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PRIMARY LEIOMYOSARCOMA OF TESTIS: A RARE TESTICULAR TUMOUR WITH BETTER OUTCOME.

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Abstract:

Aim of the Study: To review and suggest treatment approach for rare diseases Leiomyosarcoma of testis.

Material and Method: Here, we have reviewed management of Primary Leiomyosarcoma of the testis by search of case reports in PubMed Central, Embase, Cochrane, and Web of Science Central database. We have classified the obtained information as per Oxford Centre for Evidence Based Medicine (OCEBM) level of evidence, and National Comprehensive Cancer Network (NCCN) Categories of Evidence and Consensus.

Here, current treatment scenario for sarcoma and its outcome will be discussed for a new case of low grade primary leiomyosarcoma of testis that was confirmed with Immuno-histochemistry after high inguinal orchidectomy, for painless testicular mass. Systematic review, line listing of old reported cases and treatment evidences were analysed by reviewing various international databases.

Results: Leiomyosarcoma is a very rare disease, and only few cases have been reported on online databases. It is usually reported among elderly men following irradiation or long-term anabolic steroid use. Intensive search reveals lack of definitive guidelines for management of leiomyosarcoma because available evidence is level V as per OCEBM and level C as per NCCN.

Conclusion: Even though early diagnosis and treatment by high inguinal orchidectomy improves survival and decreases risk of recurrence of leiomyosarcoma, there is need of research and definitive chemotherapy guidelines, similar to sarcoma of other site of the body.

INTRODUCTION: Testicular cancers have good outcome due to potential of cure even in the presence of metastatic disease. In case of cancer progression or recurrence after initial chemotherapy, these patients are candidates for salvage therapy. Among all tumours, non-seminoma is more aggressive than seminoma. If both seminoma and non-seminoma are present with elevated alpha-fetoprotein (AFP) concentration, the tumour should be treated as a non-seminoma.

Initial therapy of testicular tumour is selected according to the American Joint Committee on Cancer (AJCC 2010) stage group; risk stratification (good, intermediate, or poor risk), as per the guidelines of the International Germ Cell Cancer Collaborative Group;[1] and histology (seminoma versus non-seminoma).2 National Comprehensive Cancer Network (NCCN 2016) and National Cancer Institute recommend treatment as per AJCC staging.[3, 4]

Concept of Rare Disease

As per WHO, a rare disease is defined as any disease affecting fewer than 5 in 10,000 people. Rare diseases range from cystic fibrosis and haemophilia to Angelman Syndrome, with an incidence of about 1 in 15,000, to Opitz trigonocephaly syndrome, which is extremely rare with about one case per million people.[5]

In this review, we will focus on primary testicular leiomyosarcoma, which is very rare with only a few cases being reported in the literature till date. They should be differentiated from epididymo-orchitis, sarcomas of the spermatic cord and germ cell tumours. For this tumour; due to lack of data on the natural history, histological criteria for diagnosis and treatment recommendations; there is lack of guidelines regarding treatment. Most of the reported cases in previous literatures indicate that this may be an indolent tumour with a potential for cure if treated early.[6]

Search Methodology

Here, we had searched about "Management of primary leiomyosarcoma of the testis" through search of various evidences in PubMed Central, Embase, Cochrane, and Web of Science Central database. We have classified obtained information as per Oxford Centre for Evidence Based Medicine (OCEBM) level of evidence, and as per the National Comprehensive Cancer Network (NCCN) Categories of Evidence and Consensus [Table 3].

Case Summary

This 50 years old male patient, without any history of radiotherapy or anabolic steroid intake, presented with complaint of testicular swelling and pain for one year and six months. Serum tumour markers were within normal range (S. LDH was 624 U/L, β-HCG level was <0.005 mIU/mL, and AFP level was 2.27 ng/mL).

Radiological evaluation (CT scan) revealed 8.8 x 6.6 x 6.3 cm^3 mass in left scrotal sac - displacing the left testis anteriorly. There was a marked attenuation of infra-renal IVC, showing calcified foci with multiple thoraco-abdominal wall venous collaterals. Few sub-centimetres sized non necrotic left iliac lymph nodes were also observed.

Caudate and left lobe of liver, were enlarged with relative atrophy of right lobe along with surface nodularity and marked attenuation of left portal vein. Multiple periportal, peri-gastric, perio-esophageal, peri-splenic, and lieno-renal collaterals were seen.

To diagnose the type of testicular mass, the patient underwent left high inguinal orchidectomy, under general anaesthesia. Histopathological analysis of operative specimen was conclusive of well differentiated leiomyosarcoma.

