Dysgerminoma

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It is generally accepted that the dysgerminoma is a tumour arising from the ovarian germ cells. It is identical with its male counterpart, the seminoma, and with tumours found in other areas where germ cells may be present—retroperitoneally and in the thymus and pineal. The origin of this type of tumour from the spermatogonia of atrophic tubules has been demonstrated in dogs (Scully & Coffin, 1952) although these tumours, whilst similar in some aspects to the classical human seminoma, in others resemble the human spermatocytic seminoma (Scully, 1961). Histological relations of the dysgerminoma indicate an origin from oöcytes of the normal female germinal lineage (Hughesdon, 1959).

The typical histological pattern is easily recognizable, with large nuclei distorted from their basic spherical shape, with one or more nucleoli.

The cytoplasm is clear except where retracted by fixation. There is a striking picture of uniformity of the cells which are arranged in an alveolar pattern, being separated by fibrous septa infiltrated by lymphocytes. In some areas a columnar arrangement may predominate. There may be areas of necrosis and symplastic giant cell formation.

The clinical features of dysgerminoma have been studied in a series from the Tumour Registry of the Royal College of Obstetricians and Gynaecologists and compared with previous important collections of cases (Novak & Gray, 1938; Seegar, 1938; Sjövall, 1943; Santesson, 1947; Mueller, Topkins & Lapp, 1950; Pedowitz, Felms & Grayzel, 1955; Thoeny *et al.*, 1961; Koller & Gjonnaess, 1964; Pece, 1964).

The series, up to the end of 1965, contained twenty-nine cases. One of these was combined with

FIG. 1. Dysgerminoma.

a teratoma, the patient dying of leukaemia (Chalmers, 1950). This tumour behaved differently from the rest, the teratomatous element predominating, and has been excluded from this series. It is of interest that one of the patients with a combined teratoma and seminoma studied by the Testicular Tumour Panel and Registry also died of leukaemia (Collins & Pugh, 1964).

Clinical features

Age incidence (Table 1)

The tumour is principally one of young adults. In about 70% of cases the age of onset is between 10 and 30. It is rare after the menopause and in girls in whom it occurs before the reproductive age is often accompanied by hormonal changes.

TABLE 1
Age incidence

Age (years)	500 cases from literature (%)	Twenty-eight cases from Tumour Registry (%)
0-10	7	4
10-20	37	25
20-30	34	46
30-40	12	21
40-50	5	4
50+	5	0

Duration of symptoms (Table 2)

This is a rapidly growing tumour, usually bringing the patient to hospital within weeks of the onset of symptoms. It may, however, be asymptomatic, being found on routine antenatal examination or during the investigation of primary amenorrhoea.

TABLE 2
Duration of symptoms

Duration of symptoms	Sixty-nine cases from literature (%)	Twenty-six cases from Tumour Registry (%)
Acute	15	8
< 3 months	54	57
3-6 months	7	19
6-12 months	10	8
> 12 months	7	0
Asymptomatic	7	8

Symptoms (Table 3)

The commonest presenting symptoms are an abdominal mass, abdominal pain, or both. Although the tumour is generally regarded as being hormonally inactive, about 20% of patients had some menstrual upset. Precocious puberty or the onset of vaginal bleeding in patients with primary amenorrhoea may be the presenting symptom.

Some of the women are admitted in an emergency, either with abdominal pain due to accidents to the tumour, or, as two of the Tumour Registry cases were, because of acute retention of urine. There can also be difficulty with micturition of less dramatic onset.

Other less frequent symptoms were: upset bowel habit, either constipation or diarrhoea, dysmenorrhoea, general malaise. In two patients the tumour was found antenatally (Bigby, 1961).

TABLE 3
Symptoms

Symptoms	210 cases from literature (%)	Twenty-six cases from Tumour Registry (%)
Lump	35	58
Pain	36	46
Lump + pain	—	27
Menstrual upset	—	19
Emergency	14	15
Urinary upset	—	12

Ovary involved (Table 4)

The two ovaries are not involved to an equal extent, the right and left ovaries being affected in the ratio of 5 : 4. This is the same as for involvement of the testes with seminoma and is evidence against some of the bizarre theories advanced to explain this discrepancy in the male. It is probably of more relevance that in most normal female birds the right gonad is a rudimentary structure as a result of an organ specific inhibitory substance produced in the left gonad (Gardner, Wood & Taber, 1964).

