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Case Report

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Intra-Abdominal Testicular Seminoma In A Phenotypic Female: A Case of XY, Disorder of Sex Development Complicated with Seminoma

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Abstract:

Disorder of sex development (DSD) complicated with seminoma is infrequently encountered in clinical practice. In order to diagnose the condition histopathological, immunohistochemical, and karyotype analysis can play the pivotal role. Additionally, prognosis of such patients largely depends upon the pathological staging at the time of initial diagnosis. Hence, the aim of this study was to determine the significance of macroscopic and microscopic examination together with immunohistochemical analysis in diagnosis and prognosis of XY, Disorder of sex development (DSD) which is often known to be complicated by intra-abdominal seminoma. A twenty eight year old patient was admitted into Bangabandhu Sheikh Mujib Medical University (BSMMU) presenting with a right sided adnexal mass for one year. Magnetic Resonance Imaging (MRI) showed a large lobulated soft tissue mass in right adnexal region accompanied by infantile uterus. Interestingly, chromosomal analysis of this patient was found to be 46 XY. Post-resection histological studies revealed an intra-abdominal seminoma at a stage of $pT_2N_xM_x$. The tumour cells expressed immunoreactivity to both Placental Alkaline Phosphatase (PLAP) and C-kit.

Introduction:

Usually, newborns are given with a sexual identity at their birth based on the physical characteristics that they are born with. However, as many as 1 out of 3,000 exceptional babies are born who become designated as intersexed (1) and, thereafter, impose a difficult challenge in determining the actual gender. Previously used nomenclatures, for instance, "intersex", "hermaphrodite" and "pseudohermaphrodite" etc. are now rather obsolete. Upon revoking these old-fashioned and vulnerable titles, a new conducive nomenclature, disorder of sex development , was endorsed by the Chicago Consensus held in 2005 (2).Disorder of Sex Development (DSD) may be defined by any problem recognized as early as at birth in which the genitalia are divergent in relation to the chromosomes or gonads. Genetic, developmental and hormonal variations are attributable to this erratic development of genitalia. Such ailments can be detected as early as at birth due to presence of equivocal genitals, whereas, some others may appear late with virilization, absent or delayed puberty, or even with infertility.

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Patients with DSD tend to possess anomalous testicular differentiation, defective testosterone biosynthesis and jeopardized action of testosterone. As a result, testicular feminization, also known as Androgen Insensitivity Syndrome (AIS) (3), ensues entailing inhibition of spermatogenesis and dominance of sertoli cells. AIS is resulted by mutations in the androgen receptor gene that imposes as a risk factor for germ cell malignancies (4). In addition to that, maldescended testes and advancing age are also known to increase the risk of neoplasia (5).

Case History:

In the month of September,2019 a twenty eight year old married lady hailing from Gazipur, Bagladesh presented in the department of Urology, BSMMU with the complaints of difficulty during sexual intercourse and gradually enlarging right sided lower abdominal lump for past one year. The patient experienced no other relatable constitutional symptoms including weight loss. Her past medical history was unremarkable.

Physical examinations revealed under-developed breasts, deep coarse voice (due to deficient secondary sexual characteristics). A firm, non-tender mass was palpable involving right lower abdomino-pelvic region. Gynaecological examination showed sparse pubic hair, clitoromegaly, normal labia, non-spacious vagina, and a high up and small cervix.

A right adnexal complex mass and an immature uterus were seen during sonological investigation. MRI of pelvis with contrast showed a large, lobulated, soft tissue mass measuring about 4.5 cm x 3.8 cm x 3.2 cm in the right adnexal region being attached with the right ovary. However, the left ovary could not be visualized and an infantile uterus was present.

Surprisingly, pre-operative chromosomal analysis had revealed a male karyotype (46, XY). Following these laboratory workups, the patient had undergone laparotomy with excision of the adnexal mass under general anaesthesia on 08.09.2019. The excised mass was then sent to the department of Pathology in BSMMU on the same day for further histological analysis.

