SERTOLI CELL ONLY SYNDROME (SECOS): LESSONS FROM CASE STUDIES

Pages with reference to book, From 219 To 223

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ABSTRACT

Between June 85 and December 87, 69 testicular biopsies were submitted for histopathological examination during investigation of infertility; ten (14%) patients had a Sertoli cell only syndrome. The history, clinical features, and hormonal profiles were analyzed in an attempt to categorize these patients on aetiological basis. Two followed treatment of malignancy - one by radiation for testicular cancer and one by cyclophosphamide for a lymphoma. One had unilateral cryptorchidism. Mumps was etiological factor in one patient. FSH levels determined in 6 patients were elevated in all suggesting a possible dependence of (sick) Sertoli cells on spermatogenic cells for production of inhibin. Alternative explanations include changes in sertoli cell enzymes or FSH receptors. Testosterone levels are in the low normal range suggesting that Leydig cells may also be affected by the etiological factor producing the syndrome. Two patients who had earlier received a higher Johansen score were found to have a sertoli cell only syndrome on expert review of testicular biopsies. It is suggested that the condition is more common than hitherto reported and is often confused with maturation arrest. Testicular histopathology should be done by specialists in testicnlar pathology (JPMA 41: 219, 1991).

INTRODUCTION

The Sertoli cell only syndrome (SECOS) is a condition in which there is an absence of germ cells and the seminiferous tubules contain only Sertoli cells. Reproduction is therefore impossible and the patient is sterile. Thirty percent of our referred infertile population has azoospermia as compared to 5% in the west[1]. Accurate determination of the cause of azoospermia is necessary as treatment is helpful in the obstructive azoospermia but impossible in the Sertoli cell only syndrome.
A retrospective review of all testicular biopsies was undertaken by a clinician and histopathologists with a view to categorizing testicular pathology accurately. The records of the subset of 10 patients with SECOS were reviewed retrospectively.

MATERIALS AND METHODS

All (69) testicular biopsies done during investigation of infertility on patients attending the Aga Khan University Hospital infertility clinic between June 85 and December 87 were reviewed by two histopathologists and a urologist with special interest in andrology. Ten patients were detected as having SECOS. (Figure).

