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Testicular Regression Syndrome: Useful Diagnostic Approach

*[1]Mohammed Shakir Ali, M.D[1], Mary Mathew, M.D[2]
1(Department of Pathology, P.K Das Institute of Medical Sciences, Kerala University of Health Sciences, India)
2(Department of Pathology, Kasturba Medical College, Manipal, Manipal University, India)
Corresponding Author: Mohammed Shakir Ali

Abstract :
Introduction:*Testicular regression syndrome (TRS) also known as "vanishing testis" is an entity characterized by subsequent atrophy and disappearance in fetal life of a primarily normal testis. It has an incidence of 35% to 60% in patients with cryptorchidism. Diagnostic controversies exist regarding approach to absence of testis.* ***Aim*** *of the study is to provide an approach helpful for diagnosis of testicular regression syndrome.*
Materials & Methods:*Cases with TRS were selected among all undescended testes operated during a period of 7 years from 2007 to 2013. Diagnostic criteria include vascularized fibrous nodule with paratesticular element(s) in proximity.*
Results:*Out of 19 TRS cases, 15 were from prepubertal and 4 from postpubertal group. Combination of paratesticular structures were noted grossly. The characteristic microscopic features include residual testicular parenchyma, nodular or discrete vascular fibrosis, dystrophic calcification, and hemosiderin deposition.*
Conclusion: *TRS constitute the major bulk in prepubertal cryptorchid patients. Microscopic features of TRS have to be correlated with intra-operative findings before rendering a diagnosis. It can help pathologist as well as surgeon to solve problems related to absent testis/ no testicular parenchyma.*
Keywords: *Atrophy, Cryptorchidism, Testis, Undescended, Vanishing,*

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I. Introduction

Testicular regression syndrome (TRS) also recognized as "vanishing testis" is an entity familiar to urologists and pediatric surgeons. It is coupled with absent testis with a blind-ending spermatic cord. Such individuals are genetically male (46, XY), presenting with unilateral or bilateral absence of recognizable testicular structures [1]. Five subtypes are documented depending upon the time of arrest of testicular development during intrauterine life; these comprise gonadal aplasia, early fetal testicular dysgenesis, early, mid and late testicular regression. TRS has an **incidence** of 35% to 60% in patients with cryptorchidism (undescended testis), which is defined as "failure of complete testicular descent into the scrotum, with retention of testis anywhere along its normal route of descent from an origin below the kidneys down into the scrotal sac" [2]. It is the most common disorder of male endocrine glands in children, etiology of which is poorly understood. At birth, about 4.5 % of the boys have undescended testis. The distinctive **microscopic features of TRS** comprise nodular or discrete vascular fibrosis, dystrophic calcification and hemosiderin deposition. Leydig cells in the background and foci of atrophic residual testicular parenchyma are also reported in early stage of TRS. But there is no reported malignant tumor, to the present data, originating from testicular nubbins with one exception reported in literature [3]. Diverse **causes** for testicular regression include intrinsic gonadal disorders, infection, trauma, torsion, infarction or prenatal hormone induced atrophy resulting from overproduction of androgens. TRS might be genetically transmitted, but the gene locus has not been recognized. **Diagnostic controversies exist regarding approach to absence of testis.**

II. Research Design And Participants

All undescended testes (UDT) cases operated over a period of 7 years (4 years retrospectively and 3 years prospectively) from 2007 to 2013 were evaluated. Seventy five specimens of UDT from 71 patients received in the Department of Pathology, Kasturba Medical College (KMC) Manipal were examined.

Participants were categorized into prepubertal and postpubertal groups. Prepubertal subjects were defined as those with age <14 years and postpubertal individuals included patients with age ≥ 14 years. Out of 71 patients selected in the current study, 27 patients were prepubertal and 44 patients were postpubertal.

Pathologic assessment included identification of dystrophic calcification, hemosiderin deposit, discrete vascular fibrosis or vascularized fibrous nodule (VFN), presence of epididymis, vas deferens, dominant vein, pampiniform plexus–like vessels and other paratesticular structures. These parameters were also assessed in paired combination.

Diagnostic criteria according to Susan E. S. et al [1] for TRS incorporated:

- A vascularized fibrous nodule with calcification and/or hemosiderin or
- A minimum of a vascularized fibrosis (nodular/discrete) with cord element(s) in proximity.

2.1. Inclusion criteria

Patients with clinical diagnosis of UDT, atrophic testis or histopathological diagnosis consistent withcryptorchidism or testicular regression syndrome (TRS) were selected in the study.