Fig.-1. *Gross examination of removed adnexal mass, sized 7cm in maximum diameter. Cut surface of the nodular piece was solid and grey white. The size of attached fallopian tube was 7cm in length.*

Macroscopically, the mass was a nodular piece of tissue measuring 7 cm in maximum diameter with a 7 cm long attached fallopian tube. Cut section of the nodular piece of tissue was solid and grey-white. Routine microscopic examination with H&E (Haematoxylline& Eosin) of the adnexal mass demonstrated a malignant tumour composed of uniform cells arranged in lobules separated by fibrous septa. The cells were large in size with distinct cell membrane, having round to oval nucleus with prominent nucleoli and clear cytoplasm [Figure: 2(a)]. Tumour cells also showed PAS positive glycogen [Figure: 2 (b)]. Furthermore, these cells were found to be immunoreactive to both PLAP and C-kit [Figure: 2 (c,d)]. Based on the routine microscopy, PAS positivity of tumour cells and immunological responses, the final diagnosis of seminoma was made.

Her hormonal assays include

Pre-operative		Post-operatve	
Testosterone	0.55 nmol/L	Beta-hCG	<2.3 IU/L
Oestrogen	27.13 pgm/ml	CA-125	17.5 U/ml
Leutinizing Hormone (LH)	20.8 mIU/ml	AFP	1.72 ng/ml
Follicular Stimulating Hormone (FSH)	60.40 mIU/ml	LDH	206 U/L
Progesterone	0.27 pgm.ml		