In some cases bilateral ovarian involvement is found at operation or on histological examination. In only one case in the series was the apparently uninvolved ovary later the seat of a dysgerminoma, after an interval of 2 years. An ovarian biopsy 6 months after the original operation had not revealed any evidence of involvement at that time.

TABLE 4
Ovary affected

Side	500 cases from literature (%)	Twenty-seven cases from Tumour Registry (%)
Right	50	44
Left	36	37
Bilateral	14	19

Mortality (Table 5)

In most patients who die from dysgerminoma, the progress of the disease is rapid and they succumb within 1 year, after which the death rate subsides, but even a 5-year interval of freedom

does not guarantee cure. One patient in the series developed metastases and died 6 years after the original operation. In Table 5, percentages are of cases surviving.

TABLE 5
Post-operative survival rates

Years	237 cases from literature (%)	Cases from Tumour Registry (%)
1	55.5	71 (from 23 cases)
5	41	59 (from 17 cases)

Survival is markedly related to the extent of the disease at operation (Table 6). Where this is limited to one ovary, the outlook is good, but where the tumour has spread, and this includes bilateral ovarian involvement, the outlook is poor.

TABLE 6
Effect of extent of disease on 5-year survival rate

Extent of disease	215 cases from literature (%)	Seventeen cases from Tumour Registry (%)
Limited	64	90
Spread	23	14

The presence of bloody ascites at operation is of grave import, clear ascites not necessarily so (Table 7). This is overemphasized in the Tumour Registry series due to the small numbers involved.

TABLE 7
Effect of ascites on 5-year survival rate

Type of ascites	Thirty-one cases from literature (%)	Six cases from Tumour Registry (%)
Clear	33	100
Bloody	12.5	0

The operative findings give a good indication of the prognosis. Those patients who at operation are found to have growths which have spread beyond one ovary, with haemorrhagic ascites, adhesion or rupture of the tumour, are killed by their disease usually within weeks of operation and almost invariably within 3 years, and in this group of patients the tumours do not readily respond to radiotherapy. In patients with a solitary encapsulated tumour, not adherent and with no ascites, there is a good prognosis, most recurrences being extremely radiosensitive and radiocurable. Only one such patient in the series died, following a recurrence at 3 years.

Spread of the disease in the pelvis can occur in any direction by infiltration. The uterus was found

to be involved at operation in three cases in the series and the Fallopian tube once, indicating that if conservative surgery is not contemplated the uterus should be removed with both tubes and ovaries. In one patient death was associated with rupture of an infiltrated bladder.

The sites of metastatic spread are difficult to define owing to the paucity of post-mortem reports in the literature and the position with regard to seminoma in the male is little better. Clinical reports cannot usually give the precise origin of deeply sited masses. Apart from the patient with the combined teratoma and dysgerminoma, only one post-mortem was performed in the series.

Common sites of metastasis appear to be along the aortic chain of lymph nodes and in the supra-clavicular nodes. Any of the abdominal viscera may be involved, particularly the liver and kidneys. Lungs, pleura and mediastinum are the sites of frequent metastasis, whilst the vertebrae in all regions of the spine seem particularly prone to involvement with large malignant masses and consequent paralysis.

Tumours of dysgenetic gonads

Robert Meyer (1931) who first suggested the name *disgerminoma* (spelled dis-) found the tumour to occur in twenty-seven intersex patients but only twenty-one apparently normal females. This ratio has not been confirmed. In the Tumour Registry series four patients had intersex states. One had a mixed gonadal dysgenesis, the chromosomal complement of patient and tumour being of the normal male type (Seligman, 1967). The precise nature of the intersex condition in the other three is not known, but testicular tissue was present in one and typical dysgenetic gonads with calcification in another.

