Case Report

Metachronous Testicular Mixed Germ Cell Tumour and Gastric Marginal Zone Lymphoma: A Case Report with An Unusual Association

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DOI: 10.21276/APALM.3234

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Submitted: 23-Nov-2022
Final Revision: 25-Aug-2023
Acceptance: 01-Sep-2023
Publication: 01-Nov-2023

Abstract

Background

Second primary malignancies (SPMs), irrespective of location, are characterized by two or more distinct neoplasms in the same patient. Gastric marginal zone lymphoma of mucosa-associated lymphoid tissue (MZL) shows a higher risk of developing a second primary malignancy and exhibits inferior overall survival.

Case Report and Discussion

We report a case of a 55-year-old male who presented with a painless, hard, right testicular mass, which progressively grew over 3 months. He was diagnosed with gastric MZL on biopsy 4 years back and was treated by CHOP regime; 6 cycles. At the time of testicular mass diagnosis, the contrast-enhancing computed tomography imaging revealed metastasis involving both lungs and retroperitoneal lymph nodes with inferior vena cava thrombus. He underwent right inguinal orchidectomy and showed histopathological features of the mixed germ cell tumour composed of seminomatous and non-seminomatous components (embryonal and yolk sac tumours). This morphology was confirmed using a wide panel of immunohistochemistry markers (OCT3/4, PLAP, c-KIT, CD30, AFP, Glypican 3, β-HCG, and EMA). He received 4 cycles of the BEP (bleomycin, etoposide, and cisplatin) regime and was doing well at 13 months of follow-up.

Conclusion

The index case highlights an exceedingly rare association of gastric MZL with testicular mixed germ cell tumour with rare age presentation. Thus, surgeons, radiologists and pathologists should be aware of considering the differential of non-lymphoid malignancy at the distant site apart from the systemic spread of primary extranodal non-Hodgkin lymphoma. This will help in deciding and providing the appropriate treatment to the patient on time.

Keywords:

Second primary malignancy, mixed germ cell tumour, testis, marginal zone lymphoma, stomach

Introduction

Second primary malignancies (SPMs) are characterized as two or more types of malignancies in an individual, independent of one another in the same or different organs. In 1932, Warren and Gates defined this entity considering the following criteria: (i) each

of the tumours must be malignant and confirmed by histology; (ii) each must be geographically separate and distinct; and (iii) the probability of one being a metastasis of the other must be excluded.[1] SPM detected within 6 months of the primary malignancy is termed synchronous, and beyond 6 months as metachronous. The synchronous or metachronous association between germ cell tumour and non-Hodgkin Lymphoma (NHL) is not uncommon, but the existence of mixed germ cell tumour in a treated case of gastric marginal zone lymphoma of mucosa-associated lymphoid tissue (MZL) is an unusual and a rare presentation. To the best of our knowledge, no such association has been reported in the literature to date.

Case Report

A 55-year-old male presented with a painless and hard right testicular mass, which rapidly progressed over 3 months. The patient was diagnosed with non-Hodgkin Lymphoma by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and subsequently confirmed as gastric MZL on gastric biopsy 4 years back as per the records. The bone marrow biopsy was free of lymphoma. He received 6 cycles of the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Post 2 cycles of therapy, he complained of cough and mucoid expectoration. The high-resolution computed tomography (HRCT) showed bilateral lung nodules with suspicion of infection versus lymphomatous infiltration. All viral markers were negative on serology. A transbronchial lung biopsy revealed features of tuberculosis (acid-fast bacilli were positive on Ziehl-Neelsen stain), for which he received anti-tuberculous therapy (ATT) and after 6 months was considered cured. Presently, the patient presented with a testicular mass with strong clinical suspicion of primary malignancy. The serum level of alpha-fetoprotein (AFP) was 251 ng/mL (reference range [RR], 10 to 20 ng/mL), lactate dehydrogenase (LDH) 1032 U/L; (RR; 140 to 280U/L) and β-HCG 2150 mIU/mL. The contrast-enhanced computed tomography (CECT) imaging revealed multiple nodules in both lungs, a conglomerate of lymph nodes in the retroperitoneum consistent with metastases, and inferior vena cava (IVC) thrombosis. The patient underwent right inguinal orchidectomy after duly informed consent at a follow-up visit.

