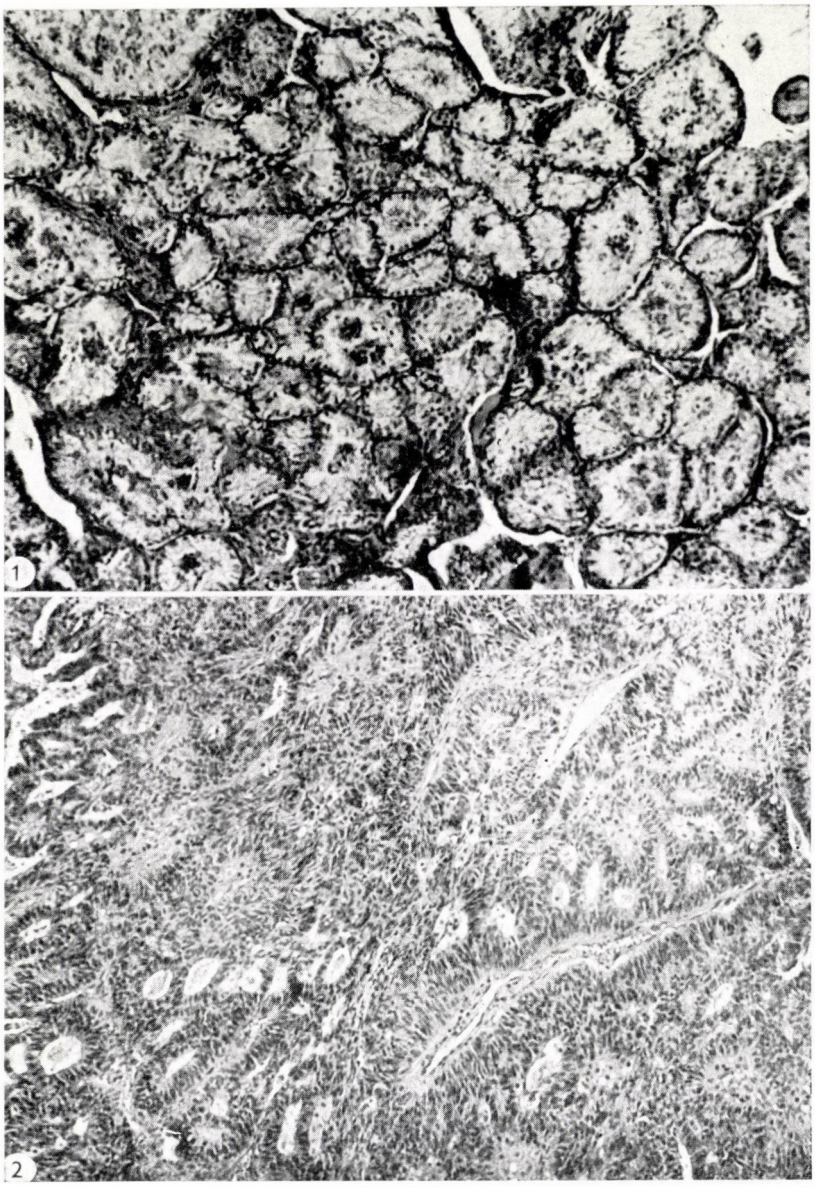

Fig. 1. D. C., 57 years of age. Feminizing mesenchymoma of predominantly tubular structure which induced irregular bleeding during menopause. The tubules are lined by a single layer of columnar epithelium

Fig. 2. J. A., 64 years of age. Feminizing hilus-cell tumour which induced bleeding and endometrial hyperplasia in the 14th year of menopause. The cytoplasm of the tumour cells is large, pale and foamy; they resemble the hilus-cells of healthy ovaries (or Leydig's interstitial cells of the testis). Septa consisting of connective-tissue cells are visible in the parenchyma of the tumour

