Original Research Paper

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General Surgery

CONCURRENT DEVELOPMENT OF TESTICULAR SEMINOMA IN UNDESCENDED TESTIS AND RETROPERITONEAL EMBRYONAL CARCINOMA PRESENTING AS A PARAAORTIC MASS: A CASE REPORT AND REVIEW OF LITERATURE ABOUT PATHOGENESIS OF GERM CELL TUMOURS.

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KEYWORDS : NSGC: Non-seminomatoustumors, GCT: Germ Cell Tumor, AFP: Alpha Fetoprotein, β-hCG: Beta Human Chorionic Gonadotropin.

BACKGROUND:

Testicular cancer is a relatively rare neoplasm. It makes up approximately two percentage of all malignant cancers in men and account for up to ten percent of all malignant diseases occurring within the male genitourinary system[1].

Most of these tumors occur in three age groups; infancy, late adolescence and early adulthood. More importantly, testicular tumors are the most common malignant diseases, developing in men between 20 and 40 years of age and are the third leading cause of death amongst men in this age group [1].

Pathologically, testicular carcinomas are divided into two classes; germ cell tumors which are derived from germinal epithelium and non germinal tumors which are of gonadal stroma origin. Tumors of germ cell origin comprise about 95% of all testicular cancers. Germ cell tumors are divided into two basic groups: Seminomas which occur in approximately 40% of the population and Non-seminomatoustumors (NSGC) which may be seen in pure or mixed form[2].

NSGCs are further divided into the following five groups:

1) embryonal carcinoma with or without seminoma, which occurs in about 25% of the group;
2) teratoma with or without seminoma, which occurs in about 7% of the group;
3) teratocarcinoma including teratoma with embryonal carcinoma, choriocarcinoma, or both with or without seminoma occurring in about 25% of the group;
4) choriocarcinoma with or without seminoma or embry- onal carcinoma or both account for the remaining 1-3%.

Mixed germ cell tumors contain more than one germ cell component and are much more common than any of the pure histologic forms representing 32%-60% of all germ cell tumors. Essentially, any admixture of the germ cell tumors as seen in pure form may be seen, one of the most common admixtures being embryonal carcinoma and teratoma [3]. Minor foci of yolk sac tumor are common, although it is usually overshadowed by other components, such as embryonal carcinoma. As is typical of embryonal carcinoma when seen in pure form, epithelium is often associated with syncytiotrophoblast giant cells when seen as part of a mixed germ cell tumor.

Although seminoma may be seen as part of a mixed germ cell tumor, in some cases one sees seminoma separate from a dominant mass of non-seminomatous mixed germ cell neoplasia, and in such cases it is probably truly multi-centric neoplasia, although for sign-out purposes it I NSGCs are further divided into the following five groups[3]:

1) Embryonal carcinoma with or without seminoma, which occurs in about 25% of the group;
2) Teratoma with or without seminoma, which occurs in about 7% of the group;
3) Teratocarcinoma including teratoma with embryonal carcinoma, choriocarcinoma, or both with or without seminoma occurring in about 25% of the group;
4) Choriocarcinoma with or without seminoma or embryonal carcinoma or both account for the remaining 1-3% of the tumors.
5) Mixed germ cell tumors contain more than one germ cell component and are much more common than any of the pure histological forms representing 32%-60% of all germ cell tumors.

Essentially, any admixture of the germ cell tumors as seen in pure form may be seen, out of which the most common admixtures being embryonal carcinoma and teratoma [3].

The average age of presentation for patients with mixed germ cell tumors is 30 years. Unfortunately, many of these patients present late, usually with some or the other complications which are difficult to treat and carry bad prognosis. Still, if they can complete the chemotherapy they have a reasonable survival period, depending on the complications they have.

Synchronous presentation of more than one germ cell tumours of different histology in the same patient is considered to be very rare. In these cases of multiple germ cell tumours, strong theoretical and clinical data suggest an underlying common pathogenetic mechanism concerning genetic instability or abnormalities during the pluripotent embryonic differentiation and maturation of the germ cell.