The right orchidectomy specimen measured 6.5x5.5x4.5cm with the attached spermatic cord of 5cm in length. The cut surface revealed a circumscribed greyish-white and firm tumour mass measuring 5.5x5.2x4cm, occupying almost the whole testis with a thin rim of normal parenchyma at the periphery, abutting the tunica albuginea and epididymis (Figure 1A). Focal areas of necrosis and haemorrhage were noted, and the spermatic cord resection margin grossly appeared to be free of tumour. Microscopically, the tumour was partially circumscribed and showed varied morphology. It was composed of variable-sized nodules separated by fibrous septae. Most of these nodules showed an embryonal carcinoma (EC) component, seen in diffuse sheets having a high N:C ratio, round to oval vesicular nuclei, prominent single to multiple nucleoli, a moderate amount of clear to pale eosinophilic cytoplasm (Figure 1B) and brisk mitotic activity. Areas of necrosis and lymphovascular emboli were present. No intra-tubular embryonal carcinoma component was identified. Small clusters of syncytiotrophoblasts (Figure 1C) were also seen in some foci. Other areas revealed nodules with the yolk sac component, where tumour cells displayed reticular growth patterns and Schiller-Duval body formation (Figure 1D).

Also, a seminomatous component in diffuse sheets, cords, and trabeculae infiltrating the native seminiferous tubules was present (Figure 1E). Occasional foci of the intratubular growth pattern of seminoma and Germ cell neoplasia in-situ (GCNIS) component were found. The tumour was seen invading the tunica albuginea as well as epididymis. The spermatic cord resection margin also showed the presence of lymphovascular tumour emboli but no infiltration by tumour (Figure 1F). No teratomatous component was identified even after extensive sampling of the tumour.

The embryonal component (occupied 70 to 75% of the tumour), highlighted by CD30 (diffuse; membranous) (Figure 2A), PLAP

(variable; weak membranous), and OCT3/4 (variable; nuclear), contributed around 60-70% of the total tumour. The AFP (Figure 2B) and β-HCG immunostains highlighted yolk sac tumour and syncytiotrophoblasts components, respectively and occupied nearly 10% of each of the whole tumours. The seminomatous component (occupied <10% of the tumour) showed positivity for c-kit (membranous) (Figure 2C), OCT3/4 (nuclear), and PLAP (membranous) (Figure 2D). Intratubular seminoma was highlighted by both c-kit and PLAP immunostains. The GCNIS component was appreciated well on OCT3/4 immunostain but was also positive for PLAP. The EMA and Glypican 3 were non-contributory. Based on the morphology and immunohistochemistry findings, the diagnosis of a mixed germ cell tumour (embryonal carcinoma, yolk sac tumour and seminoma) was rendered.

For the present malignancy, the patient received 4 cycles of BEP (bleomycin, etoposide, and cisplatin) chemotherapy regime and is doing well at 13 months of follow-up. However, the metastatic sites were not sampled given advanced clinical presentation (stage III) and did not show any progression to date. The previous slides of the gastric biopsy were reviewed and confirmed the diagnosis of MZL on morphology and immunohistochemistry (IHC) (Figures 3A and 3B). Written informed consent was taken from the patient, and approval from the Institute's Ethics Committee was obtained.

Discussion

To verify such uncommon association, we did a thorough search in the PubMed database using the combination of key terms: [(MALToma) OR (Mucosa-associated lymphoid tissue lymphoma) OR (extranodal marginal zone lymphoma) OR (Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue)] AND [(mixed germ cell tumour) OR (seminoma) OR (embryonal carcinoma) OR (yolk sac tumour) OR (endodermal sinus tumour) OR (choriocarcinoma) OR (teratoma)]. Additionally, the reference column of all the retrieved articles was also looked at. Based on this search, such a relationship has never been mentioned in the English literature. We hereby report a 55-year-old male patient who, 4 years following therapy for stomach MZL, developed a mixed germ cell tumour in the testis.

The prevalence of SPMs is about 4.5%-11.7%, with the reported median time interval of 5.5 years (range, 1–16 years) between primary and secondary malignancy.[2] Considering the diagnostic cut-off, the index patient qualified for the metachronous category since the second malignancy (testicular mixed germ cell tumour) occurred four years after the treated gastric MZL (the primary tumour). Most of the studies detected a significant increase in the incidence of SPM among the diagnosed gastric MZL cases as compared to the general population.[3-6] However, a few previous studies were exceptions and showed no significant difference.[7,8] The common sites for SPM include the digestive system, respiratory system, head and neck, nodal and extranodal tissue, and others.[3,4] At the time of chemotherapy for the gastric MZL, he was also diagnosed with pulmonary tuberculosis, for which successful anti-tubercular treatment was given.

