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Case Report

# Exclusively intertubular seminoma arising in undescended testes: Report of two cases

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ABSTRACT

Exclusively intertubular seminoma is a rare and easily overlooked variant that often poses diagnostic challenge. It is characterized by the absence of grossly apparent tumor and tumor cells dispersed in the intertubular space without forming an expansile lesion microscopically. We herein report two such cases, both arising in undescended testes in adult patients. The goal is to highlight this potential diagnostic caveat in examining orchiectomies performed for cryptorchidism in adult patients.



## 1. Introduction

Non-expansile interstitial tumor infiltration is a well-recognized growth pattern in the periphery of classic seminomas. However, seminoma with exclusive intertubular growth is a rare variant in which tumor cells are widely dispersed in the intertubular space without forming any expansile lesion and thus remains grossly undetectable. Due to its inconspicuous gross and microscopic appearance, this tumor could be overlooked by pathologists. Drs. Henley, Young and Ulbright published a seminal paper reporting 12 such cases, naming such a tumor "seminoma with exclusive intertubular growth" [1]. Ten additional cases describing similar morphology were found during literature search [2–9] (Table 1). We herein presented two seminomas with exclusive intertubular growth pattern encountered at our institution during the past three decades (1987–2017), both arising in intra-abdominal testicles in young adults.

## 2. Case reports

### 2.1. Case 1

A 24-year-old male presented with bilateral intraabdominal cryptorchidism. Physical examination noted age-consistent secondary sexual development. His serum total testosterone level was marginally subnormal (358 ng/dL). Follicle-stimulating hormone (53.0 mIU/mL) and luteinizing hormone (22.6 mIU/mL) were both elevated. No mass was found in radiological examination (Fig. 1). Preoperative serum testicular tumor markers, including alpha-fetoprotein (AFP, 1.7 ng/mL) and beta-human chorionic gonadotropin (βhCG, 2.9 mIU/mL) were normal. Serum lactate dehydrogenase (LDH) was not tested. Patient underwent prophylactic bilateral laparoscopic orchiectomy.

Grossly, both testes (measuring 2.5 cm on both sides) demonstrated homogeneous atrophic parenchyma without a discrete lesion. Microscopically, extensive intratubular germ cell neoplasia (ITGCN) was noted in the right testis (Fig. 2A). Closer examination revealed a slight cellularity increase in the intertubular space, which consisted of a mixture of Leydig cells, patchy lymphocytic infiltrates and a third population of cells with clear cytoplasm, large round nuclei, prominent nucleoli and occasional mitotic figures (Fig. 2C). Both ITGCN and invasive seminoma were positive for Oct3/4 by immunostain (Fig. 2D). Despite the fact that the seminomatous tumor cells had spread to approximately 80% of the interstitial space of the testicular parenchyma and involved the rete testis (Fig. 2B), not a single expansile tumor focus was found. Lymphovascular invasion was not identified. As a contrast, the contralateral testis demonstrated benign tubular atrophy and Leydig cell hyperplasia without any evidence of malignancy (Fig. 2E and F).

By the time of this report, the patient has been on active surveillance for 7 years. He remained free of recurrent or metastatic disease.

### 2.2. Case 2

A 23-year-old male presented with undescended left testis. The right testis was normal in the scrotum on palpation and was visualized by sonography. An MRI scan showed a 1.8 × 1.6 cm well-circumscribed oval T2 hyperintense mass in continuity with the left spermatic cord that

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**Table 1**
Clinical characteristics of reported cases of exclusively intertubular seminoma.

| Patient No. | Age | Presentation | Testicular size (cm) | Reference |
|---|---|---|---|---|
| 1 | 31 | – | 5 | [1] |
| 2 | 29 | Infertility | 3.7 | [1] |
| 3 | 35 | – | 5.2 | [1] |
| 4 | 30 | Pain | – | [1] |
| 5 | 30 | Cryptorchidism | 3.0 | [1] |
| 6 | 20 | Lung metastases | 4 | [1] |
| 7 | 32 | – | 4.5 | [1] |
| 8 | 38 | Metastases | 3.7 | [1] |
| 9 | 26 | Cryptorchidism | 4.3 | [1] |
| 10 | 34 | – | – | [1] |
| 11 | – | Infertility | – | [1] |
| 12 | 36 | Infertility | 3.5 | [1] |
| 13 | 43 | Pain | 4.5 | [2] |
| 14 | 42 | Cryptorchidism | – | [3] |
| 15 | 23 | Infertility | 3[a] | [4] |
| 16 | – | Infertility | – | [5] |
| 17 | – | Infertility | –[a] | [5] |
| 18 | 32 | Infertility | – | [6] |
| 19 | 21 | Corrected cryptorchidism; biopsy found carcinoma in situ | 0.6 | [7] |
| 20 | 32 | Cryptorchidism | 3 | [8] |
| 21 | 55 | Cryptorchidism; hematospermia | 2 | [8] |
| 22 | 13 | Cryptorchidism | 1.5 | [9] |
| 23 | 23 | Cryptorchidism | 4.2 | Current |
| 24 | 24 | Cryptorchidism | 2.9 | Current |

– Unavailable.
[a] The contralateral testis was found to contain clinically overt seminoma.

was consistent with an undescended testis. Bilateral pelvic and inguinal lymphadenopathy was observed, with the largest lymph node measuring 1.7 cm in the left inguinal area. Preoperative serum tumor markers, including LDH (190 U/L), AFP (3 ng/mL) and βhCG (<2.0 mIU/mL) were within normal limits. The patient underwent a robotic resection of left intraabdominal testis.