CASE PRESENTATION:

A 25 year old man from Gujarat presented to the out patient department of our institution with a complaint of a progressively increasing, painless, non-tender left paraumbilical abdominal mass for approximately 3 months prior to consultation. He was a laborer by occupation with no chronic medical condition or past surgeries. He had never been exposed to any carcinogenic substance; he did not consume alcohol, tobacco, or any drugs. He was married since the last 2 years and did not have any children; his birth history was normal.

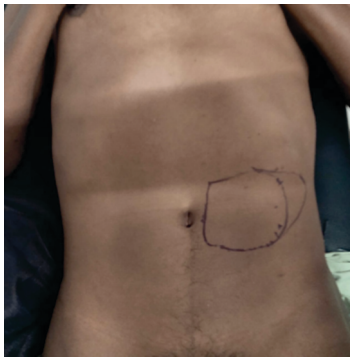

Figure 1: Clinical Image showing the outlined left paraumbilical mass.

A physical examination revealed a patient who looked well with a blood pressure of 116/74 mmHg, heart rate at 64 beats per minute (bpm), and temperature of 37.6 °C.

An abdominal examination revealed a 13*10 cm^2 irregular, hard, non-tender, non-mobile, paraortic mass, starting from the left side of umbilicus for approximately 10cm laterally. (Fig. 1).

Examination of his genitalia revealed just one testis in the right scrotum, with the left scrotum and inguinal canal being empty. There were no palpable inguinal lymph nodes. There was no ascites.

A neurological assessment revealed conserved muscle forces and sensitivity in all four limbs with all reflexes, particularly the cremasteric and abdominal reflexes, conserved.

Biochemichal investigations revealed: no hematuria and proteinuria on urine analysis, normal white cell and platelet count on the full blood count, no blast cells on the blood smear, and a negative human immunodeficiency virus (HIV) serology.

Tumor markers:
Alpha-Fetoprotein (AFP):1028 ng/ml,
Beta-HCG:514 IU/ml,
LDH:239

An abdominal+pelvis ultrasound revealed a large left sided retroperitoneal mass compressing the IVC and left ureter with enlarged paraaortic lymphnodes. USG also revealed a hard mass near the deep inguinal ring which could possibly be undescended testis.

CT scan of the abdomen showed nodular metastasis involving the interaortocaval, precaval, and left paraaortic lymph nodes. The block of enlarged lymph node was filling almost the entire left retroperitoneal space. However CECT abdomen did not reveal any evience of intrabdominal undescended testis.

Liver, pancreas, kidneys and spleen were found normal.

Both Chest x-Ray and CT scan of the chest showed metatstatic secondaries in bilateral lower lobe of the lungs.

After discussion with radiologist about sonographic findings of groin testis on left side, the patient underwent left sided inguinal exploration and the testis was found near the deep inguinal ring which appeared to be atrophied. Hence left sided orchiectomy was done. Histological examination of the testis revealed a typical seminoma consisting of large clear cytoplasm cells with hypodense nucleus and a few atypical mitosis, without any signs of infiltration of *rete testis* or the spermatic cord. Complete inhibition of spermatogenesis and hyperplastic reaction of Leydig cells were also observed.

Although immunohistochemical staining for β-hCG was positive in a few cells, their morphological characteristics did not meet the diagnostic criteria for syncytiotrophoblasts.

As a result, out of interest we requested a repeat biopsy from the testicular which surprisingly turned out to be a teratoma.

A CT guided biopsy from the paraortic mass was done which was suggestive of an embryonal carcinoma on histological examination and was confirmed by IHC study immunohistochemistry results (Cd30+, Keratin+, Oct3/4+).

Complete pre-therapeutic staging was immediately performed, including negative CT scan of the brain and negative bone scan, whereas CT scan of the thorax disclosed multiple round metastatic nodules of various size in the bilateral lungs.

The patient was referred to the tumour board which decided to proceed with chemotherapy(BEP Regime). Further plan of treatment was to be decided based upon the chemotherapy response.

At the time of reporting the patient is undergoing chemotherapy after pre chemotherapy workup.

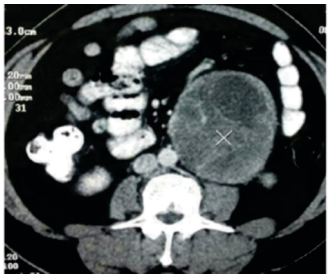

Figure 2: Contrast enhanced computer tomography abdomen showing a well-defined rounded heterogeneous mass in the left para-aortic region (white cross).

