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Case Report

Review of Cyclin D1 and T (11;14) Negative Mantle Cell Lymphoma and Report of a New Case

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Abstract

Mantle Cell Lymphoma (MCL) represents a sub-type of Non-Hodgkin's Lymphoma (NHL) with a heterogeneous clinical course. Cyclin D1 overexpression is considered essential in the pathogenesis of Mantle Cell Lymphoma (MCL) and hall-marked by IGH-mediated t(11;14)(q13;q32) resulting in deregulation of CCND1. Extremely rarely CCND1-negative MCL with a poor clinical outcome exists and thus challenges the idea that cyclin D1 over expression is essential in the pathogenesis of MCL. One study suggested 100% of Cyclin D1 negative MCL cases were SOX11 positive and SOX11 has been shown to be a good marker to identify MCL cases with poor outcome. Despite the improvement in response durations with current chemo-immunotherapies, most MCL patients usually relapse. Some targeted therapies Bruton Tyrosine Kinase Inhibitors (BTKI) are approved in the relapsed setting and few of them are undergoing clinical trials in combination with standard frontline therapy. Hence there is an urgent need for finding the appropriate regimen that combines BTKIs like ibrutinib and other drugs to prolong response duration as well as there are an unmet need for the development of other novel agents for ibrutinib refractory disease.

Keywords: Mantel cell lymphoma; Cyclin d1 negative; t(11;14) negative; Ibrutinib; Venetoclax; CCND1; SOX11

Introduction

Mantle Cell Lymphoma (MCL) is a subtype of B-cell Non-Hodgkin's Lymphoma (NHL) with a usually aggressive and heterogeneous, clinical course. MCL comprises 3-10% of adult NHL in western countries [1,2]. Cyclin D1 overexpression is considered essential in the pathogenesis of MCL as a result the existence of cyclin D1-negative MCL has been controversial and it was difficult to substantiate [3]. Mantle Cell Lymphoma (MCL) is hall-marked by IGH-mediated t(11;14)(q13;q32) resulting in deregulation of CCND1. This gene encodes cyclin D1 that together with cyclin D2 and D3 plays a key role in progression of cell cycle. Given that cyclin D1 is not expressed by normal B lymphocytes, its aberrant expression in lymphoma has a diagnostic value [4]. It is an extremely rare event to diagnose MCL case who is negative for negative for both Cyclin D1 and t(11;14) as I am describing a case here and reviewed the literature.

Search strategy

A review was conducted from databases PubMed, Google scholar and Medline, searching for studies published between 1990 and 2020 with keywords: 'mantle cell`, 'lymphoma`, 't(11;14)', 'cyclin d1', 'cyclin d2/d3', 'ccnd1', 'gene rearrangement', 'SOX11', 'non-hodgkin', 'targeted treatment', 'ibrutinib`, 'venetoclax` and 'CAR-T' appearing in the abstracts. Various combinations were used to search for all databases.

Inclusion criteria

Prospective, comparative, exploratory, longitudinal or cross-sectional studies were analysed. Papers focusing on lymphoma patients with chemotherapy, chemo-immunotherapy, immunotherapy, targeted therapy, CAR-T therapy were included.

Case Presentation

70 yr old gentleman presented with 2 days history of generalised abdominal pain and vomiting to hospital emergency department. Physical examination revealed a large abdominal mass. CT scan of chest, abdomen and pelvis confirmed widespread lymphadenopathy including large nodal mass in superior mediastinum, para-aortic, retroperitoneal, with extensive abdominal and pelvic lymph nodes. His initial blood test reveal Hemoglobin 129 g/L, WBC 19 x10^9/L, neutrophils 10 x10^9/L and lymphocytes 8 x10^9/L and Platelet count of 275 x10^9/L. Lactate Dehydrogenase (LDH) was elevated at 349 u/L. HIV, Hepatitis B & C serology negative. Echocardiogram showed Normal Left Ventricular Function. Peripheral blood film examination suggested neoplastic looking lymphoid cells suggestive of Lymphoproliferative Disorder (LPD) and a subsequent immunophenotyping on the peripheral blood sample was consistent with clonal B cell, likely MCL. A core biopsy from a neck lymph node was obtained and immunohistochemistry of the biopsy sample was consistent with a diagnosis of MCL (Table 1). Fluorescence In Situ Hybridization (FISH) studies showed the lymphoma cell were negative for Cyclin D1 as well t(11;14) but neoplastic cell were positive for SOX11 (Table 1). The tumor cells showed high proliferation rate with Ki-67 of 70%. He has started his treatment as per Nordic Protocol [5].