The resected testis (1.8 cm) demonstrated unremarkable atrophic testicular parenchyma without a grossly apparent lesion. Nevertheless, the testis was extensively involved by ITGCN under microscopic examination. The intertubular space was multifocally hypercellular due to infiltration by seminomatous cells admixed with Leydig cells and scattered lymphocytes (Fig. 3A). Occasional small lymphocyte clusters were present adjacent to the infiltrating tumor cells. Rare foci of intratubular microcalcifications were also noted. Oct3/4 immunohistochemistry highlighted the infiltrating tumor cells in addition to ITGCN (Fig. 3B). Rete testis invasion was present. Lymphovascular invasion was not identified. No expansile tumor growth was found after the entire testis was examined microscopically.

Postoperatively, a sonography-guided biopsy of the largest left inguinal node found no tumor involvement. At the time of this report, the patient has been postoperatively followed for 8 months without evidence of recurrent or metastatic disease.

## 3. Discussion

Seminoma with exclusive intertubular growth is a rare and easily missed variant. Approximately 22 cases have been published in English literature [1–9] (Table 1). The age of the patients ranged from 13 to 55 years; the median was 31 years. The majority of the reported patients presented with cryptorchidism or infertility, while testicular pain was the presenting complaint of two patients. Of note, two patients presented with metastatic disease at the time of diagnosis [1]. The affected testes were usually normal-sized or small for age. None of these cases showed grossly identifiable tumor, although a subset of them showed ill-defined firm area or area of whitish to pale brown discoloration in the affected testes [1].

Microscopically, seminoma with exclusive intertubular growth is characterized by non-expansile infiltration by seminomatous tumor cells between seminiferous tubules, which is usually subtle. The histologic architecture of testicular parenchyma is undisturbed. To further heighten the diagnostic challenge, Leydig cells and inflammatory cells frequently intermix with tumor cells and obscure histologic evaluation. In the absence of an overtly expansile mass, a slightly increased intertubular cellularity could be easily misinterpreted as chronic orchitis and/or Leydig cell hyperplasia if the examination is not careful enough with alertness to this rare variant. Misdiagnoses such as benign atrophy or ITGCN have been rendered when intertubular tumor cells were overlooked [1].

In both of our cases, we found it helpful to first notice diffuse ITGCN and a mild increase in cellularity within the intertubular space under low-power magnification. Nevertheless, recognizing ITGCN is sometimes challenging in a background of tubular atrophy and thickened basement membrane, which are expected findings in undescended testes and also frequently seen in non-cryptorchid cases [1]. It is therefore important to closely evaluate cytologic features for seminomatous tumor cells such as enlarged nuclei, prominent nucleoli and clear cytoplasm. Presence of patchy lymphocytic infiltrates in the second case also provided a helpful clue to possible underlying tumor infiltration. In problematic cases, a low threshold for utilizing immunostains, such as OCT3/4 or CD117, may help avoid errors.

Other differential diagnoses to consider when encountering intertubular malignant cells include hematologic tumors, such as lymphoma and plasmacytoma, or metastatic malignancies. While prostatic adenocarcinoma is the most common metastatic carcinoma to the testes, renourinary and gastrointestinal tumors have also contributed to a number of documented cases [10]. Surprisingly, as noted in recent series [10], a known history of extratesticular primary tumor and/or bilateral testicular involvement was present only in a minor subgroup of these patients. The absence of ITGCN in such cases is often helpful for the distinction. However, a subset of metastatic tumors to the testes and testicular lymphomas can have conspicuous intra-rete and/or intratubular involvement, which could potentially mimic ITGCN [10]. Therefore, a thorough radiographic search for extratesticular tumors, careful

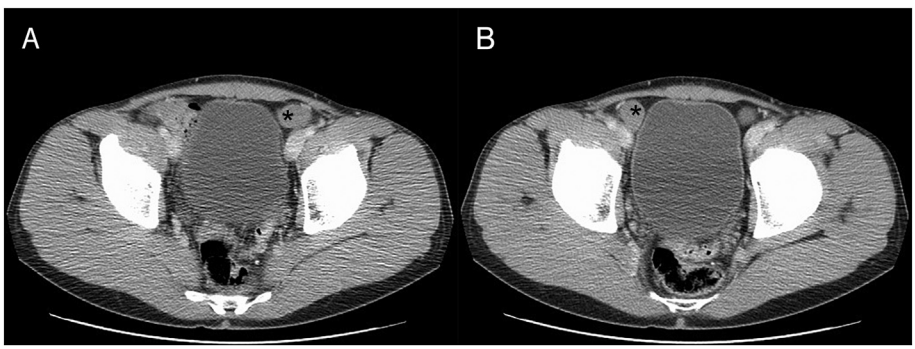


**Fig. 1.** Case 1, preoperative CT scan showed intraabdominal left (2.5 × 1.8 cm) and right (2.5 × 1.9 cm) testes, marked with the star symbol "*". Apparent mass/lesion was not observed.