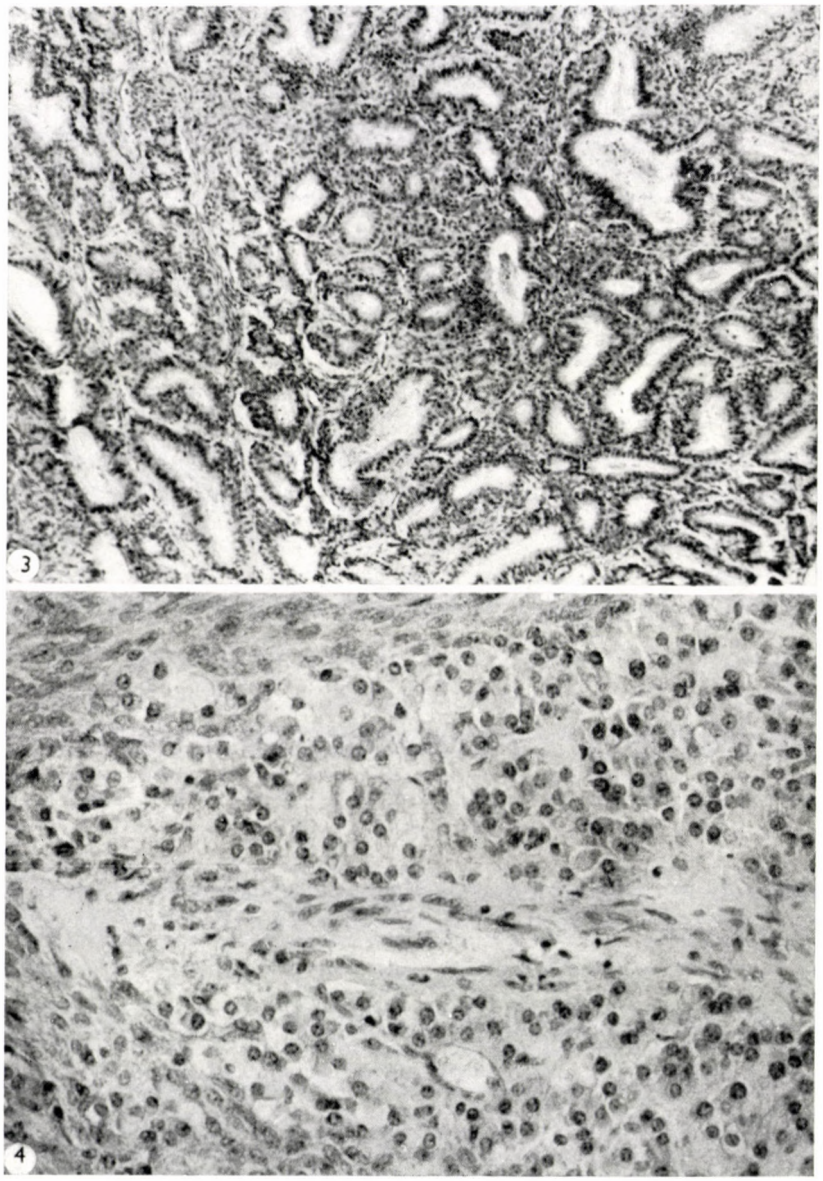

Fig. 3. J. S., 26 years of age. Feminizing androblastoma which induced hyperoestrogenic amenorrhoea and uterine hypertrophy. The polyhedral or elongated cylindrical parenchyma cells form irregular tubules. Some of the tubules contain eosinophil secretion

Fig. 4. I. T., 52 years of age. Feminizing androblastoma and/or mesenchymoma. The wall of the tubules consists of a layer of cylindrical cells. Some of the tubules have no lumen; the cells of the parenchyma are slightly spindle-shaped; a trabecular structure, suggestive of that seen in the germinal primordium, has developed. Note sporadic islets of granulosa cells

tous structures was more or less the same in our earlier animal experiments[4]. It was then possible to produce 30 feminizing tumours by transplanting the ovary of castrated rats into the spleen. Twelve of these tumours contained parts of androblastomatous structure.

Parts of this kind may be glandular with a tubular structure or, else he morphological picture may resemble the ductules of a developing testis and testis without spermatogenesis. Another type consists of columns of connective-tissue-like cells resembling the structure of primitive sex cords. There occur also epitheloid cells arranged in two rows which sometimes look as if they belonged to tubules sectioned parallel to their longitudinal axis. Again, we found in certain instances distorted canals, epithelial rolls or small bundles composed of elongated cells of a connective-tissue character.