Discussion

Almost all cases MCL carry the translocation t(11;14)(q13;q32), which leads to the juxtaposition of CCND1/CYCLIND1 gene to the

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heavy chain (IGH) region of immunoglobulin, resulting in cyclin D1 over expression. [6-8]. The presence of cyclin D1 negative MCL has been a controversial scenario but it is now substantiated by gene expression profiling [9]. MCL shows heterogeneous clinical characteristics, some show very indolent course and some behave very aggressively and later group most commonly treated with combination chemo-immunotherapy at diagnosis because of the poor prognosis. MCL with indolent presentations can defer initial therapy and continue active surveillance initially without adverse impact on survival [10,11]. World Health Organization updated classification mentioned 2 subtypes-classical MCL and leukemic variant MCL, each with different molecular features and clinical presentations [12-14].

The incidence of MCL in Asian countries is lower in compare to western countries and Asian MCL patients have lower median age at presentation [15]. Overall Caucasians have a higher incidence of MCL in compare to other ethnicities [16]. MCL currently an incurable condition with low long-term survival rate. Specific risk factors for MCL have not been identified however, association with Borrelia infection [17] and familial [18] have been reported. A link with autoimmune disease and increased incidence of MCL has been observed [19].

Our case has identified a new variant of MCL, which we designated as cyclin D1-negative MCL as previously shown in one study [20]. Our case also lacked the characteristic IGH/CCND1 fusion by FISH analysis and was negative for cyclin D1 protein expression by immunostains. However, our case exhibited the characteristic pathologic features of MCL and shared the characteristic MCL gene expression profile by microarray analysis. Therefore, this case was regarded as cyclin D1-negative MCL. The existence of such case challenges the idea that cyclin D1 over-expression is essential in the pathogenesis of MCL. Cytogenetic assessment with Fluorescent In Situ Hybridization (FISH) testing showed translocation t(11;14) (q13; q32) in the majority (90%) of MCL cases [21]. However, rare case of MCL like our case may present with Cyclin D1 negativity and negative for t (11;14). It is mandatory to obtain the Ki-67% of MCL cells from the involved non-marrow tissue biopsies for prognostic purpose [22]. Biopsies may show presence of cyclin D1+ cells in the inner mantle zone of lymphoid follicles (termed as in situ mantle cell neoplasia) which should not lead to a diagnosis of MCL [23]. These patients have a very low risk of progression to overt MCL and should not get systemic therapy.

MCL is characterized by small to medium-sized lymphoid cells with CD5+, CD10-, CD23- phenotype as was found in our patient [24]. CCND1 rearrangement and/or CCND1 immunostaining is a hallmark of diagnosis. However, it has been known that CCND1-negative MCL with a poor clinical outcome exists. Recently, SOX11 has been shown to be a good marker to identify such cases with poor outcome [25], however this association has been questioned [26]. One study showed that CCND2 gene rearrangement is frequently found (22 of 40 CCND1-negative MCL cases, 55%) and is a molecular basis for CCND1-negative SOX11-positive MCL [27]. Further study on molecular mechanisms of CCND1-negative CCND2-negative SOX 11-positive MCL with a poor clinical outcome to provide appropriate therapy is needed. Controversies exist on SOX11 staining and clinical outcome of MCL, hence further study exploring other diagnostic markers and molecular basis is warranted.

CCND1-negative MCL is extremely rare and the underlying pathogenic mechanism for this type of MCL is not well understood at present time. Careful morphologic examination is critical in order to suspect a diagnosis of cyclin D1-negative MCL as this will lead to further analysis including FISH study. One study suggested 100% of Cyclin D1 negative MCL cases were SOX11 positive [28] and another study suggested SOX11 positivity may indicate indolent course of MCL with favourable prognosis [25]. Diagnosis of Cyclin D1 negative MCL may be challenging, particularly since some cases are weakly positive for. In our patient morphologic features and CD5 positivity leads to further investigations and subsequent diagnosis of MCL. In this type of cases, positive immunostains for cyclin D2 or D3 may be supportive of this diagnosis. It is critical examine carefully to rule out other types of low grade B-cell NHL as many such NHL may also be positive for cyclin D2 or D3. A panel of immunostains based on the MCL antigenic signature as well as gene expression profile, can help to reach this diagnosis.

Although there is no universally standard of care for MCL, aggressive chemo-immunotherapy regimens that contain rituximab and cytarabine followed by Autologous Stem Cell Transplantation (ASCT) consolidation and rituximab maintenance is commonly used approach in young fit patients [29]. For older and unfit patients chemo-immunotherapy followed by rituximab maintenance, is most commonly used [30]. Lenalidomide and rituximab combination is also shown to be effective for this frail MCL patient [31,32].