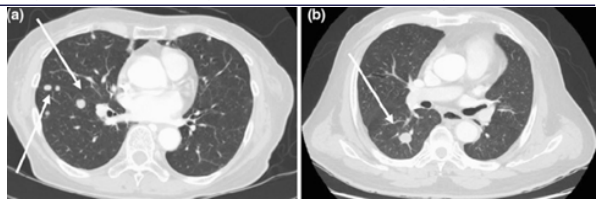

Figure 3: CT Chest showing pulmonary metastasis in the lung fields (Predominantly on the Right Side).

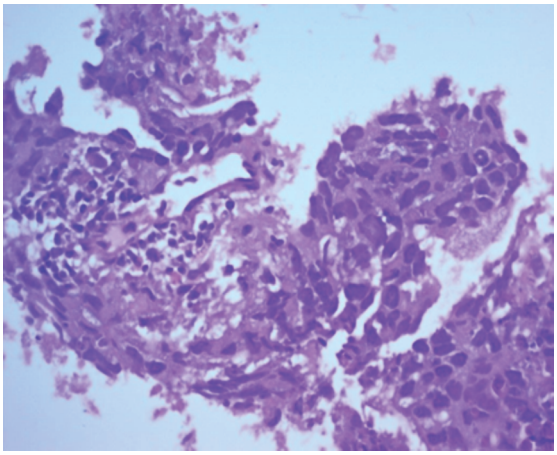

Figure 4: Histological view of biopsy from the left paraortic mass showing large highly pleomorphic tumor cells. Immunohistochemisty: Cd30+, Keratin+, Oct3/4+.

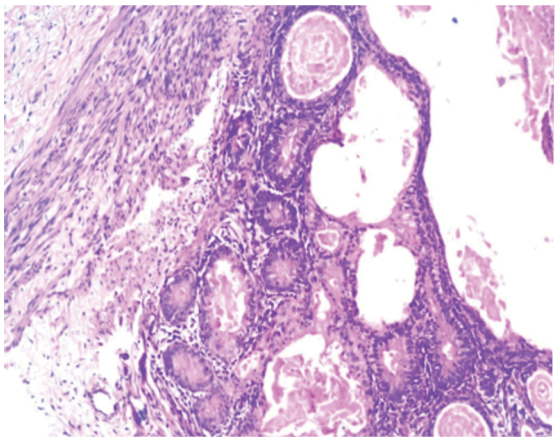

Figure 5: Histological view of biopsy from the left testis mass showing features of teratoma.

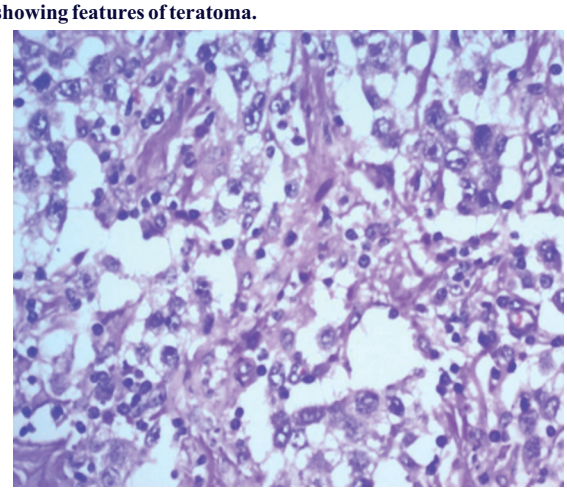

Figure 6: Histological view of biopsy from the left testis mass showing uniform tumor cells with abundant clear cytoplasm, distinct cell border, and large central nuclei with prominent 1-2 nucleoli suggestive of seminoma.

DISCUSSION:

GCTs are generally malignant and represent 93% of all testicular neoplasms[4].

At least half of them are of seminomatous cell origin, being either "typical" seminomas or containing mixed elements of non-seminomatous origin (embryonal or choriocarcinoma elements such as syncytiotrophoblasts) which do not usually affect the good prognosis of seminomas[5]. On the other hand, non-seminomatous GCTs, represent a more heterogenous group comprising four main subtypes (embryonal carcinoma, teratoma, choriocarcinoma and yolk sac tumor) with significant overlapping and increased frequency of mixed histological pictures[6].

