Urology Case Reports 51 (2023) 102612

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr

Oncology

Metachronous bilateral testicular germ cell tumors with different histopathology: A case report

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ARTICLE INFO

Keywords:
Bilateral testicular tumors
Metachronous tumors
Different histopathology

ABSTRACT

Background: Testicular cancer is the most common solid tumor affecting men aged 20–39 years old. About 95% of all testicular tumor is testicular germ cell tumor. Bilateral testicular tumor is a rare incident and has similar histopathology only in less than 5% of all testicular cancer patients. Besides oncological issues, bilateral testicular tumors could lead to further consequences, such as psychosocial and hormonal issues. This article shows a case of different histopathology in the metachronous bilateral testicular tumors.

Case presentation: A 34-years-old male came with right radical orchiectomy due to testicular pure seminoma pT1N0M0S0 three and half years ago. He underwent bleomycin, etoposide phosphate (BEP) chemotherapy for progressive multiple lymphadenopathies in paracaval and interaortacaval region from positron emission tomography (PET)/computerized tomography (CT) scan a year later. Sperm banking was done before initiated chemotherapy. High metabolic activity was detected in contralateral testis from follow up PET-scan. Left testicle enlargement with hard consistency was found on physical examination and there is an elevation of alpha-feto protein (AFP) and β-hCG. Intraoperatively, the frozen section identified a malignant tumor and the patient was decided to undergo radical left orchiectomy. Postoperative pathological results showed a mixed germ cell tumor of 3.5 × 2.5 × 2 cm consisting of immature teratoma, yolk sac tumor and embryonic carcinoma without lympho-vascular invasion and involvement of the spermatic cord. Post-operative imaging and testicular tumor marker did not identify any metastases. BEP chemotherapy, testosterone replacement therapy was planned for further management in this patient with complete blood count, prostate serum antigen (PSA) and digital rectal examination should be measured three to six weeks after initiation.

Conclusion: Metachronous bilateral TGCT with different histopathology is a rare disease. The treatment depends on histology of second tumor and its stage. TRT is mandatory for patient undergoing bilateral orchidectomy to address lack if testosterone.

1. Introduction

Testicular cancer is one of the most prevalent solid tumors affecting young adult males between the ages of 20–39.[1] Bilateral testicular tumor is a rare entity accounting for less than 5% of testicular cancer. Although it is uncommon, bilateral testicular tumor has been reported to have detrimental psychological and hormonal effects.[2]

Based on its presentation, bilateral testicular tumors may either be "synchronous" (apparent at time of diagnosis or within two months since diagnosis) or "metachronous" (developed at two different time). Metachronous tumors are reported to be two times more prevalent compared to synchronous and with longest interval of approximately 40 years.[3,4] Most cases often present with similar bilateral histopathology.[5] However, different histopathology may also occur, especially in metachronous tumors, thus affecting its oncological approach and prognostication. Due to the scarcity of the case, it is still unclear whether the oncological based on the current guideline may cater similar curative potential to the particularly metachronous bilateral testicular tumors

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https://doi.org/10.1016/j.eucr.2023.102612
Received 10 September 2023; Received in revised form 19 October 2023; Accepted 6 November 2023
Available online 9 November 2023

with different histological feature. The current case presents a rare case of different histopathology in metachronous bilateral testicular tumor patient. The patient gives his consent to the study.

2. Case Presentation

The patient is a 63-year-old man presenting to our clinic with history of right radical orchidectomy 3.5 years ago due to testicular pure seminoma pT1N0M0S0. Prior to the radical orchidectomy, biopsy was also performed using the inguinal approach with isolation. Following the orchidectomy, the patient had four cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy for multiple lymphadenopathies in paracaval and interaortocaval region as according to findings in PET/CT-scan. Sperm banking was performed prior to chemotherapy initiation.