On the other hand, these same human and animal tumours were characterized by the typical structure of feminizing mesenchymomas and they were found to be in no way different from them. Their size, too, showed the same variability (parts of this kind were contained, among others, in a tumour with twice the size of a human head). Like true feminizing mesenchymomas, they may occur at any age. Their occurrence according to age is given in Table 1.

Like typical and true feminizing tumours, the growths with such a mixed histological pattern produce oestrogen, and give rise to the same clinical symptoms in little girls they induce precocious pseudopuberty [10], and in sexually mature individuals they may provoke irregular bleedings. They may also give rise to opposite symptoms, such as amenorrhoea (so-called hyperoestrogenic amenorrhoea), and delay the onset of the menopause. Continued production of hormones may have the effect that irregular bleedings occur in the sixth decade and that complaints usually associated with the onset of menopause (e. g. heat waves), fail to appear. Again, cases have been observed in which tumours of this kind gave rise to bleedings at the outset, while, subsequently, they ceased to provoke endocrine manifestations. It is quite possible that — as is sometimes the case with growths consisting mainly of theca cells — the tumours in question became "hormonally exhausted". If appearing in the menopause, such tumours usually provoke irregular bleedings.

The fact that the two kinds of structure occur in the same tumour, argues in favour of the assumption that these growths derive from the same ovarian tissue, and, in addition, points to a common aetiology. It would follow that an increased production of pituitary gonadotrophin is responsible for the development of androblastomas. Arrhenoblastomas, too, derive, according to FISCHEL [6], from the ovarian mesenchyme.

Let us note that the nucleolar satellite sex chromatin, discovered by BARR and BERTRAM [1], occurs not only in the so-called androblastomatous parts but in more than 50 per cent of the cell nuclei in true androblastomas as

well. This sex chromatin is very rare in males but most cells of virilizing ovarian tumours contain it [9, 15, 20]. If classification were based upon this factor, androblastomas ought not to be regarded as belonging to a separate category. It seems, therefore, safe to conclude that, while certain considerations justify the establishment of a separate group for androblastomas, it has no great significance. The maintenance of a separate group for these growths is justifiable on the grounds of our present knowledge according to which their structure is different from that of the granulosa and theca cell tumours, although there seems to be no difference as regards the endocrine symptoms. Of course, it still remains doubtful whether there is sufficient reason for the maintenance of the term "androblastoma" and the establishment of a separate category for tumours so designated, especially if it is remembered that androblastomas, granulosa and theca cell tumours have been observed which, instead of inducing feminization, gave rise to masculinization. The phenomenon that a neoplasm with the structure of a male gonad produces female sex hormones explains why, for the time being, the classification of such growths has to rely on histological features alone.

It is quite possible that the present classification of hormone-producing ovarian tumours will soon be replaced by a simpler one, and it might be reasonable even now to abandon the existing terminology and speak of feminizing and virilizing mesenchymomas. This would perhaps help us in overcoming the present contradiction between structure and function.

Summary

Feminizing mesenchymomas and androblastomas constitute the two most frequent categories of sex-hormone-producing ovarian tumours. Although the overwhelming majority of feminizing mesenchymomas produce oestrogens, also progesterone-producing luteinized tumours have been observed, and there are even reports on the occurrence of virilizing tumours of this kind. The structure of androblastomas is like that of male gonads or testicular tumours; this notwithstanding, they sometimes induce feminization instead of masculinization. The existing distinction between feminizing mesenchymomas and androblastomas relies, therefore, on histological considerations and disregards the nature of hormones produced by them. To pay regard to the functional factor would only complicate the present classification. The occurrence of both kinds of structure in one and the same tumour has repeatedly been observed. Not less than a third of the mesenchymomas on which the present study has been based contained elements which were suggestive of primitive sex cords or developing or mature male gonads without spermatogenesis; in other words they contained parts with the structure of androblastomas. The incidence of this phenomenon is identical in experimentally induced tumours. Such joint occurrence of feminine and masculine features argues for a common origin and, possibly, for a common aetiology.