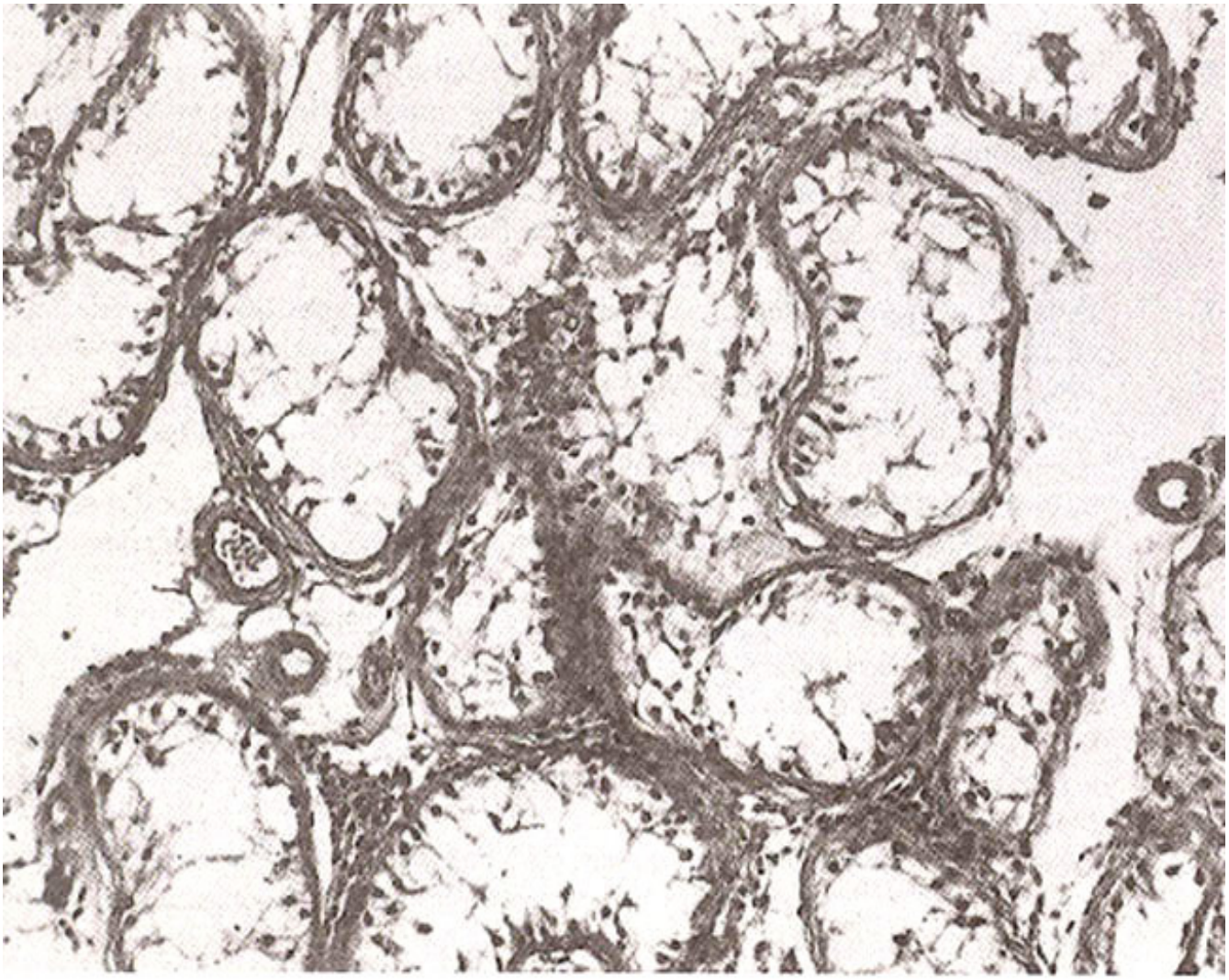

Figure . Histopathological appearance of Sertoli cell only syndrome.

The History, Physical Findings, Hormonal status and semenalysis of these 10 patients were reviewed in order to detect etiological factors and clinicopathological features of this syndrome. Testicular measurements were done by transparent ruler and hormone analysis by radioimmunoassay.

Results

TABLE I. Duration of infertile marriage before discovery of sertoli cell only syndrome.

	Duration of marriage	Husband's age	Wife's age
1	3	26	27
2	3	33	29
3	4	30	22
4	3	27	22
5	7	36	28
6	2	31	21
7	NR	27	25
8	4	28	20
9	6	28	NR
10	5	35	25
Mean	4.1	30.1	24.3
Range	2-7	26-36	20-29

Table 1 gives the patient's and spouse age and duration of infertility.

TABLE II. Sertoli Cell only Syndrome: etiological factors.

	Mumps	Irradiation	Chemotherapy	Smoking	Insecticide	Cryptorchidism	Estrogen	Occupation
1	0	0	0	0	0	0	0	BSNS
2	0	0	0	0	0	0	0	SERV
3	0	+	0	+	0	+	0	SERV
4	0	0	0	+	0	0	0	BSNS
5	+	0	0	0	0	0	0	NAVY
6	0	0	0	0	0	0	0	SERV
7	+	0	0	0	0	0	0	BSNS
8	0	0	0	0	0	0	0	ENG
9	0	+	+	0	0	0	0	BSNS
10	0	0	0	+	+	0	0	Farmer

TABLE III. Sertoli Cell only Syndrome: Past history of illness, medications & operations.

1	Typhoid 5 years previously, Jaundice 10 years age, Tagamate & antibodies
2	Hyperlipidemia, hypertension (age 33 years) (Inderal)
3	Mumps at age 12
4	Fracture tibia, Peptic ulcer, (Tagamate for 60 days) Appendicitis
5	Neonatal pneumonia, typhoid
6	Tonsillectomy
7	Gonococcal urethritis, Mumps
8	0
9	0
10	0

Tables II and III mention associated conditions which may contribute as possible etiological factors. All testes (Table IV)

TABLE IV. Sertoli Cell only Syndrome Testicular size & Testosterone levels.

	Test. Size R	L	Testosterone ng/dl	Mumps	Patients age history
1	3.5	(Orchidectomy)	600	0	26
2	3.5	3.5	526	0	33
3	'V. small'	4.0	457	0	30
4	3.5	3.5	456	0	27
5	"Small"	"Small"	ND	+	36
6	3.5	4.0	452	0	31
7	5	5	ND	+	27
8	4	3	ND	0	28
9	4	4	390	0	28
10	"Small"	"Small"	ND	0	35

except six were 3.5 cm or larger in their long axis as measured by transparent plastic ruler. Five of the 12 testes were 4 cm or larger. Of the two patients who had mumps, one had normal sized testes indicating that mumps had probably not affected the testes. All the patients were young and hence any reduction in testicular size was not related to age.

TABLE V. Sertoli Cell only Syndrome: Hormonal profile.