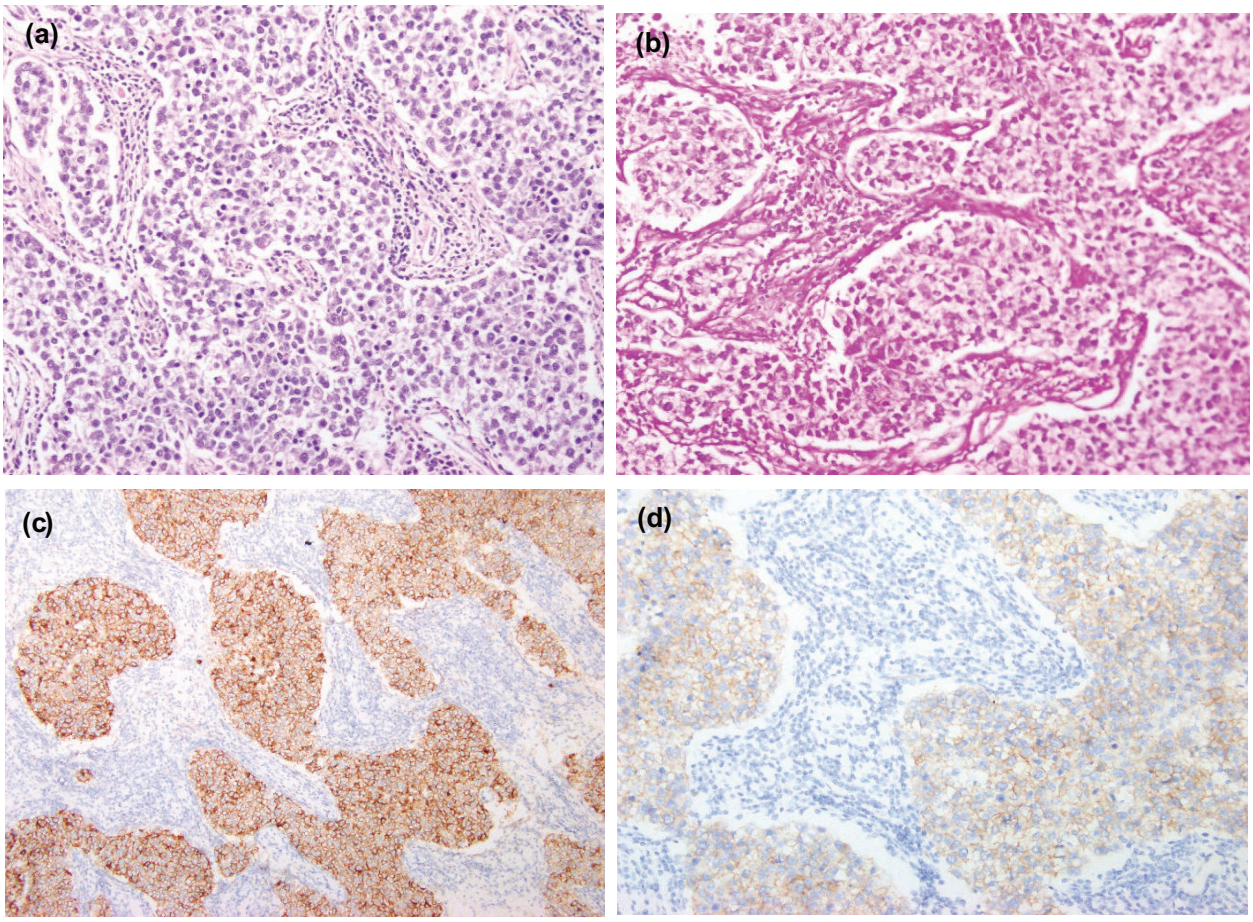

Figure: Histology of adnexal mass. (a) Classical seminoma, with uniformly distributed tumor cells arranged in lobules, demarcated by dense fibrous septae infiltrated by lymphocytes, H&E x 100. (b) Large polygonal neoplastic cells, with clear,glycogen-rich cytoplasm, PAS x100. (c) Tumor cells are reactive to immune stain placental alkalaine phosphatase x100 (d) Tumour cells are reactive to immune stain cKit x100

Discussion:

Sexual development is a highly intricate process that essentially begins with fertilization of an ovum and then gradually evolving throughout gestation, following delivery until adulthood. A number of factors, namely spatio-temporal sequence as well as several ambivalent inciting and opposing factors act in co-ordination in an effort to ensure normal sex development. During morphogenesis, SRY gene on Y chromosome stimulates the commencement of molecular events, ultimately resulting in male sex development (6). However, ambiguous genitalia may result from disparity at any level of development. Testicular feminizing syndrome is recognized as the most common cause for XY, DSD. This syndrome is a sex-linked recessive disorder distinguished by androgen insensitivity by the peripheral organs. Patients with 46 XY DSD, Complete Androgen Insentivity Syndrome (CAIS), usually, are regarded and raised as females in childhood until perimenarchal age (2). Suspicion arises due to failure to menstruate often in early second to third decennary. Very rarely such diagnosis is drawn up beyond fourth or fifth decades(5). Morphologically, testes are undescended, while the female reproductive organs, such as, ovaries, uterus, fallopian tubes along with upper third of the vagina are usually absent. Also, well-formed labia majora and labia minora are seen.

As assistive tools to reach at a diagnosis, performing hormonal assays, imaging techniques, e.g. USG, CT and MRI, are imperative. Nevertheless, karyotype analysis and histological examinations are essential in determining the definitive diagnosis.

Gonadal tumours are well-recognized sequelae of CAIS. Therefore, prophylactic surgical resection of gonads is advisable as a standard scheme in the clinical management of these patients. It is also speculated that, early removal of the gonads during post-pubertal period reduces the probability of malignant transformation. Conversely, increased incidence of malignancy with advancing age is observed to be related with a delay in gonadectomy at post-puberty.[7] Gonadal malignancies often present with late clinical symptoms. Also, being positioned inside the abdomen, palpation of the testes is difficult. Furthermore, neither any imaging technique nor the non-specific tumour markers can reliably detect any premalignant changes. Hence, an attempt to conserve the gonads may render the patient precarious. Of note, testicular feminization poses only 5% estimated risk of malignancy.[5]

