Abstract: The Leydig cell tumor (LCT) is a rare interstitial cell tumor that comprises 1 to 3% of all testicular tumors with 3% of them occurring bilaterally (1). They produce endocrine changes due to increased production of androgens and or estrogens. About 10% of all LCT are malignant and are larger with an average size of 7.5cm. These tumors are usually treated with orchidectomy. We report a case of a 31 year old gentleman who was incidentally diagnosed with a left testicular tumor, while being investigated for infertility. He was otherwise asymptomatic with insignificant past history. Clinical examinations including his scrotum and testis were normal. Scrotal ultrasonography and contrast enhanced computed tomography of abdomen revealed a lesion in the left testis with no evidence of metastasis. Provisional diagnosis of a testicular neoplasm was made. Serum Lactate dehydrogenase (LDH) was raised. Beta-chorionic gonadotropin (-hCG) and Alfaetoprotein (AFP) levels were normal. Left high orchidectomy was performed. Specimen was sent for histopathological examination which showed the histology of a benign Leydig cell tumour. The couple had a female baby after eighteen months of surgery.

Keyword: Leydig cell tumor, LDH, orchidectomy.

Introduction: The Leydig cell tumor is an interstitial cell tumor that comprises 1% to 3% of all testicular tumors with 3% of them occurring bilaterally. They produce endocrine changes due to increased production of androgens and /or estrogens. About 10% of all Leydig cell tumors are malignant and are larger with an average size of 7.5cm. These tumors are usually treated with orchidectomy.

Case presentation
A 31 years old gentleman married since 4 years came for treatment of primary infertility. He was otherwise asymptomatic with insignificant past history. Systemic examination was normal and his secondary sexual characters were well developed. Local examination of scrotum and testis was normal. There was no evidence of varicocele, hydrocele or testicular mass. Testicular sensation was present. Semen analysis revealed oligospermia (13 million/ml) with decreased percentage of motile sperms (<40%). Hormonal assays including serum testosterone (17.1 nmol/L), Serum oestrogen (20 pg/ml), Luteinizing hormone (LH) & Follicular stimulating hormone (FSH) were within normal limits. His wife’s examination for infertility was normal.

Doppler ultrasonography of scrotum showed a hypo-echoic mass lesion measuring 1.8×1.5×1.2 cm in the upper pole of left testis with increased vascularity (Figure 1). The CECT abdomen revealed a well-defined brightly enhancing lesion in the left testis with no evidence of metastasis (Figure 2).

CECT abdomen

Serum LDH (176UL) was raised. -hCG (0.1pmol/L) and AFP (1.1ug/L) were within normal limits.
Provisional diagnosis of left testicular non-seminomatous germ cell tumour was made. Left sided high orchidectomy was performed and the specimen was sent for histopathological examination. Post-operatively the patient was treated with intravenous fluid, antibiotics and analgesics. Patient was discharged on the seventh post-operative day after removal of stitches. Macroscopically the left testis and attached spermatic cord were unremarkable. On cut section, a well circumscribed solid, brown, nodular mass was identified on the upper pole of testis measuring 2.9x2.9x2cm (Figure 3)

Gross examination (cut section)

- The surrounding testis and epididymis were unremarkable. Microscopic examination revealed a tumor consisting of solid sheets of cells with deeply eosinophilic and occasional clear cytoplasm with round to oval nuclei. Some of the nuclei showed grooving with no features of malignancy (Figure 4)

**Microscopy**

- Immunohistochemistry showed inhibin and vimentin positive. A diagnosis of a benign Leydig cell tumor was made. Three monthly serial semen analysis showed increase in the percentage of motile sperms. The couple had a female baby after 19 months of surgery and the patient is asymptomatic.

**Discussion:**

A German anatomist, Franz Leydig, first described Leydig cells in 1870 (1). Leydig cell tumour (LCT) may arise in pure or mixed forms with other sex cord-stromal or germ cell tumors. The natural history LCTs is not well known and differentiation between malignant and benign forms is not easy. Etiology is unclear and predominantly occurs in males with the ovarian counterpart usually being malignant. Unlike germ cell neoplasms, there is no clear association with cryptorchidism. Epidemiologically it comprises 1% to 3% of all testicular neoplasms and approximately 10% are malignant (2). It is usually unilateral with a wide age range at presentation (20-60 yrs) with one peak in childhood and the other in the adulthood. Common clinical presentation is incidental finding of a testicular lesion on scrotal ultrasonography during evaluation of hydroceles or varicoceles or infertility, like in our present case who was diagnosed while being investigated for infertility. Malignant tumors are associated with older age group. Sometimes a non-tender palpable testicular mass may be noted. The endocrinological manifestation may precede the palpable testicular mass or they can present as non hormone secreting mass (3). The tumor frequently leads to feminizing or virilizing syndromes and the feminizing syndrome occurs due to the peripheral aromatization of testosterone or directly by oestrogen production (4). Steroid secretion varies but serum testosterone is usually elevated and the patient is asymptomatic.

