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Primary Testicular Mantle Cell Lymphoma in a 23-Year-Old Man: A Case Report and Review of the Literature

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Case Report

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Abstract

Background: Primary testicular mantle cell lymphoma (PTMCL) is a very rare disease, mostly occurred in elderly men, usually diagnosed at an advanced stage. Mantle cell lymphoma (MCL) has a distinctive immunophenotype, positive for CD5 and cyclin D1, but negative for CD10 and CD23. The genetic hallmark of MCL is t(11;14)(q13;q32).

Case presentation: Here we reported a case of 23-year-old man who presented with a tumor in the testis. Surgical excision and pathological examination revealed the lesion was a primary testicular mantle cell lymphoma with aberrant expression of CD10 and loss of CD5.

Conclusion: This study reports the first case of PTMCL in a 23-year-old man with aberrant expression of CD10 and loss of CD5, summarizes PTMCL reported in PUBMED and found that CD5 might be an independent factor that influences not only the diagnosis but also the prognosis of MCL.

Background

Primary testicular non-Hodgkin's lymphoma (PTL) is a rare disease, which represents 1–2% of all non-Hodgkin's lymphoma and about 9% of testicular neoplasms. It is the most common testicular malignancy in men over 60 years of age. Most of PTLs (80–98%) are diffuse large B cell lymphoma (DLBCL) and rare subtypes include mantle cell lymphoma, NK/T-cell lymphoma, follicular lymphomas, peripheral T-cell lymphoma, extranodal marginal zone lymphoma and ALK^- large cell lymphoma[1–5]. Primary testicular mantle cell lymphoma (PTMCL) is very rare, only reported in sporadic case reports. Mantle cell lymphoma (MCL) is characterized by t(11;14)(q13;q32) rearrangement, which juxtaposes *CCND1* on chromosome 11q13 with *IGH* on chromosome 14q32. Morphologically, MCL is divided into classical and variant subtype, the latter consists of aggressive variants (blastoid and pleomorphic) and other variants (small-cell and marginal zone-like). MCL has a typical immunophenotype, positive for pan B-cell markers, CD5 and cyclinD1, but negative for CD10 and CD23[6]. However, few cases of MCL that express CD10 and lack of CD5 expression have been reported[7–9], which makes diagnosis more challenging. Here we reported a 23-year-old PTMCL with aberrant immunophenotype, reviewed the clinicopathological charateristics of PTMCL reported in PUBMED and investigated the clinical significance of unusual immunophenotype.

Case Presentation

A 23-year-old man accidentally found his left testicular enlargement in April 2018, without pain or any other symptoms and had a testicular biopsy. Post-biopsy pathological diagnosis considered B cell lymphoma. Immunohistochemical (IHC) staining showed CD20, BCL2, CD10 and MUM1 were positive CD3, CD5, BCL6, C-MYC, CyclinD1, SOX11 and CD30 were negative, supporting diffuse large B cell lymphoma, germinal center B cell subtype (DLBCL, GCB; HANS classification).

Soon he underwent a left orchiectomy, the neoplastic mass was measured 5.5cmX4.5cmX4cm with a soft, white to tan cut surface. Histologically, the mass was occupied by diffuse infiltrative medium to large-sized atypical lymphoid cells, which resembled bastoid cells with scant cytoplasm, irregular nuclear contours, dispersed chromatin, high N:C ratio, and a high mitotic rate. Residual seminiferous tubules were entrapped in lymphomatous tissue. In some areas a so-called 'starry sky' pattern was present. The paramount consideration for the differential diagnosis in a 23-year-old man include （1）lymphoblastic lymphoma (LBL); （2）Burkitt's lymphoma(BL)（3）DLBCL or high-grade B-cell lymphoma(HGBL). Based on the pre-operation pathological result and morphology, IHC staining with a panel of markers (CD20, CD3, CD5, CD10, MUM1, BCL2, BCL6, C-MYC, Ki67, TdT, CyclinD1) were performed. The result showed CD20, CD10 and BCL2 were positive, CD3, CD5, BCL6, C-MYC, MUM1 and TdT were negative, and Ki67 proliferation rate was up to 90% (Figure 1). CD20 expression and high Ki67 proliferation rate confirmed it an aggressive B-cell lymphoma. BL was excluded due to negative C-MYC and positive BCL2. Positive CD20 and negative TdT helped exclude the diagnosis of LBL. Unexpectedly, CyclinD1 was diffusely and strongly positive compared to the former biopsy sample, which really made us confused. Previous studies showed CyclinD1^{+}DLBCL was often considered to be a post-germinal center-type lymphoma without *CCND1* gene alteration, and negative for SOX11[10, 11]. As to our case, can it be a DLBCL (GCB) with aberrant expression of CyclinD1? Or is it possible a MCL? Although cases of CD5^{-} MCL have also been reported, until now such a young patient with MCL is still rather rare. That's why MCL was not considered as one of the differential diagnosis initially. While SOX11 is positive in >90% of MCL including CyclinD1^{-} and blastoid cases[6], we performed IHC staining with SOX11, and found SOX11 was positive (Figure 1). Despite negative CD5, both positive CyclinD1 and SOX11 indicated it was most likely MCL. To further clarify the diagnosis, *IGH/ CCND1* rearrangement was detected by fluorescence in situ hybridization (FISH) analysis, and 72.5% of the examined cells were positive (Figure 1). Therefore, the diagnosis of MCL was confirmed.

