First case of bilateral, synchronous anaplastic variant of spermatocytic seminoma treated with radical orchifunicolectomy as single approach: Case report and review of the literature

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INTRODUCTION

Spermatocytic Seminoma (SS) is a rare germ cell tumor, firstly described in 1946 by *Masson*, who assumed this kind of neoplasm to be a variant of the *classic seminoma* (CS) (1). Nowadays, the *World Health Organization* (WHO) classifies the SS in a distinct subgroup of testicular germ cell tumor (TGCT) in contrast with CS, basing on genetic, molecular, histological and clinical characteristics (2). Even if both CS and SS originate from the germ cell line, the general opinion is that these two different testicular germ cell neoplasms develop from different gene rearrangements, taking place in different periods of germ cell differentiation. In details, the current tendency is to believe that SS originate from more mature germ cells (3-4).

The gain of the short arm of the chromosome 12 is generally found in all TGCTs, especially in CS. This genomic modification may take place in an early phase of cellular development, i.e. during the mitosis, as confirmed by the expression, in CS, of both the markers of pluripotency (such as OCT3/4) and of proteins which are distinctive of primordial germ cells (such as alkaline phosphatase, PLAP, and c-Kit, CD117).

On the other hand, several evidences coming from animal models show that SS has a different genomic pattern, and no mutations on the short arm of chromosome 12 have been found. Conversely, super-numerical copies of chromosome 9 with no translocation, deletion or amplification are often detected, with an overexpression of the gene DMRT1, that is a transcription factor usually expressed by spermatocytes during meiosis when germ cells reach a higher level of maturation and lose their pluripotency (3). Interestingly, the histological patterns of CS and SS are quite different as well. In fact, while the former usually consists in sheets of cells with polygonal nuclei and clear cytoplasm, with the cells divided into nests by fibrovascular septa that contain lymphocytes (5), the latter shows a nodular growth pattern containing three types of cells: the first are of medium size, with eosinophilic cytoplasm and round nuclei (usually the majority of the tumor cells); the second are a small cells with dark-staining nuclei and scanty eosinophilic cytoplasm (lymphocyte-like); the third are a large and giant cell mono or multinucleated. All these cells are usually characterized, differently from CS, by the lack of cytoplasmic glycogen and poor lymphocyte infiltration (6).

The most important difference between CS and SS lies in their different natural behavior, which changes dramatically the prognosis of these neoplasms; in fact, while the CS usually originates from intratubular germ cell neoplasia unclassified (IGCNU) and has a rapid development and a high tendency to metastasis, the precursor of SS is the intratubular spermatocytic seminoma, very different from IGCNU, being more differentiated, developing only in the gonads with a very low rate of metastasis and very similar to other benign testicular neoplasm (3, 7, 8); indeed in literature there are only three cases of metastatic SS out of more than 200 cases reported (9).

Spermatocytic Seminoma is less common than CS, as its incidence ranges between 1.3% and 2.3% of all seminomas. Generally SS is diagnosed in men older than 50 years, while CS is more frequently in the age between 30 and 40 years (10). The incidence of bilateral testicular occurrence is higher in SS when compared to CS (10), even if the extra-testicular extension is an exceptional finding in SS patients. Usually SS has an indolent behavior, with an asymptomatic slow growth, and a low tendency to metastasis; these features give this tumor a good prognosis and generally radical orchiectomy is sufficient to control the disease. Surveillance after surgery is the favorite management option (10). Conversely, in some cases SS may be more aggressive, especially in those cases with sarcomatoid transformation, presenting a rapid increase in size and a significant risk of metastatic disease; in these cases a multimodal approach (surgical treatment and adjuvant chemotherapy or radiotherapy) is more appropriate (11, 12). The histology, molecular and clinical features of this variant of SS are well described elsewhere (13). The most rare kind of SS reported in literature is the anaplastic vari-

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ant. This tumor is characterized by an earlier onset, but a benign behavior has been reported in spite of its histological patterns similar to CS histology. The histology of the anaplastic variant of SS is represented by a polymorphic cell population (small, medium and large cells) with a nodular growth pattern, such as SS, associated with cluster of cells, mainly giant cells, with a solid growth pattern, showing prominent nucleoli and a high mitotic figures index, blood vessels invasions, intratubular growth and extensive necrosis in absence of lymphocytic infiltration (6). After an extensive review of the literature, at the best of our knowledge only six cases of anaplastic variant of SS have been described in literature: one study reporting 4 cases (6) and another two cases reported individually (9, 14). In this paper we report the seventh case, for the first time with a bilateral and synchronous presentation and unusual clinical features.