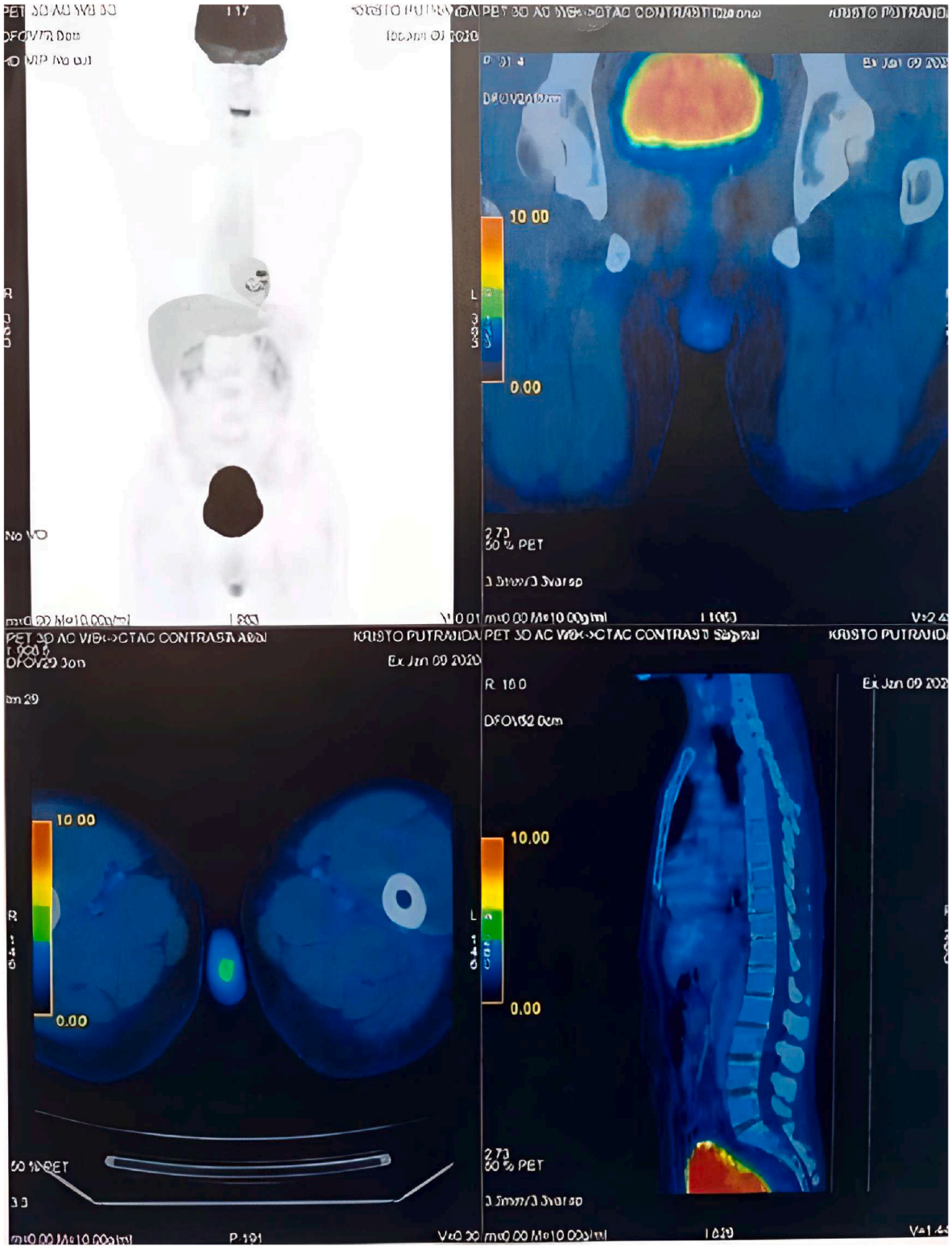

Fig. 1. High metabolic activity in left testis from PET-scan.

The patient was in a complete remission until a PET-scan follow-up two months ago showed high metabolic activity of the contralateral testis (Fig. 1).

Physical examination revealed left testicle enlargement with hard consistency. Laboratory examination showed elevated tumor marker, alpha-fetoprotein/AFP (434.90 ng/mL) and β-hCG (5609 mIU/mL). The patient underwent surgery where malignant tumor with germ cell tumor features were identified from the frozen section, therefore left radical orchidectomy was subsequently decided to be performed. The pathological result showed 3.5 × 2.5 × 2 cm mixed germ cell tumor consisting of immature teratoma, yolk sac tumor, and embryonal carcinoma without lympho-vascular invasion and spermatic cord involvement (Fig. 2).

Furthermore, no metastasis was identified from post-operative imaging and testicular tumor marker was within normal limit. The patient was planned for BEP chemotherapy and testosterone replacement therapy (TRT) for further management. A complete blood count, PSA, and digital rectal examination would be measured in three to six weeks' time after initiation, then annually if laboratory results are within normal limit.