The general conditions of the patient were evaluated by positron emission tomography–CT (PET-CT) before and after surgery, which both revealed no superficial lymphadenopathy, no abnormal uptake within right testis and no evidence of metastatic disease. Biochemical assays for carcino-embryonic antigen, alpha-fetoprotein and beta-human chorionic gonadotrophin were within normal range. In addition, a bone marrow biopsy demonstrated normal cellularity with tri-lineage hematopoiesis and no evidence of lymphoma. These indicated that MCL was limited to the left testis, a definite diagnosis of PTMCL was thus made.

Discussion And Literature Review

The most unique of our case is the site and age, which make us easily ignore MCL. We investigated 58 cases of PTL diagnosed between January 2013 to December 2019 at Tianjin Medical University Cancer Institute & Hospital, there was only one case of PTMCL. Contemporaneously, there were 5761 cases of non-Hodgkin lymphoma (NHL) and 179 cases of MCL. The proportion of PTL is 1% (58/5761) of all NHL, which is consistent with that reported in previous studies. PTMCL is only 0.17‰ (1/5761)of all NHL,

0.6‰ of all MCL (1/179) and 1.7% of PTL (1/58) in our database. Moreover, we searched PTMCL reported in PUBMED between the year 1996 and 2020, only found seven cases, and summarized in Table 1 and 2. Table 1 show that PTMCLs occur in middle-aged to older men, ranging from 45 to 87.5 years old, the average age is 69.8 years. Most PTMCLs are unilateral, prefer to involve right testis and present with advanced stage, usually stage Ⅳ. Previous statistics show the spectrum of NHL subtype varies with age, the relative frequency of MCL is zero before 30 years of age[12]. These indicate our case is the youngest patient with PTMCL that have ever been reported.

What's more, the rare immunophenotype of negative CD5 and positive CD10 in MCL increases the diagnostic difficulties. Table 2 summarized the morphological characteristics and immunophenotype of PTMCL. Morphology vary from classical to other variants, but more often demonstrate pleomorphic variant. The IHC analysis often show $CD5^+$CyclinD1$^+$, and CD10 staining varies. Of these cases, there is only one occurred in an 80-year old man with pleomorphic pathology demonstrate $CD5^-CD10^+$[16]. MCL are usually $CD5^+CD10^-$, $CD5^-$MCL and $CD10^+$MCL accounts only for 6-11% and 3.7-6.7% of all MCL, respectively[7, 8, 14, 19-21]. Moreover, there is still no systematic research on $CD5^-CD10^+$MCL.
Here, we searched de novo MCL with $CD5^-CD10^+$ immunophenotype reported in PUBMED, only found 4 case reports and 2 cases included in related study, all confirmed by *CCND1* translocation (3 in lymph node, 1 in submandibular area, 1 in tonsil, 1 in peripheral blood and bone marrow) [14, 22-25]. These indicate MCL that show $CD5^-$ and $CD10^+$ immunophenotype are unusual patterns.

Thus, a 23-year-old man with testis lymphoma, with simultaneously existed aberrant immunophenotype of CD5 and CD10 make the diagnosis rather challenging. However, the morphology demonstrates the tumor consists of blastoid cells, reminding us of the differential diagnosis of the HGBL described in the 2017 revised WHO classification[6]. The most important differential diagnosis consist of LBL, BL, CyclinD1$^+$DLBCL, and HGBL. IHC and molecular genetic analysis are helpful. The expression of TdT assists in the diagnosis of LBL. BL is characterized by an MYC translocation with strong expression of C-MYC, and negative BCL2. CyclinD1$^+$DLBCL do not harbor *CCND1* translocation and lack SOX11 expression. The presence of *CCND1* translocation can also exclude HGBL. However, what's really puzzling is the inconsistent IHC staining of CyclinD1 and SOX11 in biopsy and orchiectomy sections. To explore the factors that result in the staining difference, we reviewed the biopsy sections and found that the biopsy sections were frozen before making paraffin sections. Frozen tissue often makes morphological features and IHC staining suboptimal, leading to misdiagnosis. As to our case, considering the patient's age, immunophenotype with negative CD5, CyclinD1 and SOX11 as well as positive CD10 excluded the diagnosis of MCL，resulting in misdiagnosis of the biopsy specimen. Therefore, every step in the process of making paraffin sections is vital to morphology, immunophenotype and molecular genetics of histological specimen, which are all indispensable to the correct diagnosis.

In addition, the clinicopathological features of $CD5^-$ and $CD10^+$ MCL have also been reported, but cohort study are less and controversial. Some supposed the clinicopathological features of $CD5^-$MCL was similar to that of $CD5^+$MCL[19]. Some reported that all $CD5^-$MCL cases showed classical morphology

with a low Ki67 proliferation rate (<5%), and appeared to have a better prognosis and overall survival than classic MCL[20]. However, only 12 cases with follow-up data were involved in these previous studies. Recently, 58 cases of $CD5^-$MCL were involved in a relatively comprehensive study, and no significant difference was found between the morphology of $CD5^-$ and $CD5^+$MCL, while patients with $CD5^-$MCL showed a significantly longer progression-free survival and a tendency for longer overall survival than $CD5^+$MCL patients. Furthermore, high Ki67 proliferation rate and clinical stage were not associated with prognosis in $CD5^-$MCL. CD5 was thought to be an independent prognostic factor in patients with MCL[8]. CD10 is usually expressed by centrocytes and centroblasts in the germinal center (GC) and by their neoplastic counterparts, rare cases of MCL have been reported to express CD10. However, it is still controversial whether CD10 expression in MCL is related to GC. Some estimated CD10 expression in MCL did not reflect derivation from GC B cells[14]. Others suggested CD10 expression was related to a distinct GC signature in MCL[26]. Moreover, $CD10^+$MCL showed a female predominance, more often had a diffuse growth pattern, and was more frequently associated with variant morphology. But there was no significant difference in the prognosis between $CD10^+$ and $CD10^-$MCL[7, 14, 21, 26]. In conclusion, CD5 might be an independent prognostic factor of MCL and $CD10^+$MCL might have some special pathological features.

Our patient underwent localized radiotherapy and six cycles of R-DHAP chemotherapy. Currently, he continues to be healthy with no apparent manifestation of the disease by PET-CT. These indicate that PTMCL confined to the testis with loss of CD5 seems to have a better prognosis. However, cases of $CD5^-$ and $CD10^+$ MCL involved in previous studies are limited, further study is still needed for exploring the biological and clinicopathological significance of these rare cases.

To our knowledge, this is the youngest PTMCL so far, and aberrant CD5 and CD10 expression aggravates its rarity. Whether $CD5^-$ and $CD10^+$MCL is a new entity still needs a larger cohort with close follow-up, which might provide certain basis for stratified treatment of MCL in the future.

Conclusions

In summary, we have reported the first case of PTMCL in a 23-year-old man with aberrant expression of CD10 and loss of CD5. Integration of morphology, immunophenotype and molecular genetics should be taken into account in order to make precise diagnosis of a young man with MCL.

Abbreviations

PTMCL: Primary testicular mantle cell lymphoma

MCL: mantle cell lymphoma

HE: Hematoxylin Eosin

NHL: non-Hodgkin lymphoma

PTL: Primary testicular non-Hodgkin's lymphoma

DLBCL: diffuse large B cell lymphoma

IHC: Immunohistochemical staining

GCB: germinal center B cell

HGBL: high-grade B-cell lymphoma

LBL: lymphoblastic lymphoma

BL: Burkitt's lymphoma

FISH: fluorescence in situ hybridization analysis

PET-CT: positron emission tomography–CT

Declarations

Availability of data and materials

ALL data generated or analyzed during this study are available from the corresponding author on reasonable request.

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Contributions

All authors contributed to the writing of the manuscript and read and approved the final manuscript

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Ethics declarations

Ethics approval and consent to participate

The research was prospectively reviewed and approved by Tianjin Medical University Cancer Institute and Hospital,

Consent for publication

ALL authors consent to the publication of manuscript in Diagnostic Pathology.

Competing interests

All authors declare no conflict of interest.

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Tables

Table 1 Clinical features of PTMCL.

References	Age（year）	Site	Stage
Iwuanyanwu et al[13]	53	right	NM
Zanetto et al[14]	75	NM	□
Kemmerling et al[15]	87.5	left	□
Kemmerling et al[15]	79.1	right	□
Epstein et al[16]	80	left	□EA
Licci et al[17]	45	right	NM
Andhavarapu et al[18]	69	right	□

NM: Not mentioned in the references.

Table 2. Morphological and immunophenotypic features of PTMCL.

References	Morphology	Immunophenotype
Iwuanyanwu et al[13]	classical	CyclinD1^{+}CD5/CD10^{NM}
Zanetto et al[14]	classical	CD5^{+}CyclinD1^{+}CD10^{+}
Kemmerling et al[15]	pleomorphic	CD5^{+}CyclinD1^{+}CD10^{NM}
Kemmerling et al[15]	pleomorphic	CD5^{+}CyclinD1^{+}CD10^{NM}
Epstein et al[16]	pleomorphic	CD5^{-}CyclinD1^{+}CD10^{+}
Licci et al[17]	blastoid	CD5^{+}CyclinD1^{+}CD10^{-}
Andhavarapu et al[18]	Combined with DLBCL	CD5^{+}CyclinD1^{+}CD10^{-}

^{NM}: Not mentioned in the references, DLBCL: diffuse large B cell lymphoma.

Figures

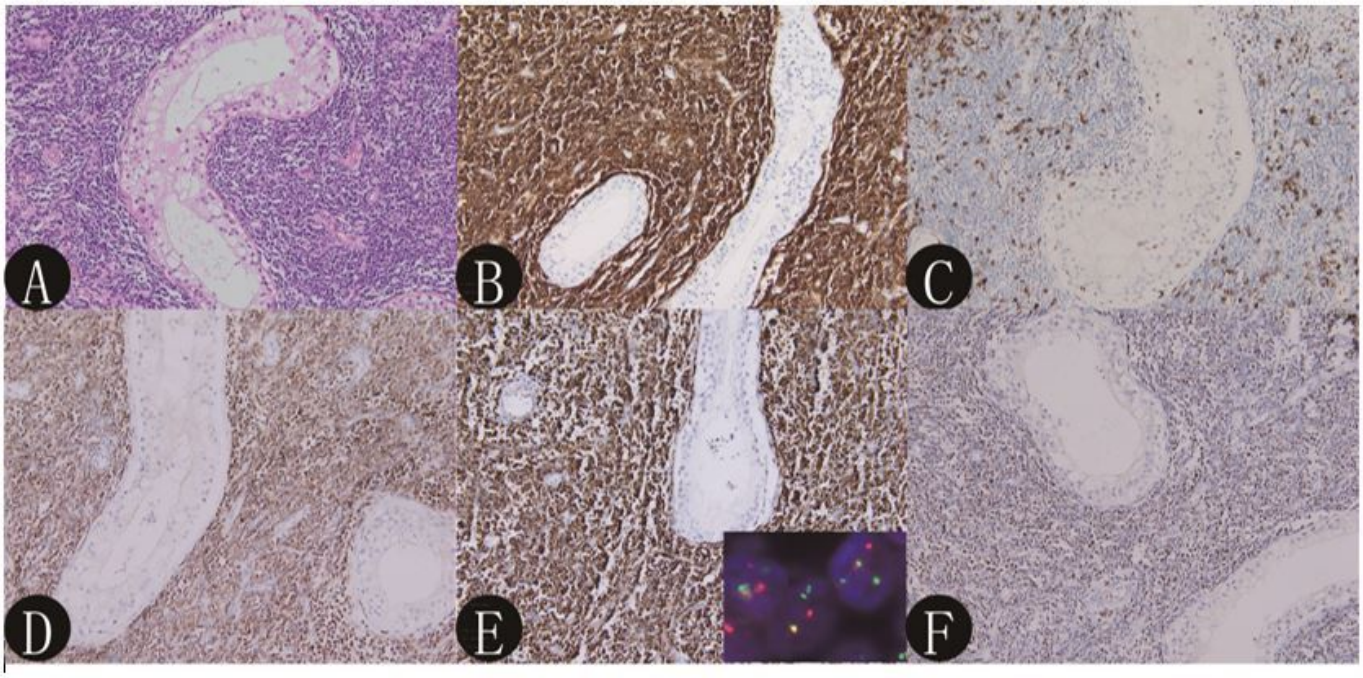

Figure 1

Histopathological features of primary testicular MCL. A. Hematoxylin and Eosin Staining, showing medium-large atypical lymphoid cells. B. IHC staining of CD20. C. IHC staining of CD5. D. IHC staining of

CD10. E. IHC staining of CyclinD1 (Inset: Fluorescence In Situ Hybridization evaluation of CCND1/IgH). F. IHC staining of SOX11.

Supplementary Files

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- SupplementalTable1.docx