The pathogenesis behind the occurrence of SPM is still not understood. However, the contributing factors for the emergence of second primary cancers include (i) common risk factors between the cancers, including environmental exposures and genetic factors, or (ii) effects of treatment, particularly chemo- and radiotherapy for the first primaries.[9] Amiot et al on examining 175 cases of gastric MZL, found a significantly elevated risk of SPM in patients receiving immune/chemotherapy but not in patients treated with Helicobacter pylori eradication alone.[4] A similar finding was seen in a recent large population-based study on gastric MZL, where in addition to chemotherapy, radiotherapy (alone or in combination) also contributed as a risk factor.[3] The therapy received for primary malignancy causes immune suppression, proto-oncogene activation, and genetic mutation.[3,4] In the index case, the possibility of chemotherapy as the risk factor for the mixed germ cell tumour was kept.

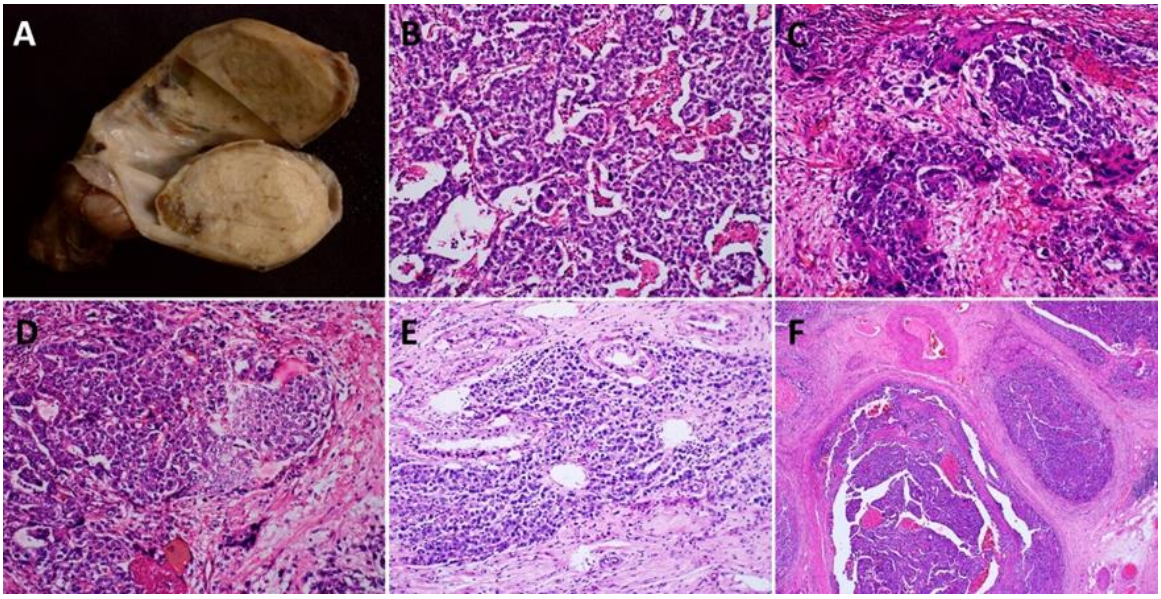

Figure 1: Mixed germ cell tumour. A) The cut surface reveals a well-circumscribed, greyish-white, firm, tumour that occupies almost the whole of the right testis leaving behind a thin rim of normal parenchyma at the periphery. The tumour is seen abutting the tunica albuginea and epididymis (scale bar = 3 cm). B) This tumour cell in solid sheets depicts a moderate degree of nuclear pleomorphism and prominent nucleoli indicating embryonal component (H&E, x200). C) Embryonal carcinoma with admixed syncytiotrophoblasts (H&E, x200). D) Yolk sac component (H&E, x200). E) Seminomatous component (H&E, x200). F) Vascular emboli in pampiniform plexus at spermatic cord margin (H&E, x40).