3. Discussion

In the last three decades, testicular cancer incidence has been reported to rapidly increase with 3–6 in 100,000 are reported every year as new cases of testicular cancer.[6,7] The number has doubled in the past 40 years. Testicular germ cells tumor (TGCTs) contributes to more than 95% of testicular tumors.[8,9] Men with TGCTs are approximately 27 times at higher risk to develop subsequent tumor of the contralateral testicle.[9] In spite of that, very few literatures have investigated on metachronous bilateral testicular tumor patients. The latest we could identify was a systematic review was by Zequi et al. (2012) involving 50, 376 men that reported a prevalence of 1.82% of testicular germ cell tumors (TGCT) during 1991–2011. More than two-third (69.2%) of the TGCT patients presented with metachronous tumors.[8] The mean age of overall subjects was approximately thirty years old upon first tumor diagnosis, and 49.8% cases of seminoma was found as their first tumor. Most of the patients with metachronous contralateral TGCT were initially diagnosed in stage I (73.3%). About 61.4% of metachronous contralateral TGCT showed similar histopathology with previous tumor, while within those with different histopathology, only 36.3% was found as non-seminoma. The median interval time of second tumor diagnosis from the first one in metachronous TGCT is different between studies, ranging from 2 to 8.5 years with more than 60% of them occurred in less than 10 years.[8] Compared to previous study, our patient's age upon initial presentation was older than average. It is still unclear whether the patient is simply a representation of the minority of approximately 13% patients aged older than 54 years old at first diagnosis or other factors such as geography and race might contribute to this finding. Apart from age, our patient was not different from the subjects' characteristics presented in systematic review, as he was initially diagnosed with stage I TGCT and was later diagnosed with metachronous tumor after two years.

The risk of contralateral TGCT occurrences is higher in patient that was initially diagnosed as seminoma compared to non-seminoma, and greater risk occurs if diagnoses were established before the age of 30 years old.[10] It is still contradictive whether chemotherapy could reduce the risk of contralateral TGCT occurrences since the majority of seminoma TGCT patients on "active surveillance" showed >99% of cancer-specific survival rate.[11,12] One study showed reduced risk of contralateral occurrences in non-seminoma patient receiving chemotherapy, about 0.3 times lower compared to those not receiving chemotherapy.[10] Other risk factors that increase the risks of contralateral TGCT occurrences tumor are germ cell neoplasia in situ (GCNIS), tumor less than 12 ml of testicular volume, and history of undescended testis.[13] In this case, those risk factors are not notable.

TGCTs spread through the lymphatic channels. For TGCTs arising in the right, the infrarenal inter-aortacaval lymph nodes are the primary landing zone, along with the paracaval and para-aortic lymph nodes.[14,15] Right-to-left retroperitoneal spread of TGCTs are more commonly seen compared to left-to-right spread.[16] In our case, the multiple lymphadenopathies in the area of paracaval and para-aortic zone was found, therefore it is easy to assume that it may be due to the right-to-left retroperitoneal spread. However, the different pathology between the right and the left testicles might challenge the idea that development of subsequent left testicular tumor is a result of tumor dissemination from the right.