Case report

A 63-year-old, obese man presented in our Department in October 2010 with an exceptional scrotal enlargement due to two voluminous, painless bilateral testicular masses (Figure 1). The patient complained a gradual increasing of those masses already for 5 years, but he kept the problem hidden because of shame and fear of surgical intervention. There was no history of cryptorchidism, scrotal pain, local trauma or hereditary disease. On physical examination the huge testicular masses appeared well defined, adherent to scrotal skin and with a non-tender consistence; no superficial palpable lymph nodes were found. The patient was completely asymptomatic, with no relevant co-morbidities, except for a mild hypertension. The masses were firstly evaluated through Doppler ultrasonography, which revealed bilateral heterogeneous, hyper-vascularized testicular masses measuring approximately 11 cm and 18 cm on the right and left side respectively; the testicular pattern appeared completely subverted in the whole testis. Total Body Computed Tomography was negative for lymph node enlargements or distant metastases, and confirmed the wide neoplastic infiltration of both testes. Pre-operative serum level of α-fetoprotein (α-FP) and β-human chorionic gonadotropin (β-HCG) were within the normal ranges, while serum lactate dehydrogenase (LDH) was found to be elevated (426 IU/L). One month after the first visit, the patient underwent bilateral radical orchifunicolectomy with successive scrotoplasty in order to reduce exuberant scrotal skin. At gross examination the left testis was 20 x 14 x 10 cm and weighed 1515 g, the right testis was 10 x 7 x 5 cm and weighed 375 g (Figure 2). Both testes were completely replaced by a pale-grey firm mass with mild mixoid features that included both the didymus and the rete testis (Figure 3). There was no macroscopic invasion of tunica albuginea. On histological grounds, the tumor showed a triple cell population of non-cohesive spermatic cells, typical of spermatocytic seminoma with intermingled anaplastic cells. At immunohistochemistry, the neoplastic cells resulted immunoreactive for CD117, some scattered cells were positive for PLAP, while CD45 and OCT-4 turned out negative. The histological features and the immunohistochemical results were consistent with the diagnosis of bilateral spermatocytic seminoma showing vascular infiltration with anaplastic cells. The pathological staging was pT2 Nx Mx according to the *American Joint Committee on Cancer* (AJCC). After surgery the patient was proposed to undergo a consolidative chemotherapy, but he refused any adjuvant treatment. Disease re-staging was performed six months after surgery through positron emission tomography with fludeoxyglucose (PET18F-FDG) and contrast enhanced whole body CT (resulted negative) and then annually. Currently the patient is free of disease 36 months after the bilateral orchiectomy. Moreover he started testosterone replacement therapy, through monthly intramuscular injection with a rapid normalization of testosterone level and a self defined satisfactory erectile function supported by the assumption Tadalafil 5 mg once a day.

Table 1.

Clinical and pathological features of anaplastic SS currently available in literature.

Case	Age	Clinical presentation	Side	Size (cm)	Positive markers	Treatment	Outcome	Authors
1	38	Painless mass Unknown duration	R	5.5x5x4	-	O + RT	DF at 38 month	J. Albores Saavedra et al. 1996
2	33	Painless mass 9 month duration	R	10x6x5.5	-	O + RT	DF at 27 month	J. Albores Saavedra et al. 1996
3	43	Painless mass 18 month duration	L	8x5x3	-	O + RT	DF at 4 month	J. Albores Saavedra et al. 1996
4	42	Painless mass Incidental discovery	L	2.5x2.5x2.5	-	O	DF at 3 month	J. Albores Saavedra et al. 1996
5	56	Testicular enlargement	L	10x7.5x6.5	CD117	O + 2 carboplatin cycles	DF at 38 month	P. Dundr et al. 2007
6	46	Testicular mass	L	8	-	O + 2 cycles of cisplatin, etoposide, bleomycin.	DF after chemotheraphy	M. Lombardi et al. 2011
7	63	Bilateral testicular masses 5 years duration	R+L	20x14x10(L) 10x7x5(R)	CD117 PLAP	O	DF at 36 month	Present paper

RT = radioteraphy to pelvic and retroperitoneal lymph nodes; O = orchiectomy; DF = disease free.

