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The Amalgamated Sophomore-Gonadoblastoma

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Case Report

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Abstract

Gonadoblastoma emerges as a benign gonadal neoplasm composed of germ cells and descendants of sex cord-stromal cells reminiscent of immature granulosa cells and Sertoli cells. Neoplasm is preponderantly associated with disorders of sexual development wherein majority (~80%) of neoplasms articulate phenotypic females. Tumefaction expounds primary amenorrhea and delayed sexual maturation with delayed development of genitalia and emergence of secondary sexual characters. Gonadoblastoma locus appears to be situated adjacent to Y centromere wherein TSPY gene is implicated in carcinogenesis. Commonly discerned distinct morphological configurations appear comprised of spherical or irregular clusters of immature Sertoli cells admixed with germ cells and circumscribing basement membrane. Intervening stroma exhibits enlarged, polygonal cells simulating Leydig cells admixed with focal calcification. Germ cells appear immune reactive to p53, placental alkaline phosphatase (PLAP), CD117/c-KIT and VASA protein or encoded testis specific Y protein. Testicular gonadoblastoma requires segregation from neoplasms such as Sertoli cell tumour. Genetic karyotyping is an essential investigation for distinguishing individuals with intersex disorders and potential occurrence of gonadoblastoma. Surgical extermination is a recommended mode of therapy for alleviating gonadoblastoma.

Keywords: Germ Cells; Immature Sex Cord Stromal Cells; Intersex Disorder

Introduction

Gonadoblastoma is an exceptionally discerned, benign neoplasm implicating the gonads. Tumefaction is composed of germ cells and descendants of sex cord-stromal cells reminiscent of immature granulosa cells and Sertoli cells. Initially scripted by Scully in 1970, tumefaction appears to simulate morphology of a normal developing gonad [1].

Majority of neoplasms arise within 20 years and ~90% tumours are observed within 30 years. Neoplasms demonstrating partial dysgenesis or genetic mosaicism may be discerned prior to puberty. Nevertheless, tumefaction associated with complete insensitivity to androgen may be detected following puberty. Gonadoblastoma is preponderantly associated with disorders of sexual development. Almost ~10% individuals delineating dysgenetic gonads may display gonadoblastoma or seminoma by 10 years.

Nearly~25% subjects expounding mixed gonadal dysgenesis and Y component may exemplify gonadoblastoma or germ cell tumour by 40 years. Commonly, gonadoblastoma arises within abdominal, inguinal or undescended gonads and testis. Tumefaction may appear within ovaries of female subjects expounding unaltered phenotype and genotype [2,3].

Factors Contributing to Emergence of Gonadoblastoma as Disorders of Sexual Development Configure As

- Complete androgen insensitivity with 46 XY genotype
- Pure gonadal dysgenesis or Swyer syndrome with 46 XY genotype
- Mixed gonadal dysgenesis with 45 X or 46 XY genotype
- Turner syndrome with XY mosaicism and 45 XO genotype
- Molecular concurrence of Y chromosome induces an enhanced incidence of gonadoblastoma
- Frasier syndrome is an exceptional disorder of sexual development associated with 46 XY genotype and genomic mutation within WT1 gene
- Maternal exposure to androgens, drugs, alcohol or first trimester illness appears concordant with gonadal dysgenesis and intersex disorders. However, concurrent emergence of gonadoblastoma remains debatable.

Majority (~80%) of neoplasms articulate phenotypic females associated with miniscule anomalies of sexual development. Instances demonstrating pure gonadal dysgenesis comprehensively appear as normal females. Incriminated subjects may delineate clitoromegaly or abnormal hirsutism. Aforesaid anomalies may be appropriately detected with karyotype analysis, an investigative modality which is necessitated to exclude intersex disorders [2,3]. Nearly ~20% of implicated subjects appear as phenotypic males and exhibit gynecomastia, hypospadias or cryptorchidism and 46XY or 45X / 46XY genotype. Nearly one third (~33%) of subjects delineate bilateral gonadoblastoma [2,3].