Unfortunately most patients usually relapse despite the improvement in response durations with current therapies. Few targeted therapies are approved in the relapsed setting and few of them are undergoing clinical trials in combination with standard frontline therapy. Bruton Tyrosine Kinase (BTK) inhibitor such as ibrutinib has shown an impressive result in relapse/refractory MCL trials [33,34]. Similarly other BTKIs has also shown to be effective in this setting. [35,36]. Another group of targeting agent Bcl-2 antagonist such as venetoclax has also been tried in the relapse MCL clinical trial with excellent result [37]. In a phase 2 clinical trial Ibrutinib plus Venetoclax were given as treatment of relapsed MCL. Patients were 47 to 81 years of age, and the number of previous treatments ranged from none to six. Half the patients had aberrations of TP53,

Table 1: Lymph node Immunohistochemistry and FISH results.

Microscopic finding: This single core of lymphoid tissue shows effacement of the normal architectural by a diffuse population of predominantly medium sized lymphoid cells, which have irregular nuclear contours and only occasional small nucleoli. Numerous macrophages containing apoptotic debris are present.
Immunohistochemistry: The neoplastic lymphoid cells express CD79a, CD20, BCL2, MUM1 (weak), CD5 (majority of cells) and SOX11. They do not express BCL6, CD10, CD30, cyclin D1, CD23 or TdT. EBER(ISH) is negative. The MIB1 proliferative index is around 70%. **Comment:** The appearances are those of a B-cell non-Hodgkin lymphoma, the immunophenotype of which is that of cyclin D1-negative mantle cell lymphoma. Although the morphology is not typical of blastoid mantle cell lymphoma, the high proliferative index suggests this lymphoma may behave in a similar way to blastoid mantle cell lymphoma.
FISH: MYC not rearranged; 2-3 copies of MYC (8q24), BCL6 not rearranged; 2-3 copies of BCL6 (3q27), IGH-BCL2 negative, IGH-CCND1 negative. **Comment:** The absence of IGH-CCND1 translocation does not exclude a diagnosis of Mantle Cell Lymphoma, especially as a fusion probe is used, so other translocations involving Cyclin D1/D2/D3 would not be demonstrated.

and 75% had a high-risk prognostic score. The complete response rate according to computed tomography at week 16 was 42%, which was higher than the historical result of 9% at this time point with ibrutinib monotherapy (P<0.001). The rate of complete response as assessed by positron-emission tomography was 62% at week 16 and 71% overall. MRD clearance was confirmed by flow cytometry in 67% of the patients and by ASO-PCR in 38%. In a time-to-event analysis, 78% of the patients with a response were estimated to have an ongoing response at 15 months [38].

Conclusion

These targeted novel drugs have changed treatment options dramatically for relapsed MCL. These agents have shown significant efficacy, durable response and safety profile either as single agent or as combinations in various age groups and disease subsets of MCL [34,39]. Approval of ibrutinib for relapsed MCL has changed the treatment algorithm. However, there is a potential problem with ibrutinib discontinuation as patient does not like to continue long term treatment [40]. Another potential challenge is the management of ibrutinib-refractory disease and development of ibrutinib resistance and prognosis is poor after progression on ibrutinib [41,42]. Hence there is a need for finding the appropriate regimen that combines ibrutinib and other drugs to prolong response duration as well as there are an unmet need for the development of other novel agents for ibrutinib refractory disease. Venetoclax is effective in MCL even among patients who have progressed on BTK inhibitors [43]. The future treatment for MCL therapy will need to incorporate drugs based on risk-stratification, non-chemotherapeutic approaches and Chimeric Antigen Receptor T-cell therapy (CAR-T).

Microscopic finding

This single core of lymphoid tissue shows effacement of the normal architectural by a diffuse population of predominantly medium sized lymphoid cells, which have irregular nuclear contours and only occasional small nucleoli. Numerous macrophages containing apoptotic debris are present.

Immunohistochemistry: The neoplastic lymphoid cells express CD79a, CD20, BCL2, MUM1 (weak), CD5 (majority of cells) and SOX11. They do not express BCL6, CD10, CD30, cyclin D1, CD23 or TdT. EBER(ISH) is negative. The MIB1 proliferative index is around 70%.

Comment: The appearances are those of a B-cell non-Hodgkin lymphoma, the immunophenotype of which is that of cyclin D1-negative mantle cell lymphoma. Although the morphology is not typical of blastoid mantle cell lymphoma, the high proliferative index suggests this lymphoma may behave in a similar way to blastoid mantle cell lymphoma.

FISH

MYC not rearranged; 2-3 copies of MYC (8q24), BCL6 not rearranged; 2-3 copies of BCL6 (3q27), IGH-BCL2 negative, IGH-CCND1 negative.

Comment: The absence of IGH-CCND1 translocation does not exclude a diagnosis of Mantle Cell Lymphoma, especially as a fusion probe is used, so other translocations involving Cyclin D1/D2/D3 would not be demonstrated.

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Authors' Contribution

MSI designed the manuscript, searched the literature, written the manuscript, participated in the diagnosis and treatment of the patient and MTK participated in the diagnosis and treatment of the patient. Both authors agreed on the final contents of the manuscript.

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