# Morphological profile of testicular biopsies associated with infertility

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## ABSTRACT

**Objectives:** Based on testicular biopsies examined at King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia, the goal of this retrospective study is identification and systemization of the histopathological patterns of testicular biopsies received especially for investigating male infertility and further more to compare the findings of our study with similar studies in the literature.

**Methods:** Our study group consisted of 164 testicular biopsies, which were examined in the Department of Histopathology at King Abdulaziz University Hospital in Jeddah, over a period of 10 years. The data was retrieved and analyzed and the available histopathological results were grouped into 8 different morphological categories.

**Results:** The findings of the biopsies associated with infertility were complied as follows: 45 (27%) showed normal spermatogenesis of which 15% showed active spermatogenesis associated with duct obstruction, 41 (25%) with hypospermatogenesis, 39 (24%) showed end stage tubular sclerosis with interstitial fibrosis, 27 (16.5%) with germ cell aplasia (with or without focal spermatogenesis), 11 (7%) biopsies showed maturation arrest and only on biopsy were associated with karyotpic abnormalities.

**Conclusion:** A higher percentage of hypospermatogenesis and end stage tubular sclerosis with interstitial fibrosis was noticed in this study when compared with the other studies reported from Saudi Arabia. A high percentage (27%) of the biopsies show normal spermatogenesis with or without duct obstruction.

**Keywords:** Male infertility, testicular biopsies.

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Male infertility represents an important factor as the cause of infertility amongst infertile couples. Investigation of male infertility includes clinical history, physical examination, biochemical investigation, semen analysis and testicular biopsy. Histomorphological patterns of testicular biopsies associated with infertility are variable as reported in studies from different countries. In this study, we retrospectively reviewed 164 testicular biopsies obtained from male patients with infertility. We used a classical pathological classification for their categorization and compared the results with those of other similar studies. A discussion of each diagnosis and comparison with literature is included. The majority of the classifications used mainly focused on morphological changes and etiological factors.

**Methods.** Our study group consisted of 164 testicular biopsies, which were examined and analyzed in the Department of Histopathology at King Abdulaziz University Hospital, Jeddah over a period of 10 years (from January 1990 to December 2000). Histopathological reports for these cases were retrieved, analyzed and the histopathological patterns grouped into 8 different categories. Each diagnosis was analyzed for frequency and age distribution as shown in Table 1. The morphological observation assessed the presence and amount of germinal cells and their maturation, size of seminiferous tubules and the presence or absence of associated tubular atrophy, fibrosis and Leydig cell hyperplasia or both.[1-3] The results were categorized into the

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**Table 1 -** Summary of histopathological diagnosis of male infertile cases.

| Diagnosis | Frequency | % |
|---|---|---|
| Normal biospy | 20 | 12 |
| Active spermatogenesis with evidence of obstruction | 25 | 15 |
| Hypospermatogenesis | 41 | 25 |
| End stage testis | 39 | 24 |
| Marked germ cell aplasia | 17 | 10 |
| Germ cell aplasia with focal spermatogenesis | 10 | 6 |
| Maturation arrest | 11 | 7 |
| Testicular feminisation | 1 | 1 |
| **Total** | **164** | **100** |

following main categories: 1: Normal spermatogenesis (tubules have mosaic appearance), 2: Active spermatogenesis compatible with recurrent duct obstruction, 3: Hypospermatogenesis (reduced number of germinal cells), 4: Tubular sclerosis and interstitial fibrosis (end-stage testis), 5: Germinal cell aplasia (complete absence of germ cells in tubules), 6: Germinal cell aplasia with focal spermatogenesis (indicate that 2 populations of tubules exist, some exhibiting germinal cell aplasia and others showing spermatogenesis which is usually reduced, 7: Maturation arrest, 8: Testicular changes associated with karyotypic abnormalities. (Table 1).

**Results.** One hundred and sixty-four biopsies displayed findings associated with infertility as follows: 45 showed normal spermatogenesis. Among these 25 (15%) were diagnosed to be associated with recurrent duct obstruction. Forty-one biopsies showed hypospermatogenesis, 39 biopsies showed end stage tubular sclerosis with interstitial fibrosis. Germinal cell aplasia with and without focal spermatogenesis was found in 27 biopsies. Eleven biopsies showed maturation arrest and only one case was noted to show features associated with karyotpic abnormalities (Table 1).