On gross examination, it was a low grade i.e. Grade-I, 8.5x7.5x6.0 cm^3 mass with tumour located in extra testicular and para-testicular region. Epididymis was normal. As shown in Figure 1 (1A, 1B and 1C), histopathology suggested that it was a tumour arising from tunica dartos muscle that was well demarcated without infiltrative margins. There were 3 to 4 mitotic activities per 10 high power fields.

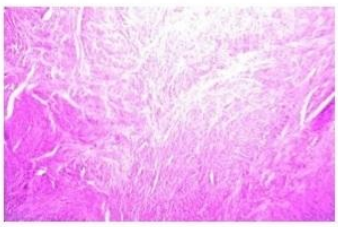


Figure 1. A. (4x)

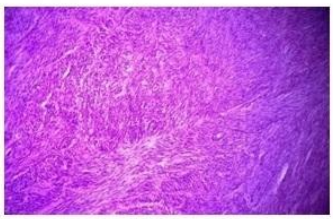


Figure 1. B. (10x)

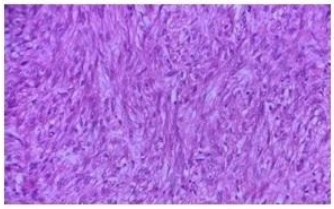
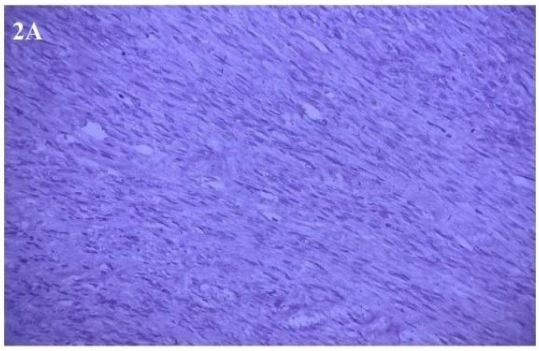


Figure 1. C. (40x)

Figure 1. Histo-pathological finding on low power (4x, 10x) and high power microscopy (×40) showing testicular parenchyma being compressed by tumour tissue composed of interlacing fascicles and whorls of elongated spindle cells.

As shown in figure 2A and 2B, Immuno-histochemistry stain was positive for Desmin but negative for S-100, findings being consistent with the diagnosis of a primary low-grade intra-testicular leiomyosarcoma that can be classified as Stage - IA according to TNM staging given by the AJCC 2010 [Table 1. A, B and C].



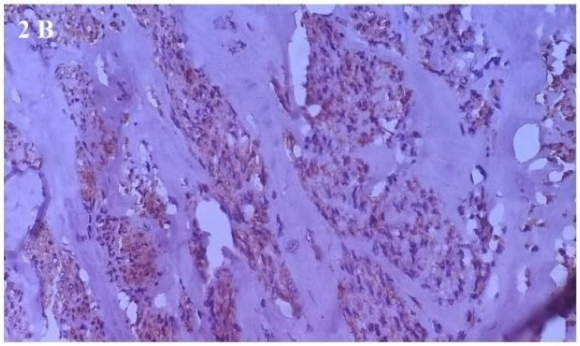


Figure 2A. Immuno-histochemistry staining negative for S- 100; 2B. Immuno-histochemistry staining positive for Desmin

Postoperatively, the patient received no adjuvant therapy. Since, the patient was of disease status stage IA and as per NCCN guidelines there was no indication for adjuvant chemotherapy/radiotherapy, patient was advised to come for routine follow up every three months.

Table 1A. AJCC staging (2010) of testicular tumour (NCCN -Version 1.2016)	
Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Intratubular germ cell neoplasia
T1	Tumour limited to the testis and epididymis or tumour invasion into the tunica albuginea only
T2	Tumour extending through the tunica albuginea with involvement of the tunica vaginalis
T3	Tumour invades the spermatic cord
T4	Tumour invades the scrotum

Regional lymph nodes — clinical (N) or pathologic (pN) staging	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to single or multiple lymph nodes, each < 2 cm in size
N2	Metastases to single or multiple lymph nodes, >2 cm but < 5 cm in size
N3	Metastases to lymph node, >5 cm in greatest dimension
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional nodal or pulmonary metastasis
M1b	Distant metastasis other than pulmonary metastasis.
Courtesy: NCCN Clinical Practice Guidelines in Oncology: Testicular Cancer. V1.2016	