2.2. Exclusion criteria

Following cases were excluded from the study

- Infarction/ torsion of testicular parenchyma
- Ambiguous genitalia

III. Results

3.1 Histopathological Diagnosis

Diagnosis of cryptorchidism was signed out in 56 cases (74.7%) and TRS in 19 (25.3%). In prepubertal subjects, cryptorchidism was reported in 12 cases and TRS constituted rest of the diagnosis. Among postpubertal group, diagnosis of cryptorchidism was made in 44 cases and TRS in 4 cases. (Table 1)

Table 1: Distribution of Histopathological Diagnosis Among Cases Studied (n = 75)

	CRYPTORCHID TESTIS	TRS	TOTAL
Prepubertal cases	12 (44.5%)	15 (55.5%)	27
Postpubertal cases	44 (91.7%)	4 (8.3%)	48
Total	56 (74.7%)	19 (25.3%)	75

3.2. Microscopic features of testicular regression syndrome (TRS)

Among 15 prepubertal TRS specimens, fibrosis and increased vascularity were present in all cases, whereas calcification and hemosiderin deposits were noted in 11 cases separately. Fibrovascular nodule (FVN) was observed in 2 cases and discrete vascular fibrosis (DVF) in 13 cases (86.7%) Among 4 postpubertal TRS specimens, fibrosis, increased vascularity and discrete vascular fibrosis (DVF) were observed in all cases, whereas calcification was noted in 3 (75.0%) and hemosiderin deposit in 2 cases (50.0%). (Table 2; fig. 1)

Table 2: Distribution of Microscopic Features in TRS Cases (n=19)

	PREPUBERTAL	POSTPUBERTAL	ALL CASES
Calcification	11(73.3%)	3(75.0%)	14(73.7%)
Hemosiderin deposit	11(73.3%)	2(50.0%)	13(68.4%)
Fibrosis	15(100.0%)	4(100.0%)	19(100.0%)
Increased blood vessels	15(100.0%)	4(100.0%)	19(100.0%)
Fibrovascular nodule	2(13.3%)	0	2(10.5%)
Discrete vascular fibrosis	13(86.7%)	4(100.0%)	17(89.5%)

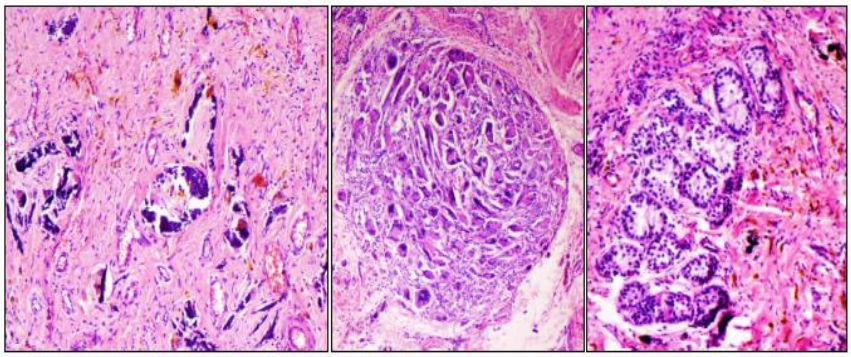

Figure 1: A, Testis with calcification, fibrosis, ectatic vessels and hemosiderin deposit; B, Giant cell response ; C, Foci of residual seminiferous tubules

3.3. Paratesticular structures in TRS cases

Out of 19 TRS cases, characteristic epididymis was present in 17 cases, pampiniform plexus in 12 cases, rete testis in 6, and ductus (vas) deferens or spermatic cord in 3 cases. In addition, ductuli efferentes was reported in 2 cases and dominant or feeding vein in only 1 case. Major combinations include epididymis with pampiniform plexus (PP) in 5 cases, rete testis (RT) with epididymis in 3 cases and rete testis with pampiniform plexus in 2 cases. One case each was reported in remaining combination of paratesticular structures. (Table 3)

Table 3: Distribution of Paratesticular Structures in TRS Cases (n = 19)

PARATESTICULAR STRUCTURES	NUMBER OF CASES	PERCENT
Epididymis	4	21.1%
RT+EPI	3	15.8%
RT+PP	2	10.5%
EPI+PP	5	26.3%
RT+EPI+PP	1	5.3%
DE+EPI+PP	1	5.3%
EPI+DD+PP	1	5.3%
DE+EPI+DD+PP	1	5.3%
EPI+DD+PP+DV	1	5.3%
Total	19	100%