Routine biopsy of the contralateral testis is still a contradictive

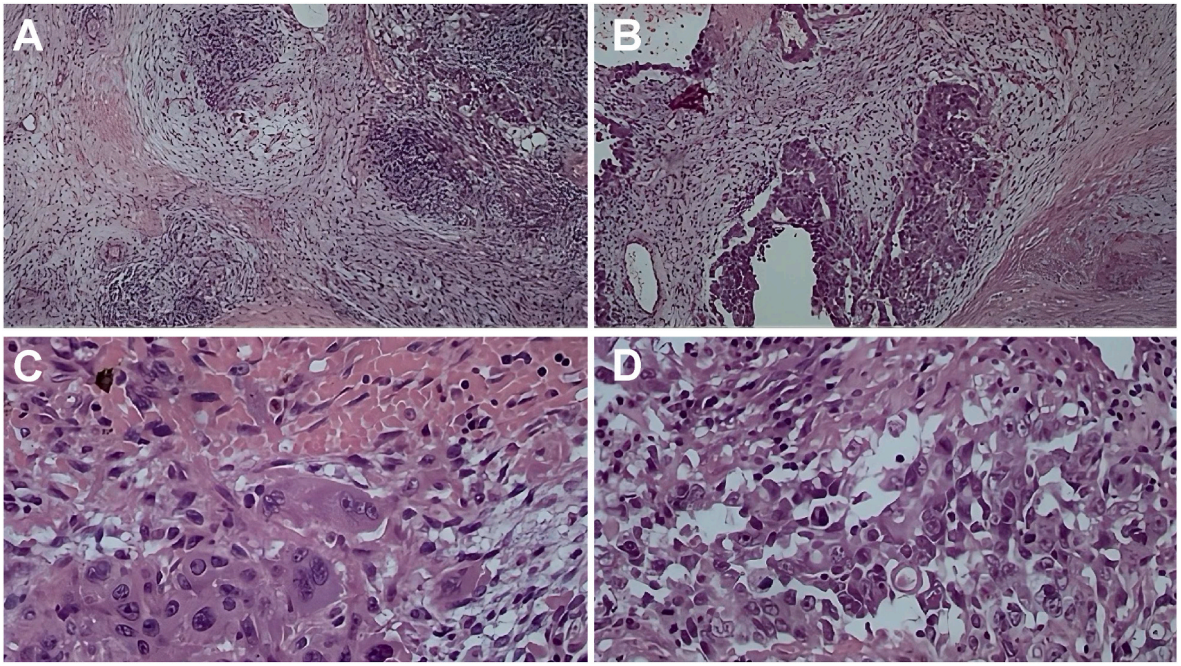

Fig. 2. (A) Yolk sac component. (B) Teratoma component. (C) Syncytiotrophoblast component. (D) embryonal carcinoma component.

matter in patients with first TGCT occurrence. It is not recommended due to excellent prognosis of metachronous testicular germ cell tumors. In addition to that, the manipulation in *trans*-scrotal biopsy may establish new lymphatic drainage pathways, thus increasing the risk of local dissemination.[17] However, National Comprehensive Cancer Network (NCCN) guideline recommends inguinal contralateral biopsy if the following conditions present: suspicious contralateral testicular mass or contralateral intratesticular cancer from ultrasonography examination, contralateral testicular cryptorchidism, and testicular atrophy.[18] In our case, previous right testicular biopsy was performed using the inguinal approach during first TGCT management, therefore the attempt to reduce the risk of local dissemination was already minimized.

For this case we decided to avoid testis-sparing surgery (TSS). Although TSS could be a choice of treatment for a patient with solitary testis or bilateral testicular cancer. TSS would only be eligible if the patient has excellent compliance, a single tumor of less than 2 cm that is located at the lower pole of the testis and endocrine function within normal limit.[12] In our case, malignant histopathology was found in frozen section tumor was more than 2 cm and more than 30% of testicular volume, therefore, we proceed with the justification for radical orchidectomy procedure. Testosterone replacement therapy (TRT) was planned for this case of bilateral orchidectomy. TRT was considered to preserve hormonal function, as testosterone deficiency is associated with symptoms disrupting quality of life, including irritability and mood changes, reduced libido, decreased erection, and to extend osteoporosis, metabolic syndrome, and type 2 diabetes.[18] Adverse events should be monitored regularly and pre-existing prostate cancer should be checked before TRT. Three to six months after initiation of treatment, patients should be reassessed for therapeutic response and adverse effects. If the results of the laboratory are within normal limit, an annual re-evaluation may be carried out.[18]

The treatment of contralateral TGCT is based on the form and histology of the second tumor and could be treated similarly to the first tumor depending on its stage. However, the choice of treatment must be considered case-by-case and taking patient preferences into account.

Higher overall survival (OS) and disease-specific survival are higher in a metachronous tumor than synchronous tumor. Five-year and 10-year OS for metachronous contralateral TGCT are 93–95% and 86.1%, respectively.[18] Factors which could negatively impact overall survival in metachronous contralateral TGCT are higher clinical stage, later than 5 years interval time of contralateral TGCN diagnosis, and concordant histopathology result between first and second tumor, especially in seminoma histopathology. Moreover, patient with metachronous contralateral TGCT has increased risk of 2.3 times in other invasive cancer development.[18] Specifically, the International Germ Cell Collaborative group (IGCCCG) made prognostic-based system for staging of metastatic germ cell cancer that groups patients into good-prognosis group, intermediate-prognosis group, and poor-prognosis group for each seminoma and nonseminoma TGCT based on site of primary tumor, presence of nonpulmonary visceral metastases, level of AFP hCG, and lactate dehydrogenase (LDH). Based on that classification, the five-year progression-free survival (PFS) of this patient was 90% and five-year survival is 96%.[19,20]

4. Conclusion

This study reports a case of metachronous bilateral TGCT with different histopathology. This case is quite rare and future studies reporting similar cases are still needed to understand the underlying pathology, possible best approach can be given, and future prognosis. Based on the available limited studies, prognosis of the patient is intermediate.