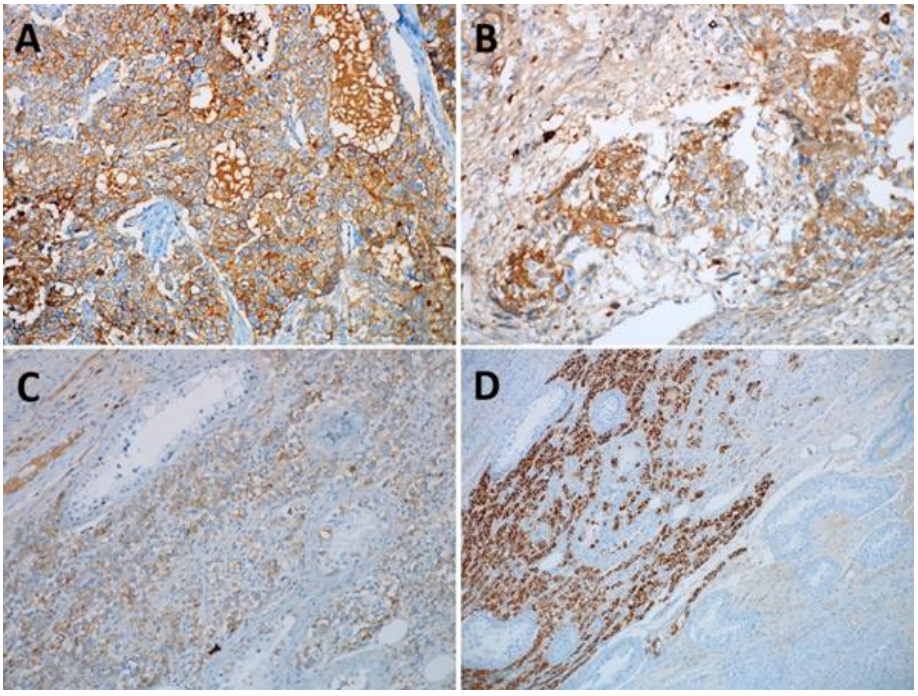

Figure 2: Mixed germ cell tumour. A) The embryonal component shows diffuse membranous immunoreactivity for CD30 immunostain (x200). B) Alpha-fetoprotein (AFP) demonstrates the yolk sac component (x200). C and D) The seminoma component is positive for c-Kit (C, membranous, x200) and placental alkaline phosphatase (D, cytoplasmic membrane; C, x200).

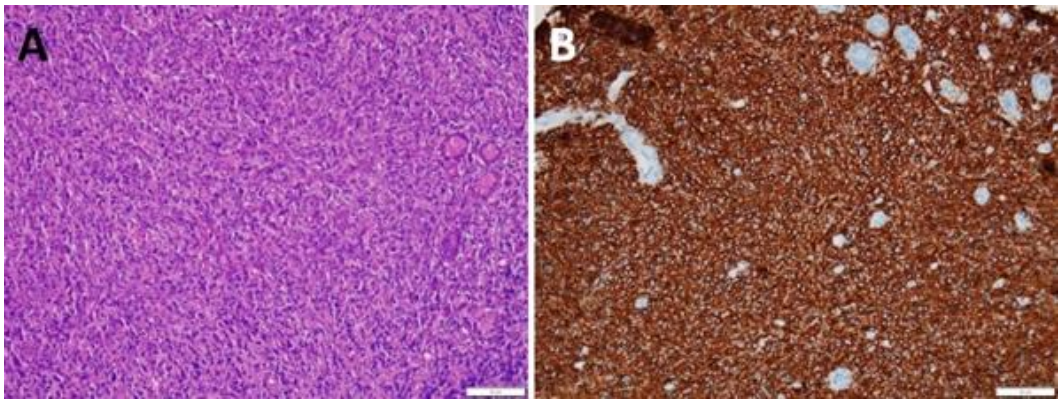

Figure 3: Gastric marginal zone mucosa-associated lymphoid tissue lymphoma. A) Diffuse infiltrate of neoplastic lymphoid cells within the gastric lamina propria, disrupting the mucosal glands and muscularis mucosae (H&E, x100). B) CD20 expression is diffuse and membranous (x100).