Development of testicular carcinoma-in-situ and germ cell tumour including seminoma, non-seminoma, gonadoblastoma and dysgerminoma are known sequelae in afflicted DSD patients. Factors including Y chromosomal material as well as gonadal position, mainly for streak gonads seem to impact more for cancer development.[8] Noticeably, seminoma is the commonest outcome of malignant transformation of the undescended testes.[9] In contrast, in dysgenetic gonads, gonadoblasoma is the commonest transformed tumour.[5]

A study involving 43 patients suffering from testicular feminization was conducted by Rutger et al. and it demonstrated that malignant transformation of the testes had occoured in four (9%) patients. Among them, two were seminomas, one was germ cell neoplasm and another one was malignant sex cord stromal tumour. Notably, germ cell neoplasms are the commonest tumour detected in both cryptorchidism and testicular feminization syndrome.[3]

A conclusive diagnosis of testicular tumour demands histopatholoical and a number of immunohistochemical analyses. Extensive membranous positivity for PLAP and CD117 (C-kit) expression can be regarded as suggestive owing to high sensitivity index. However, immuno-responsiveness to PLAP lacks sufficient specificity for seminoma. Considerably, usual seminomas exhibit 90% to 100% membrane positivity for PLAP as well as 90% to 100% expression of CD117 (C-kit) in a cytoplasmic membrane pattern. In comparison, most of the embryonal carcinoma show no immunoreactivity to CD117.[10]

Another study by Sean et al. looked into forty germ cell neoplasms including 19 seminomas, 3 embryonal carcinomas, 3 teratomas, 1 yolk sac tumour and 14 mixed germ cell tumours. D2-40 monoclonal antibody with characteristic reactivity with an oncofetal antigen that is expressed by fetal germ cells and testicular germ cells tumours. Exclusively, each of the seminomas and the seminomatous components of mixed germ cell tumours displayed positivity for D2-40 with diffuse membrane staining, whereas, 29% of the embryonal carcinoma specimens had also manifested positivity for D2-40 focally along the apical surfaces of the neoplastic cells. Positive CD117 staining was found in 92% of the seminoma specimens and 0% of the embryonal carcinoma specimens. To contrast, 93% of the embryonal carcinoma specimens expressed positively with CD30 staining while none of the seminomas did so. Apart from being a highly sensitive marker for seminoma, a subset of embryonal carcinoma exhibited positive expression of D2-40. Therefore, the usefulness of this antibody in discriminating the type of malignancy from these two entities is restricted (10). Unfortunately, expression of CD30 and D2-40 could not be determined in BSMMU laboratory due to inadequacy of needful resources.

Both PLAP and CD117 were positively expressed in the specimen of the patient being mentioned in this case report. Correlating with the clinical features and histopahological findings, seminoma was ascertained as the final diagnosis. For an appropriate management strategy, staging of the testicular tumour is assessed with the help of radiological impressions for the presence of any retroperitoneal mass and lymphadenopathy, assay of tumour markers, and, finally, histopathological remarks of the orchidectomy specimen. In the above mentioned case, the pathological staging was determined as $pT_2N_xM_x$ as few lymphovascular invasions were seen. Seminomas tend to spread distally via lymphatic routes. But, haematogenous spread is also likely to ensue at an advanced stage of the disease, even to skin.[11]

To summarize, hormonal assays, chromosomal study and imaging techniques provide supportive information for the diagnosis of XY, DSD. Nonetheless, a conclusive diagnosis of seminoma appearing as a complication of undescended testes requires meticulous histopathological and immunohistochemical exploration. Additionally, pathological staging, which depends on capsular and lymphovascular invasion, can be derived by microscopic assessment of the specimen. Ultimately, all of these data are imperative in further treatment of the patient and also ascertaining the prognosis.

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