RT, Rete testis; EPI, Epididymis; DE, Ductuli efferentes; DD, Ductus deferens; PP, Pampiniform plexus; DV, Dominant vein

IV. Discussion & Review of Literature

Testicular regression syndrome (TRS) or vanishing testis is a condition considered to be due to the subsequent atrophy and disappearance in fetal life of an initially normal testis. According to literature, the testis is non-palpable in 10% to 20% of cryptorchidism cases, andof these, TRS accounts for 35% to 60% [5]. In our study, TRS was reported in 55.6% (15/27) of prepubertal cryptorchid cases and all presented with empty scrotal sac or non-palpable testis, unilateral or bilateral. In majority of cases in current study, specimen received consist of a small fibrous nodule with attached paratesticular structures either individual of in combination (i.e. epididymis alone or with pampiniform plexus, rete testis, spermatic cord etc.). Microscopy confirmed gross findings of that specimen and results were comparable with previous studies described in literature.

Table 4: Histopathological Features of Testicular Regression Syndrome Studies

Studies	Haluk *et al* [4]	Susan *et al* [1]	Turk [6]	Tatjana [7]	Literature [2]	Current study
Cases	44	11		30		19
Year	2006	1999	1994	2011		2013
ST	5(11.4%)	0		12(40%)	0-40%	4(21.1%)
G. Cell	2(4.5%)	0		0		0
L. Cell		2(18%)		0		4(21.1%)
RT		2(18%)				6(31.6%)
Fibrosis	14(31.8%)			30(100%)	79-100(91%)	19(100.0%)
VFN		11(85%)				2(10.5%)
DVF		13(100%)				17(89.5%)
Cal	14(31.8%)	8(62%)	35%	16(53.3%)	35-93(61%)	14(73.7%)
H. Dep	12(27.2%)	9(69%)	30%	8(26.7%)	30-93(59%)	13(68.4%)
VD	23(52.2%)	9(69%)			79-100(87%)	
Epi stru		5(38%)			24-45(34%)	19(100%)
DV		11(85%)				1(5.9%)
Gt. Cell		6(54%)				2(10.5%)
ITGN					1 case	

ST, Seminiferous tubule; G Cell, Germ cell; L. Cell, Leydig cell; RT, Rete testis; VFN, Vascular fibrous nodule; DVF, Discrete vascular fibrosis; Cal, Calcification; H. dep, Hemosiderin deposit; VD, Vas deferens; Epi Stru, Epidydimal structure; DV, Dominant vein; Gt. Cell, Giant cell; ITGN, Intratubular germ cell neoplasia

In the current study, calcification, hemosiderin deposit and discrete vascular fibrosis were noted in >50% of cases and these findings were in concordance with results of Susan *et al* [1] and previous literature. Vascular fibrous nodule and giant cells in the background were identified in 2 cases separately. Atrophic seminiferous tubules were present in only 4 (21.1%) of testicular nubbins in our study, and it is in the range between 0 to 40% reported previously in various research publications.

According to the diagnostic criteria, presence of paratesticular structures, in addition to fibrosis of testicular tissue is required for the diagnosis of TRS. In the current study, epididymis was noted in 17 cases (89.5%) but paratesticular structures (with or without epididymis) were present in all cases. Whereas none of the testis had premalignant changes or malignancy. Malignant potential in testis with TRS is uncertain and only 1 case with intratubular germ cell neoplasm (ITGN) has been reported in literature till date. Rozanski et al. reported a 9-year old boy, whose testicular remnant had intratubular germ cell neoplasia, signifying early malignant transformation [3].

V. Summary

- Cryptorchidism is the most common disorder of male endocrine glands in children.
- The median age at presentation is 2 years in prepubertal and 29 years in postpubertal subjects. Patients may present with absent testis at any time in the life
- In >60% of the cases, the diagnosis of undescended testis is made on clinical grounds.
- Gross atrophy of testis is common in both prepubertal and postpubertal study groups and TRS constitute the major bulk in prepubertal subjects.
- TRS is characterized by calcification, hemosiderin deposit, vascular fibrosis (discrete/ nodular), residual seminiferous tubules and dominant vein, in addition to presence of paratesticular structures in various combinations.
- Position of the testes correlates with severity of the abnormal spermatogenesis in postpubertal group. Higher the position of the testis is associated with more severe abnormalities in spermatogenesis localized in basal compartment.

VI. Recommendations

Microscopic features of testicular regression syndrome discussed in the study are characteristic and has to be correlated with intraoperative findings before rendering a diagnosis. It can help pathologist as well as surgeon to solve problems related to absent testis/ no testicular parenchyma.

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