Hormonal Normal Values	FSH upto 20m IU/ml	LH upto 25m IU/ml	PRL upto 20ng/ml	Testosterone 300-1200 ng/dL	Remarks
1	21.7	ND	ND	600	
2	24.7	9.7	7.8	526	
3	42.8	29.7	8.8	457	Smoker
4	ND	26.7	ND	456	Smoker, Irradiation, Cryptorchidism
5	41.4	17.8	ND	ND	Mumps
6	36.4	19.4	15.4	52.7	
7	ND	ND	ND	ND	Mumps
8	ND	ND	ND	ND	
9	57.3	13.0	33.4	390	Irradiation, Cyclophosphamide for lymphoma
10	ND	ND	ND	ND	Smoker, Exposure to insecticides

ND - Not determined

Hormonal Status

FSH was determined in 6 patients (Table V) and ranged from 21.7 - 57.32 mIU/ml (Maximum normal 20 mIU/mI. LH levels (determined in 6 patients) were normal in four and marginally raised in two patients. Testosterone levels (estimated in 6) were normal in all patients but remained in the lower 1/2 of normal range. Prolactin level was elevated in one of the 4 patients in whom it was estimated.

DISCUSSION

Spermatogenic tubules of all vertebrates have 2 types of cells - the spermatogenic cell and the supportive Sertoli cell. For various reasons spermatogenic cells may in the embryo fail to develop or migrate, or, later under varying Chemotherapy Smoking Insecticide Cryptorchidism Estrogen Occupation circumstances be destroyed resulting in the isolation of Sertoli cells to producing a picture of Sertoli Cell only Syndrome (SECOS).

SECOS was found in 29% of testicular biopsies done for Suspected obstructive azoospermia[2]. It is difficult to find figures about incidence of SECOS in Pakistani literature. In our series 14% had SECOS. Usually testicular biopsy is not done in patients with obvious non-obstructive azoospermia in whom a diagnosis of testicular failure is made on the basis of hormonal evaluation. Sertoli Cell Only Syndrome is seen in patients with intraabdominal cryptorchidism (detected in late life), with viral infections, in patients who have received radiotherapy, chemotherapy or oestrogens and in an idiopathic variety[3].

Idiopathic (congenital) forms of SECOS may result from failure of migration of the primordial germ cells into gonadal anlage or to early destruction of the germinal epithelium by noxious substances. The etiology however remains obscure in most patients. One of our patients developed SECOS following radiotherapy to the abdomen for a seminoma; another after chemotherapy with cyclophosphamide. Two patients had a history of mumps but testicular atrophy was present in only one patient. Pakistan's population has been unable to gain access to modern medical care until recently. We have noted a large number of men with disparity in testicular size, one testes much smaller than normal. One possibility is that they have had unreported intermittent testicular torsion in childhood. SECOS could also perhaps be explained on the basis of bilateral recurrent torsion in which death of the sensitive germ cells has occurred but the more resistant Leydig cells and Sertoli cells have just managed to survive. Additionally roadside quacks prescribe medications which often contain heavy metals which may produce germ cell damage. Three of our patients were heavy smokers, but the effect of smoking on thc testes is variable[4-7] and it is not known to produce testicular atrophy. One of our patients had an intra-abdominal testis and seminoma, the opposite testis being normal. None of our patients had estrogens. One patient (a farmer) had repeatedly sprayed insecticides on his farms.

Testicular size

Despite the absence of germ cells, the testes have retained a good size in many patients. The clinical presentation is variable, at times suggestive of obstructive azoospermia with well developed testes measuring around 4.5 to 5 cm in the longitudinal axis, but many manifest as intermediate sized testes (3.5 cms) and a few have small testes. Clinical features do not help detect this syndrome which is diagnosed by biopsy alone.

Histological patterns

Histological patterns were initially misdiagnosed as maturation arrest in two patients. Diagnosis of SECOS must be water tight as patients need to be told that they are incapable of reproduction. Whilst the psychological effect of informing the patient that he cannot produce

Off spring is devastating it is inappropriate to shy away from the issue and treat such patients in vain hope that they will improve on therapy.

Histopathological appearances vary according to the cause. In the idiopathic form also called the del Costello Syndrome[8] there is great uniformity of appearance of pyramidal cells with a resulting adenoma like pattern. The cells contain a small number of inclusion bodies and elongated nuclei. FSH levels are consistently raised in this form[3].

In the form seen after chemotherapy or radiotherapy, the nuclei are of normal configuration, the cytoplasm contains phagocytosed material and large amounts of glycogen. In cryptorchids the nuclei of the sertoli cells are rounded and contain nucleoli. In some patients the cytoplasm is filled with characteristic pleomorphic inclusions.

Hormonal levels

As Sertoli cells produce inhibin, one would expect normal inhibin production (in this syndrome) and hence normal FSH levels. This is not so. Our findings of elevated FSH levels are in keeping with others[3,9,10] as also the normal LH levels and normal to lowTestosterone levels[11]. This had been noted even in the idiopathic variety which has been presumed to result from failure of migration of germ cells from the yolk sac.