In 1953, Scully described a gonadal tumour, which he named a *gonadoblastoma*, in part dysgerminoma but elsewhere composed of Sertoli or granulosa cells and Leydig or theca cells, and associated with masculinization. He refers to these cells as respectively of sex-cord and mesenchymal origin although the embryological derivation which he gives is not universally accepted (Richardson, 1966) and the female cells morphologically corresponding to the Leydig cells are the ovarian hilus cells.

The gonadoblastoma probably always arises in tissues of testicular origin containing the Y chromosome (Teter *et al.*, 1964b), the gonads being dysgenetic, that is, unlike the agenetic or streak gonads of Turner's syndrome, containing recognizable germ cells and sometimes the non-germinal elements discussed above. Degeneration and calcification are frequent in dysgenetic gonads and

the calcification may be visible on X-ray. Calcification is also found in the testes of cryptorchidism and testicular feminization. It is never observed in dysgerminoma or seminoma in patients with normal somatosexual development.

In order to understand the significance of tumours of dysgenetic gonads, some of the experimental studies on the production of gonadal tumours may be given.

Granulosa cell tumours can be produced in the experimental animal either by irradiation (Furth & Butterworth, 1936), or by inactivating the oestrogen output of the ovary in the liver by transplanting the gonad into the spleen (Biskind & Biskind, 1944). Similar tumours are produced by testicular transplantation (Biskind & Biskind, 1945) and these tumours may become malignant and metastasize (Li, 1948).

It is thought that the experimental production of these gonadal tumours is due to a constant excess secretion of gonadotrophin by a pituitary freed from oestrogenic or androgenic control (Burrows & Horning, 1952). Chorionic gonadotrophin will also produce increased activity in ovarian hilus cells (Sternberg, Segaloff & Gaskill, 1953).

The dysgenetic gonads of the intersex patient may be likened to these gonads in experimental animals, having the same hormonal environment.

There is a tendency to hyperplasia and neoplasia in dysgenetic gonads and the early stages of this have been described as gonadoblastoma-*in-situ* (Teter, Philip & Wecewicz, 1964a). The germ cells may give rise to dysgerminoma and the non-germinal elements may also form tumours, the occurrence of Leydig cell tumours being a well-recognized hazard of dysgenetic gonads (Warren *et al.*, 1964). The incidence of neoplasia in dysgenetic gonads is high. Teter & Tarlowski (1960), in thirteen personal cases, found two dysgerminomas, one gonadoblastoma and one hilus cell tumour.

In the retained testes of the testicular feminization syndrome, Morris & Mahesh (1963) found only one reported malignant tumour among teen-aged patients and two in their twenties, but in fifty cases aged 30 or over there were eleven malignant tumours, mainly germinomas, as well as fifteen tubular adenomas and ten cysts. This figure probably does not give a true incidence of neoplasia in these patients as symptoms of the tumours were the presenting features.

Gonadoblastoma: clinical features

These are benign tumours, often bilateral, and in 75% of patients are discovered in the investigation of primary amenorrhoea or other features of intersex conditions, although they have been

associated rarely with precocious puberty preceding virilization. They are sometimes palpable on clinical examination but often only revealed at laparotomy. They may be present with acute pain due to torsion. In only about 10% of cases are there symptoms indicating a rapidly growing tumour and in these cases histological examination shows the predominant tissue to be the dysgerminomatous element.

Teter (1960) has extended the classification of these tumours, mainly on a histological basis. He calls the tumours gonocytomas and describes four types.

Gonocytoma Type I. This consists of pure dysgerminoma.

Gonocytoma Type II. This is a mixed form consisting of dysgerminoma cells associated with Sertoli-granulosa type cells. These may present an ovarian follicular type pattern with Call-Exner bodies or a testicular tubular pattern and both may be present in the one tumour. Teter described this type as sometimes showing oestrogenic activity which disappears following removal of the tumour, but this is unusual and oestrogenic effects are not restricted to this group. There have been metastases from tumours of this nature, but only the dysgerminomatous elements have been affected with no evidence of follicular structures.