A future, simplified classification will presumably distinguish only between feminizing and masculinizing mesenchymomas.

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FEMINISIERENDE MESENCHYMOME BZW. ANDROBLASTOME DER EIERSTÖCKE

A. JAKOBOVITS

Die zwei häufigsten Formen der Geschlechtshormone erzeugenden Eierstockgeschwülste sind die feminisierenden Mesenchymome und die Androblastome. Die überwiegende Mehrheit der Mesenchymome synthetisiert Oestrogen, doch kommen auch Progesteron erzeugende luteinisierte Geschwülste vor, und es sind sogar mit Virilisation einhergehende Fälle bekannt. Die Androblastome erinnern an die Struktur der männlichen Gonaden oder ihrer Geschwülste. Ihrer Funktion entsprechend lösen sie aber nur in einem Teil der Fälle Virilisation aus, in anderen Fällen haben sie, gerade umgekehrt, eine feminisierende Wirkung. Die Einteilung nach feminisierenden Mesenchymomen und Androblastomen beruht demnach in erster Linie auf der histologischen Struktur, läßt aber die Hormonsynthese außer Acht. Bei Berücksichtigung der Hormonerzeugung wäre indessen die Einteilung noch komplizierter. Die Klassifikation erscheint ohnedies oft erzwungen und gekünstelt. Es kommt vor, daß in ein und derselben Geschwulst beide Tumorstrukturen gemeinsam vorkommen. In dem vorliegenden Krankengut wurde nahezu in einem Drittel der Fälle ein androblastomatöses histologisches Bild gefunden, das an den primitiven Keimstrang, den im Entwicklungsstadium befindlichen oder bereits entwickelten, doch keine Spermiogenese aufweisenden Hoden erinnerte. In den experimentell hervorgerufenen Geschwülsten kommt dieses histologische Bild in ähnlichem Prozentsatz vor. Das gemeinsame Vorkommen scheint ein Beweis des gemeinsamen Ursprungs, vielleicht eines gemeinsamen ätiologischen Faktors zu sein.

Zwecks Vereinfachung der Klassifikation wäre es angebracht, die Einteilung der Sexualhormone erzeugenden Eierstockgeschwülste auf feminisierende und virilisierende Mesenchymome durchzuführen.

ФЕМИНИЗИРУЮЩИЕ МЕЗЕНХИМОМЫ И АНДРОБЛАСТОМЫ ЯИЧНИКОВ

А. ЯКОБОВИЧ

Наиболее часто встречаемые формы опухолей яичников, синтезирующих половые гормоны — это феминизирующие мезенхимомы и андробластомы. Преобладающее большинство феминизирующих мезенхимом вырабатывает эстрогены, но встречаются также продуцирующие прогестерон лутеинизированные опухоли, и даже известны случаи, сопровождающиеся вирилизацией. Андробластомы подобны структуре мужски хполовых желез или их опухолей, но по своей функции они все же только в одной части случаев вызывают вирилизацию, а в остальных случаях они, наоборот — вызывают феминизацию. Следовательно, разделение опухолей на феминизирующие мезенхимомы и андробластомы основывается прежде всего на гистологической структуре, а производство гормонов не принимается во внимание. Если же принять во внимание и синтез гормонов, то классификация опухолей становилась бы еще более сложной. Классификация и без того часто кажется нереальной, искусственной. Встречаются случаи, когда, в одной и той же опухоли совместно существуют две различных опухолевых структуры. Автор в наблюдаемом им материале почти в одной трети случаев обнаруживал андробластоматозную гистологическую картину [напоминающую первичный зародышевый пучек, находящиеся в стадии развития или уже развитые яички, но без спермиогенеза]. В экспериментально вызванных опухолях такая картина встречается в подобном проценте. Совместная встречаемость различных опухолевых структур говорит за общее происхождение и, возможнсе, за общий этиологический фактор.

Автор предполагает, что в целях упрощения классификации, опухоли яичников, синтезирующие половые гормоны, целесообразно разделять на феминизирующие и вирилизирующие андробластомы.

Dr. Antal Jakobovits, Szeged, József Attila sút. 91. Hungary