The high levels of FSH could be explained by the following hypotheses:

1. germ cell cooperation is necessary for inhibin production.
2. Sertoli cell damage co-exists with germ cell damage.
3. Leydig cells are unable to provide enough testosterone for optimal sertoli function.

1. Germ cell cooperation

Steinberger and Steinberger[12] have shown that Sertoli Cells in culture can secrete a factor which selectively inhibits FSH. Galdieri et al[13] have shown that A.B.P. secretion by the Sertoli cell is influenced by contact with germ cells, and Ritzen et al[14] do not rule out the possibility that germ cell cooperation may enhance inhibin production, or that cells other than Sertoli are capable of producing inhibin. It is possible that potent inhibin is produced by cells other than sertoli cells.

2. Sertoli Cell Damage

This may manifest as a decreased production or altered direction of secretion of inhibin; or may result in loss of FSH receptors.

a. Decreased production of Inhibin:

Whilst Sertoli Cells may escape total annihilation, there is reason to suspect subtle damage at enzyme levels in these cells. It is known that post-irradiation damage to the sertoli cell may reduce locally produced GnRH like factor[3]. It is possible that though the cells look morphologically normal, the enzymes for production of inhibm are destroyed in much the same way as has been demonstrated for GnRH. De Kretser et al[10] have shown decreased inhibin levels in patients with gonadal damage, inhibin levels are low even though FSH rises and they propose that in many men with testicular damage the inverse relationship between inhibin and FSH is not evident.

b. Luminal vs. interstitial secretion of Inhibin:

It has recently been shown that the Sertoli Cell products can be secreted bidirectionally both into the seminiferous tubular fluid (STF) and into testicular interstitial fluid (TIF) and hence into blood[15]. Following hypophysectomy cryptorchidism, exposure to ethane dimethane sulphonate[16] or busulfation[17], the major part of androgen binding protein is secreted into testicular interstitial fluid and this has been related to absence of the pachytene spermatocytes and elongated spermatids from the tubule[15]. Selective enzyme damage may alter capacity of the Sertoli cell to secrete substances preferentially either into the lumen or blood stream. It has been shown that failure of glycosylation results in loss of the ability to secrete some of Sertoli cell proteins into the blood stream[18]. Inhibin secretion has also been shown to be bi-directiona[19]. In the Sertoli Cell Only Syndrome, it is possible that intraluminal secretion of inhibin into STF occurs instead of passage ofinhibin into the blood stream via

TIF from the basal surface of the cell. This may be because of someyet undiscovered enzyme defect. Lack of secretion into the blood stream may allow FSH levels to rise unchecked.

c. Decreased FSH receptors:

FSH and testosterone are the two main stimuli for the sertoli cell function14. Namiki et al[20] have shown that FSH binding sites were not affected by testicular organ culture at 37°C(as compared to 33°C) and they felt that short term temperature changes may not affect FSH binding sites. Presumably one would not expect a reduction in FSH receptors. Hagenas et al[21] have however shown a dramatic decrease in testicular receptors for FSH in cryptorchid rats. As Sertoli cell function is dependent on FSH, understandably the inhibin levels would fall in the absence of these receptors.

d. Age related changes in Sertoli cell:

A drop in the inhibin level would be expected with age. Our oldest patient was 36 years old and hence this is unlikely to be a cause.

3. The Leydig Cell

Whilst many authors have noted normal LH and T levels in patients with SECOS[22], we feel that the Leydig cells may also be affected to some extent in SECOS is suggested by the fact that testosterone levels are in the lower half of normal range, infact below 600 ng/dl. Leipcr et al[23] have shown decreased Leydig cell function after testicular irradiation for acute lymphoblastic leukemia. There was little increase of plasma testosterone on HCG stimulation in 10 patients, 7 of whom were pubertal. This reduction remained evident 4 years after testicular irradiation and the testicular volume remained lower than normal. Chemotherapy, however, was not as toxic. Forty six boys previously treated with chemotherapy had normal testosterone response to HCG stimulation[2] suggesting normal Leydig cell function.

It is possible that disordered Leydig cell function is responsible for the low normal testosterone levels in our patients. Sertoli cells do have a biological threshold for testosterone. In combined cell culture of pen-tubular and Sertoli cells 10 nmol/L concentrations of testosterone or dihydrotestosteronc are the minimal levels needed for Sertoli cell function[23]. It is possible that in vivo, larger peaks are needed for adequate function. The role of testosterone in controlling the Sertoli cell is still ill understood[24] and could involve the peritubular myoid cells[23] which may also be susceptible to radiation damage.

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