Table 1B. AJCC staging (2010) of testicular tumour (NCCN -Version 1.2016)	
Serum tumor markers	
S0	Normal level
SX	Unavailable or not performed
S1	Lactate dehydrogenase (LDH) level < 1.5 times normal, Human chorionic gonadotropin (HCG) level < 5000 IU/L, alpha-fetoprotein (AFP) level < 1000 ng/mL
S2	LDH 1.5–10 times normal; HCG level, 5000–50,000 IU/L; AFP level, 1000–10,000 ng/mL
S3	LDH >10 times normal; HCG level >50,000 IU/L; AFP level >10,000 ng/mL
Courtesy: NCCN Clinical Practice Guidelines in Oncology: Testicular Cancer. V1.2016.	

Table 1C. AJCC staging (2010) of testicular tumour (NCCN -Version 1.2016)				
Stage	**T**	**N**	**M**	**Serum tumour markers**
0	pTis	N0	M0	S0
I	pT1–4	N0	M0	SX
IA	pT1	N0	M0	S0
IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
IS	Any pT/TX	N0	M0	S1-3
II	Any pT/TX	N1-3	M0	SX
IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
III	Any pT/TX	Any N	M1	SX
IIIA	Any pT/TX	Any N	M1a	S0

	Any pT/TX	Any N	M1a	S1
IIIB	Any pT/TX	N1-3	M0	S2
	Any pT/TX	Any N	M1a	S2
IIIC	Any pT/TX	N1-3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S
Courtesy: NCCN Clinical Practice Guidelines in Oncology: Testicular Cancer. V1.2016.				

Discussion

In men under 60 years of age, 95% of testicular tumours originate in the germ cells, the special sperm-forming cells within the testicles. These tumours fall into two main types, seminoma or non-seminoma as per NCCN V1.2016 criteria [Figure 3].[7]

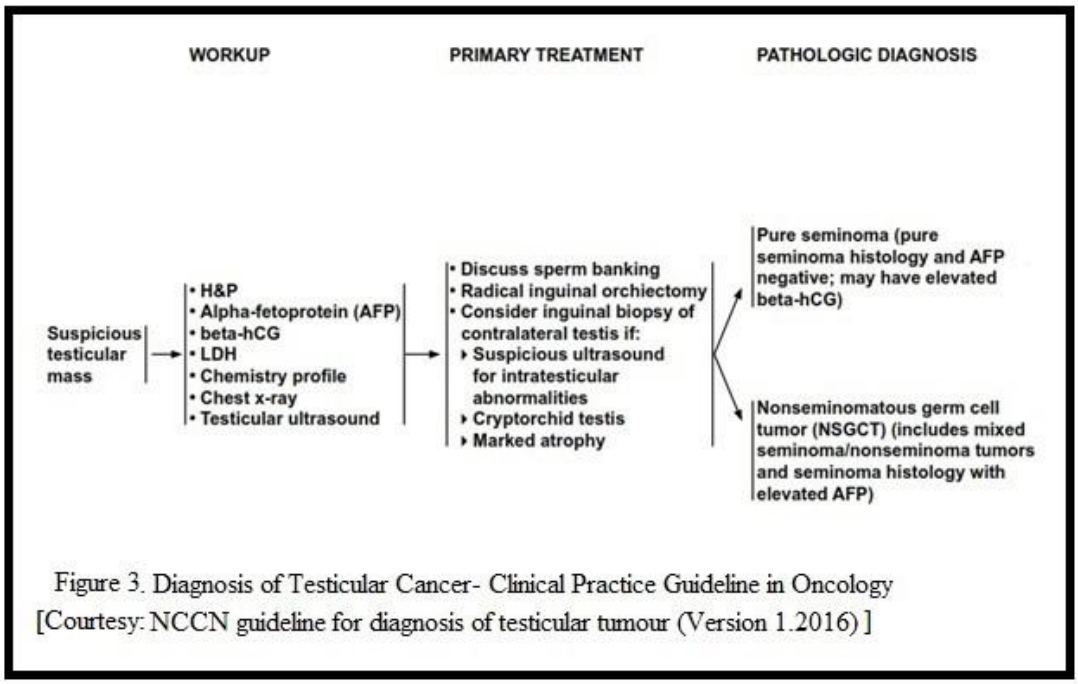


Figure 3. Diagnosis of Testicular Cancer- Clinical Practice Guideline in Oncology
[Courtesy: NCCN guideline for diagnosis of testicular tumour (Version 1.2016)]