Conclusions

To the best of our knowledge, we reported the first case of bilateral, synchronous anaplastic variant of spermatocytic seminoma with the largest dimension and the longest period of observation. Because of its histological features, the anaplastic variant of SS has been considered as an aggressive tumor, thus justifying the needing for adjuvant therapy. On the other hand, the data currently available in literature show that this tumor reveals a clinically benign behavior, and no distant metastases have been reported so far. These findings are very similar to that reported for typical SS. For this reason, even if seven cases described are insufficient and need to be confirmed by further studies with an evidence-based approach, the anaplastic variant of SS could be compared with the typical SS forms. Therefore, a close surveillance after surgery could be considered as a valid option in the management of this kind of tumor.

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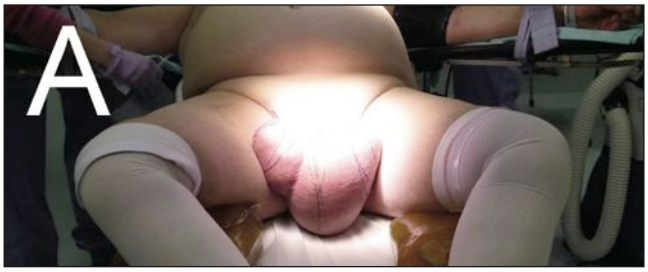

Figure 1.
Pre-operative appearance of the bilateral testicular masses.

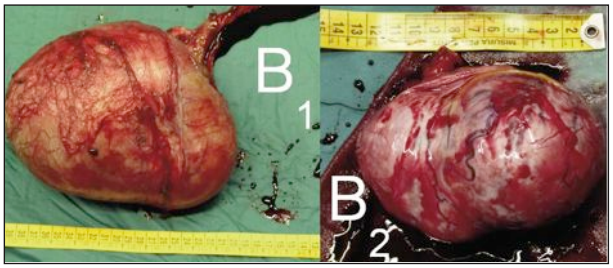

Figure 2.
Testicular masses: B1- left testicle, B2- right testicle.

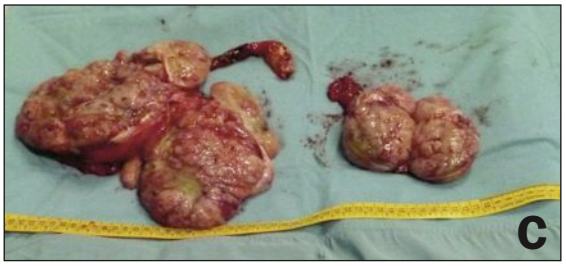

Figure 3.
Macroscopic appearance of the masses.

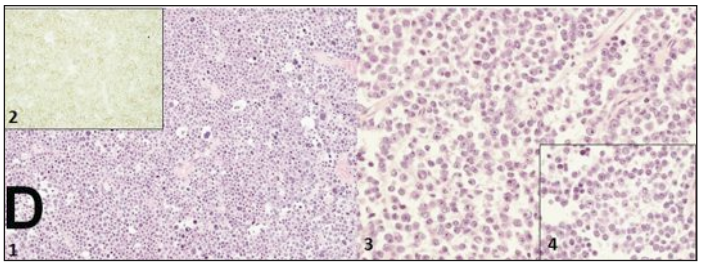

Figure 4.
D1 -H&E magnification 10x. Microscopic features of spermatocitic seminoma. D2-Immunohistochemical patterns of positivity for CD117. Magnification 20x. D3- H&E magnification 20x. "Anaplastic" features with a predominance of intermediate-size cells with prominent nucleoli. D4- H&E magnification 40x. Anaplastic features.