The patient received left radical orchidectomy and planned for chemotherapy and TRT. The patient will be continuously evaluated.

Declaration of generative AI in scientific writing

No AI tools were used in any process of this journal writing.

Declaration of competing interest

No potential conflict of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018 Nov 12;68(6):394–424.
2. Hentrich M, Weber N, Bergsdorf T, Liedl B, Hartenstein R, Gerl A. Management and outcome of bilateral testicular germ cell tumors: twenty-five year experience in Munich. *Acta Oncol (Madr).* 2005 Jan 8;44(6):529–536.
3. Fosså SD, Chen J, Schonfeld SJ, et al. Risk of contralateral testicular cancer: a population-based study of 29 515 U.S. Men. JNCI. *J Natl Cancer Inst.* 2005 Jul 20;97 (14):1056–1066.
4. Boccellino M, Vanacore D, Zappavigna S, et al. Testicular cancer from diagnosis to epigenetic factors. *Oncotarget.* 2017 Nov 28;8(61):104654–104663.
5. Stephenson AJ, Gilligan TD. Neoplasms of the testis. In: *Campbell-walsh Urology.* eleventh ed. Elsevier; 2015:784.
6. Schottenfeld D, Wa\rshauer ME, Sherlock S, Zauber AG, Leder M, Payne R. The epidemiology of testicular cancer in young adults. *Am J Epidemiol.* 1980 Aug;112(2): 232–246.
7. Sarıcı H, Telli O, Eroğlu M. Bilateral testicular germ cell tumors. *Turk J Urol.* 2013 Dec;39(4):249–252.
8. Zequi S de C, da Costa WH, Santana TBM, Favaretto RL, Sacomani CAR, Guimaraes GC. Bilateral testicular germ cell tumours: a systematic review. *BJU Int.* 2012 Oct;110(8):1102–1109.
9. Ulbright TM. Testis risk and prognostic factors: the pathologist's perspective. *Urol Clin.* 1999 Aug;26(3):611–626.
10. Schaapveld M, van den Belt-Dusebout AW, Gietema JA, et al. Risk and prognostic significance of metachronous contralateral testicular germ cell tumours. *Br J Cancer.* 2012 Oct 11;107(9):1637–1643.
11. Groll RJ, Warde P, Jewett MAS. A comprehensive systematic review of testicular germ cell tumor surveillance. *Crit Rev Oncol Hematol.* 2007 Dec;64(3):182–197.
12. Patrikidou A, Cazzaniga W, Berney D, et al. European association of urology guidelines on testicular cancer: 2023 update. *Eur Urol.* 2023 Sep;84(3):289–301.
13. Krege S, Beyer J, Souchon R, et al. European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European germ cell cancer consensus group (EGCCCG): Part I. *Eur Urol.* 2008 Mar;53(3):478–496.
14. Donohue JP. Evolution of retroperitoneal lymphadenectomy (RPLND) in the management of non-seminomatous testicular cancer (NSGCT). *Urol Oncol: Seminars Original Investigat.* 2003 Mar;21(2):129–132.
15. Sheinfeld J. Mapping studies and modified templates in nonseminomatous germ cell tumors. *Nat Clin Pract Urol.* 2007 Feb;4(2):60–61.
16. Donohue JP, Zachary JM, Maynard BR. Distribution of nodal metastases in nonseminomatous testis cancer. *J Urol.* 1982 Aug;128(2):315–320.
17. Capelouto CC, Clark PE, Ransil BJ, Loughlin KR. A review of scrotal violation in testicular cancer: is adjuvant local therapy necessary? *J Urol.* 1995 Mar;153(3 Pt 2): 981–985.
18. Gilligan T, Lin DW, Aggarwal R, et al. Testicular cancer, version 2.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw.* 2019 Dec;17(12): 1529–1554.
19. Beyer J, Collette L, Sauvé N, et al. Survival and new prognosticators in metastatic seminoma: results from the IGCCCG-update consortium. *J Clin Oncol.* 2021 May 10; 39(14):1553–1562.
20. Gillessen S, Sauvé N, Collette L, et al. Predicting outcomes in men with metastatic nonseminomatous germ cell tumors (NSGCT): results from the IGCCCG update consortium. *J Clin Oncol.* 2021 May 10;39(14):1563–1574.