The gastric MZL has different clinical characteristics, is indolent in behaviour, slow to disseminate, and most achieve complete remission following proper treatment.[10,11] In contrast to gastric MZL, mixed germ cell tumours were commonly seen at younger ages (i.e., the average patient age at presentation is 30 years) with no predisposing factor which was the opposite in the index case (55 years of age).[12] The presence and proportion of EC, choriocarcinoma element, vascular invasion, and rete testis invasion correlate with a higher risk of metastasis and aggressive behaviour, which were present in our patient.[12] According to the National Comprehensive Cancer Network guideline, chemotherapy with bleomycin, etoposide and cisplatin (BEP) is suggested as the first-line treatment for advanced non-seminomatous germ cell tumour (NSGCT); however, a concern that therapy may facilitate premature ageing was raised in one of the studies.[13,14]

Second primary malignancies have a poor prognosis with a dramatic impact on the quality of life of cancer survivors. Older age (>50 age), shorter latency period, and chemotherapy act as negative factors for the survival of gastric MZL patients with SPM.[3] Currently, the knowledge about the appropriate management in such patients is very limited in the literature and is usually decided depending on the stage of the individual tumour. Mixed germ cell tumour behaves aggressively, so their early detection is beneficial to the patient in terms of treatment and survival.[12]

Conclusion

In conclusion, we describe a rare metachronous mixed germ cell tumour in a treated gastric MZL patient. When dealing with metastatic deposits in a stomach MZL patient who has been detected and treated, oncologists and pathologists need to be extra cautious because the likelihood of non-lymphoid cancers is on the higher side nowadays. In these circumstances, long-term mandatory routine follow-up and imaging are advised for the early discovery of SPMs, proper treatment, and a better prognosis.

Acknowledgements: None

Funding: None

Competing/Conflict of Interests: None

References

1. Warren S, Gates O. Multiple primary malignant tumours: A survey of the literature and statistical study. Am J Cancer. 1932;16:1358-1414.

2. Li F, Zhong WZ, Niu FY, et al. Multiple primary malignancies involving lung cancer. BMC Cancer. 2015; 15:696.
3. Yang Y, Yang Y, Yan S. Risk and survival of second primary malignancies following diagnosis of gastric mucosa-associated lymphoid tissue lymphomas: A population-based study. Curr Probl Cancer. 2021;45(6):100735.
4. Amiot A, Jooste V, Gagniere C, et al. Second primary malignancies in patients treated for gastric mucosa-associated lymphoid tissue lymphoma. Leuk Lymphoma. 2017 Sep;58(9):1-11.
5. Tajika M, Matsuo K, Ito H, et al. Risk of second malignancies in patients with gastric marginal zone lymphomas of mucosa associate lymphoid tissue (MALT). J Gastroenterol. 2014 May;49(5):843-52.
6. Zucca E, Pinotti G, Roggero E, et al. High incidence of other neoplasms in patients with low-grade gastric MALT lymphoma. Ann Oncol. 1995 Sep;6(7):726-8.
7. Montalbàn C, Castrillo JM, López-Abente G, et al. Other cancers in patients with gastric MALT lymphoma. Leuk Lymphoma. 1999 Mar;33(1-2):161-8.
8. Au WY, Gascoyne RD, Le N, et al. Incidence of second neoplasms in patients with MALT lymphoma: no increase in risk above the background population. Ann Oncol. 1999 Mar;10(3):317-21.
9. Vogt A, Schmid S, Heinimann K, et al. Multiple primary tumours: challenges and approaches, a review. ESMO Open. 2017 May 2;2(2):e000172.
10. Raderer M, Kiesewetter B, Ferreri AJ. Clinicopathologic characteristics and treatment of marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). CA: Cancer J. 2016;66(2):153–171.
11. Stathis A, Bertoni F, Zucca E. Treatment of gastric marginal zone lymphoma of MALT type. Expert Opin Pharmacother. 2010;11(13):2141–2152.
12. Morris LG, Sikora AG, Hayes RB, Patel SG, Ganly I. Anatomic sites at elevated risk of second primary cancer after an index head and neck cancer. Cancer Causes Control. 2011; 22:671-679.
13. Gilligan T, Lin DW, Aggarwal R, et al. Testicular Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019 Dec;17(12):1529-1554.
14. Zhang L, Hemminki O, Chen T, et al. Second cancers and causes of death in patients with testicular cancer in Sweden. PLoS One. 2019 Mar 28;14(3):e0214410.