Serum estradiol is increased, if feminization is evident. Almost testosterone is usually elevated but in our patient it was normal. Endocrinology of this tumour is Independent of androgen. Our case did not have any endocrinological signs or symptoms. Ten percent of cases present with gynaecomastia due to estrogen production. Hormonal disturbances leads to loss of libido, erectile dysfunction causing infertility. Like other testicular tumours, the association of infertility with LCT is not established.

**Endocrinology of this tumour is Independent of hypotalamo-pituitary-gonadal axis (5). In LCT semen analysis may show oligosperma, cystic spermatogenesis and azoosperma. The patient's semen examination showed oligosperma with increased percentage of non-motile sperms. The couple had a baby girl after 19 months of orchidectomy. Although the available data is insufficient to suggest the return of fertility post orchidectomy**

our case would suggest a thorough examination to rule out the presence of testicular mass. Hence proper clinical, radiological and histopathological evaluation in such cases is important. Laboratory studies are usually nonspecific. AFP, beta-HCG, and LDH are usually within reference range. Several other potential Leydig cell tumour markers e.g. inhibin-alpha, calretinin and melan-A have been reported.

Among imaging studies, ultrasonography is useful in detecting testicular tumours, especially with equivocal physical findings. On ultrasound, these tumours are generally well defined, hypo echoic, solid masses and may show cystic areas, hemorrhage, and necrosis. Radiology cannot distinguish between benign and malignant cases. MRI can reveal small non-palpable lesion not otherwise visible on sonograms. CT scan of the abdomen and chest radiography is indicated if metastasis is suspected (6,7). The usual microscopic appearance is of sheets of polygonal cells with abundant eosinophilic cytoplasm. They may be divided by hyaline fibrous septa into lobules. Crystals of Reinke may be seen in 30-70% of cases. The adjacent Leydig cells may contain lipid droplets. Awareness of unusual patterns such as adipose differentiation, calcification causing psammoma bodies, ossification, and spindle shaped tumour is necessary. Immunohistochemistry is usually positive for inhibin and vimentin markers (8,9). Metastases from LCT are very uncommon and metastatic sites include retroperitoneal lymph nodes (70%), liver (45%), lungs (40%), and bone (25%). The presence of cytological atypia, necrosis, angiolymphatic invasion, increased mitotic activity, atypical mitotic figures, infiltrative margins, DNA aneuploidy and increased MIB-1 activity are all suggestive of potential metastatic behaviour. Other Features associated with malignancy are increasing age and large size (5cm). Following orchidectomy, the clinical and hormonal manifestations remit in 90% of cases (10,11).

Management is mainly surgical, which includes both inguinal orchidectomy and enucleation (12,13). Inguinal orchidectomy requires early control of spermatic cord and should be performed without violation of scrotal skin (14,15). In our case we proceeded with inguinal orchidectomy. Enucleation which is a testis sparing surgery can be done via both scrotal and inguinal approach and is performed in some centres. Intraoperatively USG localizes the mass and frozen section analysis is helpful. If malignancy is suspected inguinal orchidectomy & retroperitoneal lymph node dissection (RPLND) are carried out. Benign tumours are treated by high orchidectomy and observation is sufficient.

Ideal frequency of subsequent imaging is poorly defined in malignant cases. Chest imaging and abdominal CT 4 monthly in the 1st year, followed by 6-monthly interval in the 2nd year and yearly examinations thereafter is a reasonable follow up protocol. Long-term surveillance for 10-15 years is recommended by the reports of late onset metastasis of up to 8 years post-orchidectomy (16,17).

There is limited role of chemo radiotherapy in Leydig cell tumour. Bleomycin- etoposide-platinum regimen of malignant germ cell tumour has limited efficacy in Leydig cell tumour. Imatinib with some chemotherapeutic activity in animal models has been demonstrated but there is no human trial (13). Long term follow-up of all patients diagnosed with Leydig cell tumours is essential. This will contribute to our knowledge and understanding of these rare tumours, which appear to be diagnosed more often these days.

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Conclusion:
Leydig cell tumour which many times a non-palpable testicular lesion should be kept in mind in the evaluation of infertility cases. Ultrasonography of the scrotum is corroborative. Histopathological examination helps in the confirmation of the diagnosis. Testis-sparing surgery is required in benign lesions but the return of infertility is controversial. High orchidectomy is advocated in malignant tumours.

References: