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Testicular involvement in mantle cell lymphoma: An analysis of 16 patients.

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ABSTRACT

Mantle cell lymphoma (MCL) with testicular involvement is a rare presentation and only a few cases have been described in the literature. We present a case of MCL with testicular involvement and the first analysis of all previously reported cases assessing trends in immunohistochemical features, prognostic indicators, and survival. Our data suggest that among all MCL, testicular MCL is more likely to present with aggressive features: blastoid/pleomorphic morphology, high Ki-67 proliferative index, and CNS involvement. Testicular MCL is also associated with shorter overall survival.

1. Introduction

Primary testicular lymphoma (PTL) is a rare presentation of non-Hodgkin's lymphoma (NHL) comprising about 1–2 % of cases. In terms of testicular malignancies, PTL makes up less than 5 % of cases, but is the most common testicular malignancy in older men with a median age of onset of 67 years. The most common histological subtype of PTL is diffuse large B-cell lymphoma (DLBCL) which accounts for 80–98 % of cases [1]. Multimodality treatment is widely used to treat testicular DLBCL which includes orchiectomy, systemic chemotherapy, scrotal radiation, and prophylactic central nervous system (CNS) chemotherapy. Testicular DLBCL has a high propensity for CNS relapse, and despite appropriate prophylactic measures, the ten-year cumulative risk of CNS relapse remains as high as 21 %. The overall prognosis following CNS relapse is poor with a median survival of 10 months [2,3].

Mantle cell lymphoma (MCL) is a rare NHL subtype, with only a handful of reported cases presenting with involvement of the testes. Due to its low incidence, no clear standard of care has been established to treat MCL in the frontline. Intensive combination of cytotoxic drugs followed by consolidation with high dose chemotherapy and autologous stem cell transplantation has been widely adopted for young and fit patients [4]. The role of autologous stem cell transplant has been recently challenged by the TRIANGLE study that incorporated the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib within the induction and maintenance parts of the protocol [5]. Patients with relapsed or refractory MCL are offered salvage regimens which include BTK inhibitors and chimeric antigen receptor (CAR) T-cell therapy. Overall, MCL has a low risk of CNS relapse with an incidence of 4.1 % [6]. Blastoid morphology is recognized as a risk factor for CNS involvement and chemoprophylaxis is typically recommended in those cases. It remains unknown whether MCL with testicular involvement carries a higher risk for CNS involvement. Also unknown is whether testicular MCL is best treated by approaching it similarly to systemic MCL or testicular DLBCL or a combination of both. To our knowledge, there are only 13 cases of MCL with testicular involvement reported in the literature. To better understand this disease entity, we performed the most extensive review of all reported cases of MCL with testicular involvement and included an additional unpublished case diagnosed at our institution.

2. Methods

Collection and tabulation of testicular MCL cases: A systematic

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literature search was performed using PubMed and EMBASE databases and included studies published through August 2023 to identify papers discussing cases of testicular mantle cell lymphoma. Key words: "testicular, MCL, mantle cell lymphoma, lymphoma" were used. The selected studies included case reports of testicular MCL and systematic reviews in which cases of testicular MCL were included. A total of 13 cases of testicular MCL were identified. Upon review of data from the Surveillance, Epidemiology, and End Results Program (SEER), 7 additional instances of testicular MCL were documented. Two of these reported survival data and were included in our study in addition to the published cases. In total, data were tabulated from our case and 15 additional cases ($N = 16$) including 16 variables: CD5, cyclin D1, BCL2, CD20, BCL6, CD10, CD23, t(11;14), Ki-67 (higher or lower than 30 %), morphology, stage, CNS involvement, follow-up time, overall survival (OS), treatment, and chemotherapy regimen. Data were reported as percentage. Also reported is the total number of cases that had available data of each variable. To assess differences in OS, the Kaplan–Meier method was used.

3. Case presentation

A 71-year-old man with no significant medical history presented with a chief complaint of persistent hematuria. He also endorsed night sweats and a 25-pound weight loss over the past year. He smoked one pack of cigarettes per day for 40 years before quitting a decade ago. He noted a six-year history of daily alcohol use, averaging four drinks per day. He was independent in performing activities of daily living. Physical examination was notable for an enlarged and swollen left testicle, bilateral axillary lymphadenopathy, and a palpable spleen up to 7 cm below the costal margin. Complete blood count (CBC) was revealing of significant anemia (hemoglobin < 6 g/dL), thrombocytopenia (platelet count $< 60{,}000/\mu L$), and lymphocytosis (11,200 cells/μL) with mild neutropenia (1400 cells/μL). The patient's hematuria was worked up with cystoscopy which visualized bladder masses. A follow-up computerized tomography (CT) urogram showed a mucosal based bladder mass along with multiple enlarged pelvic lymph nodes. Following transurethral resection of bladder tumor, the lesion was confirmed on biopsy to be high grade papillary urothelial carcinoma. Subsequent positron emission tomography–computed tomography (PET-CT) demonstrated lymphadenopathy on both sides of the diaphragm including the bilateral axilla measuring up to 1.8 cm (max SUV of 1.9), and pelvic and inguinal chains measuring up to 2.1 cm (max SUV of 2.6); also seen was increased uptake in the left testis and nonspecific diffuse bone marrow metabolic activity. A scrotal ultrasound showed an enlarged and hyperemic left testis. A bone marrow aspiration and biopsy were performed and showed hypercellular marrow (85−90 %) with neoplastic lymphoid infiltrate composed mostly of small lymphocytes with occasional nuclear irregularities. The malignant clone was of classic MCL morphology without blastoid or pleomorphic features, expressing CD5, CD19, CD20, Pax-5, SOX11, and cyclin-D1, and lacking CD10 and CD23. The Ki-67 proliferation index was 10 %. Fluorescence in situ hybridization (FISH) analysis revealed translocation t(11;14)(q13;q32) confirming the diagnosis of MCL. The patient underwent a left orchiectomy with histology of the testis showing atypical lymphoid infiltrate expressing CD5, CD20, cyclin-D1, and Ki-67 (10 %) and lacking CD10, most consistent with MCL (Fig. 1). Magnetic resonance imaging of the brain and spine showed no evidence of lymphoma. Cerebrospinal fluid analysis was also negative for CNS involvement by MCL.

Treatment goals took into consideration the presence of two distinct, synchronous malignancies: bladder cancer and stage IV MCL. Following transurethral resection of bladder tumor, the patient was started on a regimen to treat MCL with bendamustine and rituximab (BR) with a goal of six cycles. Following two cycles, restaging CT scans showed resolution of lymphadenopathy in the axillary and pelvic lymph nodes, as well as decreased size of the spleen. However, a repeat cystoscopy showed recurrent bladder cancer throughout the bladder including the prostatic urethra. At this point, BR was held and cisplatin-based concurrent chemoradiation therapy was begun with a plan to consider surgery afterward. The patient completed a three-month course of radiation therapy; however, he was only able to receive four cycles of cisplatin before it was held due to persistent cytopenia. A repeat bone marrow biopsy and a PET-CT showed continuous remission from MCL at this time. The patient received prophylactic radiation to the contralateral testis. He was offered intrathecal methotrexate for CNS prophylaxis, but he declined. Given his excellent response of MCL to incomplete treatment with BR, the patient was restarted on BR and received two additional cycles, achieving four in total, before his course was again complicated by bladder cancer recurrence. Treatment of bladder cancer was started with four cycles of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC). Restaging imaging showed no evidence of metastasis. He subsequently had radical salvage cystectomy and prostatectomy that was complicated by intraabdominal abscess with fistulous connection to the small bowel. Arrangements were made for home hospice, and he passed away 19 months from his initial MCL diagnosis with no evidence of MCL relapse.

4. Results and discussion

Including data from our case, we tabulated data from a total of 16 cases of testicular MCL to assess prevalence of immunohistochemical features and prognostic indicators, as well as overall survival.

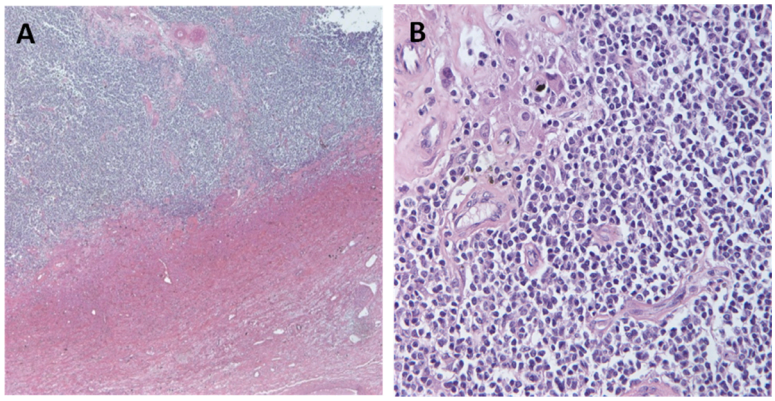

Fig. 1. Immunohistochemical stains of orchiectomy specimen. (A) H&E, 40X magnification showing a diffuse lymphoid infiltrate replacing seminiferous tubular architecture. There is peripheral coagulation necrosis at the interface with surrounding fibrous tissue. (B) H&E, 400X magnification. Higher power magnification showing monomorphic small to intermediate-sized neoplastic lymphocytes with no pleomorphism or blastoid features.