It is thought today that these common histological elements between seminomatous and non-seminomatous GCTs and also between the different subtypes of non-seminomatous GCTs reflect their common embryonic origin from the same primitive, pluripotent germ cell which has the capacity to mature and differentiate to neoplastic endodermal or ectodermal components, imitating thus the procedures of normal embryonic development[4].

Consequently, each type of germinal cancer is considered to be the "counterpart" of each stage of normal embryo development: Seminoma is the neoplastic counterpart of the spermatocyte and represents the more undifferentiated type. The next stage is that of the fertilized ovum and the formation of the blastocele which gives rise to both the embryo and the placenta: the neoplastic counterpart is the embryonal cell carcinoma, which produces high levels of AFP concentration. At a more mature stage of embryonic development, malignant transformation of the developing embryo will lead to teratomas (AFP and β-hCG production), whereas neoplastic transformation of the embryonic yolk sac cells leads to the homonymous tumours, overproducing AFP.

Finally, syncytiotrophoblastic and cytotrophoblastic components of the placenta will give rise to pure choriocarcinomas, that overproduce β-hCG. Although choriocarcinomas represent a more differentiated malignant counterpart, they are characterised by an aggressive biological behaviour with tendency for haematogenous metastasis, probably reflecting the capacity of its normal counterpart (the placenta) to invade blood vessels[7].

Thus it suggests that malignant transformation of a more mature element during embryonic development does not necessarily predict either a benign biological behaviour of the tumour or a more favourable clinical outcome[8].

The above mentioned hypothesis implies that GCTs may metastasise only as a more mature histological type in the procedure of embryogenesis and never in the opposite direction, which has been confirmed by numerous clinical observations: Metastases from embryonic carcinomas may be found to consist of both teratoma and choriocarcinoma elements, whereas choriocarcinomas metastasise only as choriocarcinomas, since they represent the more differentiated histological type of embryonic development[9].

Seminomas possess the theoretical capacity of metastasising as various histological components since they represent the malignant counterpart of the more "primitive" cell, the spermatocyte. However, some authors suggest that "typical" seminomas always metastasise keeping their original histological features: those who do not represent GCTs of mixed histology, misdiagnosed as seminomas at the original histological examination. Supporters of this theory believe that histological "conversion" can not happen either automatically or after therapeutic intervention[4].

The presenting symptom of our patient was an enlarging, abdominal mass, originally thought to be a retroperitoneal mass and is considered to be an extremely rare presentation. With the exception of choriocarcinoma, which gives early haematogenous metastases, testicular tumours usually become apparent in their primary location with painless or slightly painful enlargement of the testicle noticed accidentally by the patient himself. Discolo and Dispaquale reported a case of testicular seminoma with cervical lymphadenopathy as the presenting symptom[10]

Costal bones, brain, spleen, paracolic gutter, urethra, inferior vena cava, pancreatic and subcutaneous tissue have been reported as rare metastatic locations of primary testicular cancer but not as the presenting manifestation[11-15].

In our patient the painless retroperitoneal enlargement was due to the growing paraortic retroperitoneal embryonal carcinoma and is, to our knowledge, the first case of concurrent testicular seminoma and retroperitoneal embryonal carcinoma ever reported.

Detailed examination of the testicles including scrotal ultrasound with Doppler angiography should be performed in every diagnosed or highly suspected extra-gonadal germ cell tumour, as the latter could represent a possible metastatic site. Complete staging along with solid histological confirmation in both tumour locations are mandatory before any therapeutic intervention is initiated.

CONCLUSION:

Germ cell tumors represent a heterogeneous group of malignant cell lines with a variety of frequently overlapping histological pictures or with mixed components suggesting a common "precursor" embryonic cell dysfunction. Histological conversion to a more mature subtype is theoretically possible in a metastatic location with or without therapeutic intervention, as well as synchronous or metachronous development of two different primary germ cell tumours as a result of a common pathogenetic mechanism concerning genetic instability or abnormalities during the pluripotent embryonic germ cell differentiation and maturation.

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