Frequently, tumefaction expounds primary amenorrhea and delayed sexual maturation with delayed development of genitalia and emergence of secondary sexual characters. Nearly 50% subjects depict an abdominal mass. Malignant metamorphosis into seminoma may ensue. Tumour demonstrates distant metastasis. Misinterpretation of gonadoblastoma may occur during neonatal period wherein the neoplasm is discerned at puberty and is associated with primary amenorrhea [2,3]. Implicated subjects may display morphological features of intersex disorders as occurrence of inguinal hernia within phenotypic female neonates exhibiting male pseudo-hermaphroditism [2,3]. Bimanual abdominal palpation can be appropriately employed in order to confirm configuration of uterus within initial neonatal period which occurs due to effects of maternal human chorionic gonadotropin. Subjects associated with complete androgen insensitivity or male pseudo-hermaphroditism undiscerned within neonatal period may be eventually ascertained at puberty [2,3]. Configuration of mammary glands is normal. However, secondary sexual characters as pubic and axillary hair are rudimentary and vagina may appear hypoplastic [2,3]. Individuals with mixed gonadal dysgenesis and genotype of 45XO / 46XY demonstrate features such as ambiguous genitalia with variable phallic enlargement, undescended testis, urogenital sinus or labioscrotal fusion. Configuration of a uterus, vagina and fallopian tubes along with an ovary or streak ovary and contralateral testicle is comprehensively discerned within implicated subjects. Roughly 50% subjects appear short and ~33% manifest phenotypic similarity to individuals with Turner syndrome [3,4]. Molecular analysis exhibits aneuploidy within constituent germ cells. Gonadoblastoma locus appear situated adjacent to Y centromere. Commonly, TSPY gene is implicated in carcinogenesis. TSPY gene is expressed within adult spermatogonia and foetal gonocytes and emerges as a significant component contributing to vital functions of male stem cells or germ cell proliferation. TSPY gene enunciates ectopic expression within specific neoplasms as gonadoblastoma, seminoma, intratubular germ cell neoplasia and few nonseminomatous germ cell tumours [3,4]. Expression of TSPY gene is concordant with immune reactivity to placental alkaline phosphatase (PLAP), c-kit and OCT3 / 4. Seminomas and nonseminomatous tumours arising within dysgenetic gonad emerge as diploid neoplasms, in contrast to tumours incriminating normal gonad [3,4].

Grossly, tumour appears as a firm, encapsulated nodule with yellow to tan hue and magnitude varying from a microscopic neoplasm to 8 centimetres. Cut surface appears gritty. Foci of haemorrhage or tumour necrosis concur with metamorphosis into malignant germ cell tumour [3,4].

Upon microscopy, distinct neoplastic configurations appear as ~commonly discerned pattern comprised of spherical or irregular clusters of immature Sertoli cells admixed with germ cells and circumscribing basement membranes. Sertoli cells appear to encircle spherical nodules of hyaline substance or encompass enlarged germ cells. Germ cells appear amalgamated within centric zones of tumour cell nests encompassed within a peripheral ring comprised of Sertoli cells [3,4]. Intervening stroma exhibits enlarged, polygonal cells simulating Leydig cells, as commonly discerned within post-pubertal subjects. Frequent foci of calcification are discerned which may be extensive or focal and appear to circumscribe hyaline bodies. An estimated 50% subjects exhibit coexistent or subsequently occurring seminoma whereas ~10% individuals may develop various germ cell malignancies (Figures 1 & 2) Ultrastructural examination exhibits few cells delineating Charcot-Böttcher filaments of Sertoli cells (Table 1) [3,4].

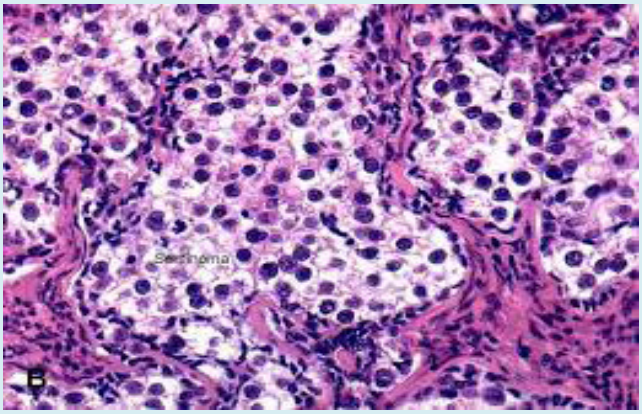

Figure 1: Gonadoblastoma demonstrating tubules lined by immature Sertoli cells, centric germ cells and surrounding basement membrane. Intervening stroma exhibits clusters of enlarged, polygonal cells akin to Leydig cells [5].