4.1. MCL with testicular involvement carries a higher prevalence of aggressive features

Notably, 73 % ($N = 8/11$) of the cases were MCLs with blastoid or pleomorphic morphology (Fig. 2). This is relatively higher than the overall prevalence rate of blastoid/pleomorphic morphology in MCL which is estimated to be around 10 % [7]. Blastoid/pleomorphic morphology of MCL is associated with poor OS and increased rates of CNS involvement when compared to all MCL (28 % vs 4 %) [8]. Among the ten cases that included data on CNS involvement, two reported dissemination to the CNS. One of these cases was reported as blastoid with the other being classic. CNS involvement in MCL is a poor prognostic indicator with a median survival of 3.7 months from diagnosis [6]. Another significant prognostic indicator in MCL is Ki-67 proliferative index. Ki-67 $\geq$ 30 % is regarded as a high proliferative index and is associated with shorter progression-free survival (PFS) and OS in MCL [9]. In our review, five of the thirteen cases reported Ki-67 expression. Of these, 80 % ($N = 4/5$) had a high proliferative index (Fig. 2). In terms of disease stage, 77 % ($N = 10/13$) of testicular MCLs were diagnosed with advanced stage (III or IV) (Fig. 2). There were only three reported cases of primary testicular MCL confined to the testis.

4.2. Aberrant expression of CD10 is encountered in testicular MCL

Notwithstanding the small number of cases, we observed a high prevalence of aberrant CD10 expression with over a third of cases reporting CD10 positivity ($N = 3/8$) (Fig. 2). This is a rare immunohistochemical finding that has been reported in a few case series. Given its rarity, the prevalence and clinical significance of aberrant CD10 expression is not yet well-defined; a study by Xu et al. found that CD10-expressing MCL was associated with shorter OS among subsets of MCL with more aggressive features (including high Ki-67 and blastoid/pleomorphic morphology) [10].

4.3. Testicular MCL is associated with decreased overall survival

We assessed trends in OS across all known cases of testicular MCL (Fig. 3). For comparison, MCL has a median OS of 4–5 years from time of diagnosis [11]. The median OS of 13 testicular MCL cases with available follow-up was 1.58 years which compares very unfavorably to the historic survival of MCL.

5. Conclusion

We present a rare case of MCL with testicular involvement and the first case series summarizing all known cases. Notably, our data suggest that testicular MCL is more likely to present with aggressive features including blastoid/pleomorphic morphology, high Ki-67 proliferative index, and CNS involvement. These features serve as poor prognostic indicators associated with shorter PFS and OS. Given the limited number of published studies, this review presents novel trends in data to suggest that testicular involvement is a negative prognostic indicator in MCL. Treatment modalities should merge systemic MCL treatment with approaches used in treating testicular DLBCL such as orchiectomy, radiation therapy, and CNS prophylaxis.

Disclosures

This research article includes a patient case identified at our institution that was described in accordance with strict ethical guidelines to ensure the confidentiality of the patient involved. All identifying information was anonymized to protect the patient's privacy. The manuscript does not include any experimentation on human subjects, and the reported treatments represent the standard of care for the reported cancers.

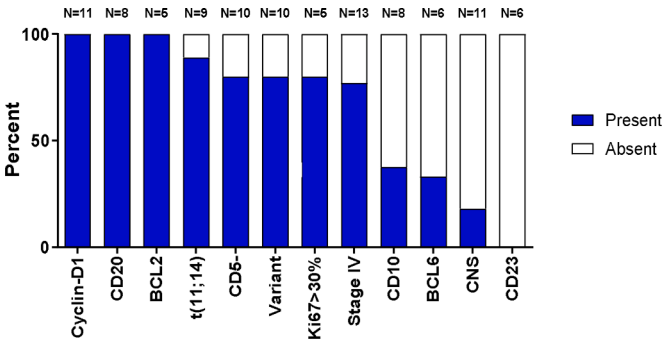

Fig. 2. Biological and clinical characteristics of testicular MCL cases. Y-axis demonstrates the percentage of cases reported to have presence of each characteristic (N = total number of cases that report either presence of absence of each characteristic).

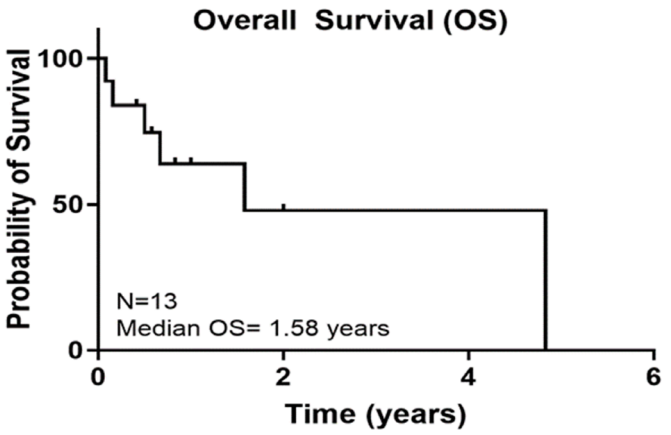

Fig. 3. Overall survival of testicular MCL cases. Probabilities of overall survival of 13 patients with MCL and testicular involvement using the Kaplan–Meier method.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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