Men over the age of 60 years can still get a germ cell tumour, but they are more likely to get leukemia, lymphoma, or a benign tumour called spermatocytic seminoma. Pure seminoma is made up of immature germ cells and accounts for about 40 percent of all testicular cancer. Usually, seminoma is slow growing and tends to stay localized in the testicle for a long period.[7]

Non-seminoma is a group of cancers that often occur in combination with chorio-carcinoma, embryonal carcinoma, immature teratoma and yolk sac tumours. Non-seminoma arises from more mature, specialized germ cells and tends to be more aggressive than seminoma.[7]

Other forms of cancer are sex cord stromal tumours, primitive neuro-ectodermal tumours, leiomyosarcoma, rhabdomyosarcoma, mesothelioma etc. that can arise in the testicle.[7]

Aetiology and pathophysiology

Leiomyosarcoma of the testis is believed to arise from undifferentiated smooth muscle cells of mesenchymal origin. Primary

Leiomyosarcoma of the testis is a rare entity and diagnosis is made on histopathological examination.[8]

In general, scrotal leiomyosarcoma can arise from either para-testicular tissue or the testicular parenchyma itself. On the other hand, intra-testicular leiomyosarcoma arises from smooth muscle cells within the testis such as blood vessels, seminiferous tubules, and tunica.

On evaluation of the history, its occurrence has been associated with radiotherapy and long term anabolic steroid use.[9]

Surgery (Excision) is preferred as a treatment in spite of having a low metastatic potential because it can coexist with germ cell tumours which have an adverse prognosis.[10, 11]

Diagnosis of Leiomyosarcoma

Before diagnosing it as primary leiomyosarcoma, the presence of germ cell elements within the tumour must be excluded.11 The diagnosis of spindle-cell leiomyosarcoma is made by the presence of significant nuclear atypia, a mitotic count ≥10/10 high-power fields and coagulative necrosis with nuclear debris.10 The same diagnostic criteria may well be used for the diagnosis of intra-testicular leiomyosarcoma, with subsequent immuno-histochemical profiling to support the diagnosis of a primary intra-testicular smooth muscle tumour.[8]

Overall, primary intra-testicular leiomyosarcoma usually occurs in fourth or fifth decades and ultrasound of the scrotum usually shows a well-circumscribed, hypo echoic mass lesion with or without calcification. CT scans of the abdomen and chest are required to rule out metastasis. High inguinal orchidectomy is the treatment of choice, which should be followed by surveillance in low grade early stages.[8]

Management Plan

In case of low grade leiomyosarcoma, surgery in the form of high inguinal orchidectomy is the treatment of choice and no adjuvant treatment is required. On the other hand, for treatment of high grade leiomyosarcoma - after high inguinal orchidectomy, doxorubicin based chemotherapy is given. The various chemotherapy regimens are - (1) AIM protocol i.e. Adriamycin (Doxorubicin), Ifosfamide, and Mesna, (2) VAC protocol i.e. Vincristine, Adriamycin and Cyclophosphamide or (3) Gemcitabine based chemotherapy e.g. Paclitaxel + Gemcitabine or Cisplatin + Gemcitabine etc.[12]

Targeted treatment is also shown to be effective in leiomyosarcoma in various studies. Most important targeted treatment is Pazopanib 800 mg per oral, once a day as per approval given by FDA.[13] For advanced, un-resectable, or metastatic soft tissue sarcoma (STS), single-agent or combination therapy with an Anthracycline or Ifosfamide remains the standard of care. On the other hand, current NCCN guidelines recommend Pazopanib as an alternative single agent palliative therapy for STSs in the extremity/trunk, head/neck, retroperitoneal, and intra-abdominal regions but cost is the major concern.[6, 12, 14]

According to AIM protocol, Doxorubicin is given at 75 mg/m^2/cycle as divided doses i.v. bolus over 3 days and Ifosfamide is given as a dose of 6–9 g/m^2/cycle, in divided doses over 3 days, usually over 3 hours with Mesna as urothelial protectant.[12]

Local radiotherapy is required if surgical margins are positive or close as per histopathological report of operated specimen. In one study, a patient with testicular leiomyosarcoma with lung metastasis was prescribed CYVADIC (Cyclophosphamide, Vincristine, Adriamycin, and Dacarbazine)

chemotherapy. On follow up, there was no progression of the metastatic lesions as of 9 months after completion of chemotherapy.[15]