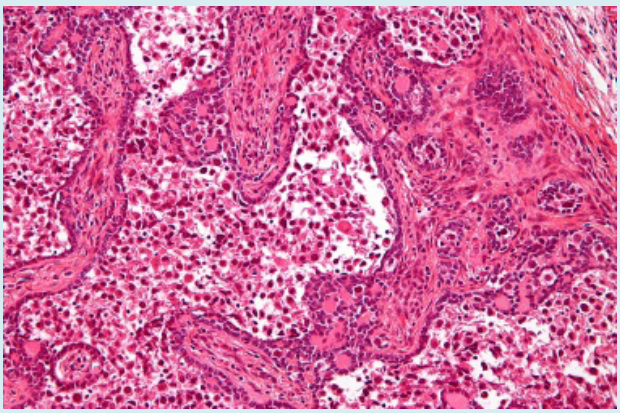

Figure 2: Gonadoblastoma delineating tubule lined by immature Sertoli cells, centric germ cells and circumscribing basement membrane. Intervening stroma exemplifies clusters of enlarged, polygonal cells akin to Leydig cells [6].

Stage	T	N	M	S
Stage 0	Tis	N0	M0	S0
Stage I	T1-T4	N0	M0	SX
Stage IA	T1	N0	M0	S0
Stage IB	T2-T4	N0	M0	S0
Stage IS	Any T/TX	N0	M0	S1-S3
Stage II	Any T/TX	N1-N3	M0	SX
Stage IIA	Any T/TX	N1	M0	S0
	Any T/TX	N1	M0	S1
Stage IIB	Any T/TX	N2	M0	S0
	Any T/TX	N2	M0	S1
Stage IIC	Any T/TX	N3	M0	S0
	Any T/TX	N3	M0	S1
Stage III	Any T/TX	Any N	M1a	SX
Stage IIIA	Any T/TX	N1-N3	M0	S0
	Any T/TX	Any N	M1a	S1
Stage IIIB	Any T/TX	N1-N3	M0	S2
	Any T/TX	Any N	M1a	S2
Stage IIIC	Any T/TX	N1-N3	M0	S3
	Any T/TX	Any N	M1a	S3
	Any T/TX	Any N	M1b	Any S

Table 1: Prognostic groups of testicular cancer as per Union for International Cancer Control (UICC) [7].

Stage IA: is comprised of primary neoplasms confined to testis and epididymis. Microscopic evidence of neoplastic vascular or lymphatic invasion appears absent. Clinical examination or imaging demonstrates absence of distant metastasis. Following orchidectomy, serum levels of tumour markers appear within normal limits.

Stage IB: is constituted of neoplasms demonstrating localized invasion of primary tumour with an absence of distant metastasis.

Stage IS: delineates persistent elevation or enhancing serum levels of tumour markers following orchidectomy, thereby indicating subclinical metastatic disease or a germ cell tumour confined to contralateral testis.

Germ cells appear immune reactive to p53, placental alkaline phosphatase (PLAP), CD117/c-KIT and VASA protein or encoded testis specific Y protein. Stromal cells appear immune reactive to inhibin or Wilm's tumour 1 (WT1) antigen. Testicular gonadoblastoma requires segregation from neoplasms such as Sertoli cell tumour [7,8]. Genetic karyotyping emerges as a crucial investigation for distinguishing individuals with intersex disorders and potential occurrence of gonadoblastoma [7,8]. Serum electrolytes may be altered, a feature which appears concordant with enhanced disease associated mortality. Pertinent hormonal evaluation is mandated to exclude emergence of anomalous sexual development and may be utilized to assess quantifiable, therapeutic hormonal replacement [7,8]. Gonadoblastoma may undergo spontaneous involution. Surgical extermination of the neoplasm is a recommended mode of therapy for alleviating gonadoblastoma. Besides, dysgenetic gonads may be excised prior to neoplastic transformation. Appropriate timing of surgical intervention is contingent to emergence of concordant disorders of sexual development [7,8]. Conditions such as mixed gonadal dysgenesis and mosaicism are suitably subjected to surgical eradication prior to puberty wherein delaying cogent surgical manoeuvers appears deleterious [7,8]. Lesions with complete androgen insensitivity or pure gonadal dysgenesis can be managed with surgical eradication subsequent to completion of puberty or preceding 20 years of age. Aforesaid therapeutic manoeuver permits development of female breasts on account of peripheral conversion of testosterone into oestrogens by aromatase [7,8]. Incidence of gonadoblastoma or diverse germ cell tumours prior to 20 years appears negligible. However, incriminated subjects are appropriately diagnosed at puberty along with initial representation of primary amenorrhea [7,8]. Gonadoblastoma is associated with superior prognostic outcomes prior to malignant transformation. Disease associated mortality appears undocumented. Nearly 30% subjects exhibit malignant germ cell tumour confined to dysgenetic or contralateral gonad. Tumour alleviation occurs in > 80% individuals, especially within instances demonstrating overgrowth of seminoma or accompanying distant metastases [7,8].

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