Gonocytoma Type III. This contains three types of cells: (1) germ cells, (2) Sertoli-granulosa cells, and (3) Leydig-thecalutein type cells. It is often associated with virilization, although such tumours have been described with oestrogenic effects (Strumpf, 1965) or precocious puberty (Borghi *et al.*, 1965). Teter regards this tumour as identical with the gonadoblastoma, but Scully makes it quite clear that the tumour may be diagnosed without all three cell types being demonstrable histologically, quoting reported cases which Teter regards as falling into Types II or IV.

Gonocytoma Type IV. This Teter describes in cases with symptoms of virilism which disappear after removal of the tumour. Histologically he describes a homogenous form of gonocytoma with proliferation of the Leydig or thecalutein type cells either marginally or in the opposite gonad. This histological picture can also be found in patients in whom the virilism is preceded by precocious isosexual puberty (Giusti *et al.*, 1962).

One of the patients in the Tumour Registry series also had precocious puberty (Hain, 1949) and this case is instructive in that after the publication further sections of the tumour showed chorion-epitheliomatous elements, emphasizing that the complete cellular composition of a tumour may not be revealed in the material taken for histological examination.

Teter's classification does not give a complete picture of the tumour and its hormonal effects, merely the cellular elements demonstrable in the sections studied. It would seem best to give a full description of both histological and hormonal features in tumours of dysgenetic gonads, this being the best generic name for the group.

Treatment of dysgerminoma

The definitive treatment of dysgerminoma is total hysterectomy with bilateral salpingo-oophorectomy followed by intense radiotherapy to the pelvis and aortic lymph nodes.

Radical surgery will usually be performed in those patients in whom a pre-operative diagnosis is possible—namely, patients with intersex conditions, in patients with obvious malignant or bilateral disease, in post-menopausal patients and in some patients where a frozen section is available at operation. Often none of these conditions will prevail and the histological diagnosis only become available after the removal of a solitary ovarian tumour. In a woman who has completed child-bearing a full course of radiotherapy should be given and this is best preceded by re-operation for removal of the uterus, Fallopian tubes and remaining ovary.

A far more difficult problem is the young patient whose years of childbearing lie ahead. There are three possible lines of treatment.

Firstly, the radical treatment already described. This may be preferred by some of the patients or their relatives and would generally be considered essential in tumours where chorion-epitheliomatous or teratomatous elements are present, although the patient already described with chorion-epithelioma (Hain, 1949) had only conservative surgery with no radiotherapy and is alive and well 17 years later.

Secondly, the patient may be given conservative radiotherapy, that is with the remaining ovary shielded. This method is recommended by the Radiumhemmet (Brody, 1961) where eighteen pregnancies occurred in ten patients. There were fifteen normal babies, one terminated pregnancy, one abortion, but one child was malformed, a definite risk under these circumstances.

The third possibility is observation, reserving radiotherapy for those patients in whom there is a recurrence (Malkasian & Symmonds, 1964).

In the Tumour Registry series there were fifteen patients with an apparently solitary lesion who have been followed for 3 years or more. Of these all except one were treated initially by a unilateral operation, although this was the only gonad in one patient. In one patient the uterus, tubes and remaining ovary were excised later. One of the

patients had an initial radical operation but it is not known if radiotherapy was given in this case. Excluding this patient, who has not had any recurrence, two patients only had radiotherapy post-operatively and neither has a recurrence.

This leaves twelve patients treated by operation only. Recurrences occurred in four of these. One, the patient with the unilateral gonad, aged 47, developed metastases 3 years after operation, was given radiotherapy but died. The remaining three developed metastases after 2 years, 2 years and 9 months which responded to irradiation and they were alive and well 9, 7 and 3 years later.

The outcome in these twelve patients may be compared with that of twenty-two patients with similar lesions who were given conservative radiotherapy at the Radiumhemmet. Two of these patients were dead within 5 years and another two developed metastases which responded to further radiotherapy. This does not demonstrate any marked superiority in the use of prophylactic conservative as against therapeutic radiotherapy reserved for recurrences. Although current opinion favours prophylactic radiotherapy, the figures from the Tumour Registry do not support this view.

Summary

A series of cases of dysgerminoma is presented to illustrate some of the clinical features of this tumour.

Related tumours having their origins from dysgenetic gonads are discussed.

Methods of treatment are considered with particular reference to conservation of function.

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