Table 2. Leiomyosarcoma of testis in previously reported cases

Case no.	Authors (reference)	Age	Side	Clinical Stage	Treatment	Follow-up (months)	Outcome	Risk Factors	Levels of Tumour Markers
1	Yachida[16]	55	R	I	Orchidectomy	24	Survived	–	Normal
2	Pellice[17]	37	L	I	Orchidectomy	24	Survived	–	Normal
3	Washecka[11]	47	R	I	Orchidectomy	49	Survived	–	Normal
4	Washecka[11]	40	R	I	Orchidectomy	42	Survived	–	Normal
5	Froehner[9]	32	R	I	Orchidectomy + RPLND*	79	Survived	Anabolic Steroid	Unknown
6	Hachi[18]	70	L	I	Orchidectomy	14	Death (Lung Metastases)	–	Normal
7	Ali[19]	65	R	I	Orchidectomy	12	Survived	Chronic Inflammation	Normal
8	Takizawa[20]	76	L	I	Orchidectomy	12	Survived	–	Normal
9	Canales[21]	30	R	I	Orchidectomy	6	Survived	Radiation	Unknown
10	Yoshimine[15]	73	L	III	Orchidectomy+ Chemotherapy	9	Survived	–	Slightly Elevated
11	Celik[22]	53	R	II	Orchidectomy	4	Survived	-	Unknown
12	Current case	50	L	I	Orchidectomy	4	Alive	-	Normal

*RPLND = Retro-peritoneal Lymph Node Dissection

Courtesy: ***Yoshimine S, Kono H, Nakagawa K, Kikuchi E, Miyajima A, Kameyama K, et al. Primary intratesticular leiomyosarcoma. Can Urol Assoc J. 2009;3:E74-6.***

The role of radiotherapy and chemotherapy are not well established due to less number of cases. As compared to leiomyosarcoma of other sites of the body, management of testicular leiomyosarcoma has shown better outcome. As summarised in **Table 2**, only few cases of primary testicular leiomyosarcoma have been reported till date, and out of eleven reported cases, one died of pulmonary metastasis.[7, 9-11, 15, 16]

In this case, the patient presented with painless testicular mass which was histo-pathologically suggestive of low grade, stage IA leiomyosarcoma of the testis. We did not offer adjuvant treatment and put the patient on close surveillance. This patient is on follow up every three months to make out any evidence of recurrence, local or distant.

Level of Evidences for Management

In case of metastasis, palliative chemotherapy with single-agent Adriamycin or Adriamycin plus Ifosfamide remains the mainstay of treatment for advanced and metastatic soft tissue sarcomas.[6, 20, 23]

Table 3. Determination of levels of evidence by NCCN Categories of Evidence and Consensus and Oxford Centre for Evidence-Based Medicine (OCEBM)

NCCN categories of evidence	Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of evidence		
	Recommendations	Evidence level	Description
Category 1: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate	A	1a	Systematic reviews (with homogeneity) of randomized controlled trials
		1b	Individual randomized controlled trials (with narrow confidence interval)
		1c	All or none randomized controlled trials (all patients die before the application of treatment, and some patients survive after treatment; or some patients die before the application of treatment and no patient dies after treatment)
Category 2A: based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate	B	2a	Systematic reviews (with homogeneity) of cohort studies
		2b	Individual cohort study or low quality randomized controlled trials (e.g., <80% follow-up)
Category 2B: based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate		3a	Systematic review (with homogeneity) of case-control studies
		3b	Individual case-control study
Category 3: based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate	C	4	Case-series (and poor quality cohort and case-control studies)
	D	5	Expert opinion or comment

Courtesy: Experts Committee on Nutritional Therapy for Cancer Patients of Chinese Society of Clinical Oncology (CSCO). Expert consensus on the nutritional therapy for patients with malignancies. Chin Clin Oncol 2013; 2(3): 24. doi: 10.3978/j.issn.2304-3865.2012.12.04.

There is a lack of research in primary testicular Leiomyosarcoma due to very limited number of case reports published in literature and scarcity of data in medical research [Table 3]. So conclusion regarding optimum stage-wise management (category 1) in primary testicular leiomyosarcoma has not been made, so far.[24]

Conclusion

Leiomyosarcoma of the testis is a rare disease occurring in elderly patients and generally mimics epididymo-orchitis or presents as a silent mass. Early diagnosis and treatment by high inguinal orchidectomy is the treatment of choice in early stage low grade leiomyosarcoma. In high grade and advanced stage tumours, chemotherapy is given as adjuvant/ palliative/ salvage treatment. But it is difficult to define the optimum management due to scarcity of the research and no consensus being available regarding standard treatment strategy for this disease.

Footnotes

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