**Discussion.** Male infertility represents a major contributor to the problem of infertility in Saudi Arabia.[4] This study was conducted to outline the histological patterns observed in infertility patients in the western province of Saudi Arabia and to compare their frequency with those previously reported. The majority of the patients were young, healthy males presenting with infertility only. Normal spermatogenesis was defined according to Heller and Clermont,[5] and in this cohort normal spermatogenesis was the most frequent pattern, with a significant number (25) associated with duct obstruction. Infertility in those without obstruction may be related to changes not able to be ascertained by optic microscopy, as has been previously remarked. It was also reported that infertility can be seen with normal spermatogenesis and with normal sperm counts. In these patients, the ultrastructural evaluation of the sperm can sometimes point to some structural abnormalities in sperm structure, such as round headed sperm or immobile cilia.[6]

Hypospermatogenesis is characterized by an appreciable reduction in the number of germinal cells. If changes are seen in occasional tubules only, than it is interpreted as mild hypospermatogenesis, and if a significant reduction in numbers of germ cell layers in virtually all tubules is seen then it is interpreted as severe. The reduction in spermatogenesis, is invariably accompanied with changes such as tunica-propria thickening with increased collagen deposition and interstitial fibrosis. Some tubules may show sclerosis, and there may be an appearance of germinal cell disorganization and sloughing into the tubular lumens.[7] Studies from the Western world[1,2,3,8,9] have revealed a high incidence of hypospermatogenesis and these results are comparable with our study which revealed that one of the major causes associated with infertility is hypospermatogenesis in the western part of Saudi Arabia. The finding of hypospermatogenesis does not indicate the etiology of the changes and such changes are not etiologically specific and may occur in a variety of circumstances. The exact etiology of hypospermatogenesis is not yet clearly identified, and may involve factors such as environment, toxic fumes, polluting chemicals, climate, excess heat, varicocele, hypothyroidisim and so forth, and all may play a role and should be taken into consideration.[7] Not all of the factors mentioned above are implemented in this region of Saudi Arabia.

Complete maturation arrest and incomplete maturation arrest (few spermatids observed in the tubules) was observed in small numbers in this study as compared to reported studies.[1-3,8,9] In both complete and incomplete maturation arrest, tubules are usually reduced in diameter,[7,10] with no increase in tubule wall thickening or histologic abnormality of interstitium or Leydig cells. Specific etiology of the changes cannot be predicted from the histology. The same clinical situation that produces hypospermatogenesis may result in germinal cell arrest.[10] In addition, postpubertal gonadotropin deficiency, alkylating agent therapy and radiation therapy may sometimes produce similar changes.

In the study by Rayes et al,[4] based on a male cohort from central Saudi Arabia, germ cell aplasia (GCA), defined as total absence of germ cells in tubules,[10,11] was the most frequent cause of infertility. However,

**Table 2 -** Comparison of distribution of histological pattern of testicular biopsies in infertile males.

| Diagnosis | Awatif et al % | Rayes % | Wong et al % | Branner % | Thomas et al % | Colgan % |
|---|---|---|---|---|---|---|
| Normal spermatogenesis | 27 | 31 | 25 | 35 | 38 | 20 |
| Hypospermatogenesis | 25 | 13 | 23 | 27 | 19 | 49 |
| Maturation arrest | 7 | 11 | 32 | 12.5 | 5 | 11 |
| Germ cell aplasia | 16.5 | 39 | 8 | 12.5 | 9 | 12 |
| Diffuse tubular atrophy (end stage) | 24 | 5 | - | - | 23 | - |
| Karyotypic abnormality | 1 | 0.5 | 5 | 12.5 | 5 | 3 |

in our study it was the 3rd most frequent histological pattern, the reason for this discrepancy is not known. The etiology of GCA is also not well defined yet. Several factors lead to this morphological pattern, such as varicocele, prepubertal gonadotrophin deficiency, estrogen treatment, irradiation therapy, cryptorchidism and Castello syndrome.[1-4,11,12] It is well recognized that alkylating agents and irradiation in sufficient doses over a significant length of time may produce GCA.[7] Germinal cell aplasia with focal spermatogenesis was observed in 6% in our study as compared to 16% in the study by Rayes et al.[4] The etiology of GCA with focal spermatogenesis is not apparent from the biopsy. It may be surmised that tubules in some parts of the testis were not populated by germinal cells during intrauterine development, or that postnatally there was a loss of germ cells resulting in the tubules without germinal cells.[7]

Other studies[4,13] on the Saudi population have revealed a significant frequency of testicular fibrosis and atrophy related to testicular infections, caused by viral, bacterial or parasitic agents, maldescendent testes, varicocele, diabetes and so forth.[13] Another study in Nigeria,[14] a neighboring African country, also demonstrated tubular atrophy and fibrosis as the most frequent histologic finding associated with infertility. Thus our study is in accordance with these reports, as end stage tubular sclerosis was 2nd in frequency. We believe that similar factors may effect our cohort (Table 2).

In summary, based on a western Saudi population, this study has demonstrated the histological patterns seen in testicle biopsies associated with infertility. Different from other studies, hypospermatogenesis in this cohort was the most frequent histological pattern. This is not well understood, and may be related to environmental differences in addition to the differences in the criteria used in the patient selection for testicular biopsies. We believe that more histological studies must be conducted for a better insight into male infertility, a clearer understanding of the etiological factors and to outline the differences between the various localities.

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