**CASE REPORT**

**“In situ” mantle cell lymphoma associated with hyaline-vascular Castleman disease**

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Abstract

Mantle cell lymphoma (MCL) is a very rare non-Hodgkin B-cell lymphoma, with an aggressive clinical course and poor response to conventional therapy. Few cases of “in situ” MCL were reported in the last years. We present the case of a 31-year-old woman with a unique cervical lymphadenopathy. The morphologic findings are of hyaline-vascular Castleman disease (HV-CD). Immunohistochemical stain for cyclin D1 detects scattered cyclin D1+ cells within the mantle zones of few reactive-appearing lymphoid follicles, corresponding to the definition of “in situ” MCL. We also performed cyclin D1 in other 27 cases of CD (13 HV-CD and 14 plasma-cell CD) but the reported case was the only who associated “in situ” MCL. An adequate immunohistochemical panel, including a marker for cyclin D1, is required to differentiate this neoplasm from follicular hyperplasia. From our knowledge, this is the first reported case of “in situ” MCL associated with HV-CD.

**Keywords:** “in situ” mantle cell lymphoma, cyclin D1, hyaline-vascular Castleman disease.

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**Introduction**

Mantle cell lymphoma (MCL) is an uncommon type of B-cell lymphoma (5% to 10% of non-Hodgkin lymphomas). MCL is more frequent in elderly males, who are diagnosed in an advanced stage of the disease with frequent extranodal involvement (e.g., bone marrow, gastrointestinal tract – lymphomatoid polyposis, or Waldeyer ring). MCL has an adverse clinical course characterized by poor response to conventional chemotherapy and a median overall survival (OS) of three to five years [1–3]. Histopathological, the malignant cell in MCL is a small/medium-sized elivated cell (“centrocyte-like”).

The growth pattern is most often diffuse (80%); more infrequently, MCL presents a nodular (about 15%) or a “mantle zone” growth pattern. If the three growth patterns described in MCL influence overall survival remain controversially. The neoplastic B-cells in MCL express genes normally detected in naive B-cells, such as IgD and the T-cell associated antigen CD5, who suggest the origin from naive, pre-germinal center B-cells [4]. A prominent marker for MCL is the translocation (11; 14)(q13; q32), resulting in a rearrangement of the gene loci for immunoglobulin heavy chain (IgH) on chromosome 14 and cyclin D1 (CCND1) on chromosome 11. This leads to a constitutional overexpression of CCND1 due to the IgH enhancer sequence located in front of CCND1 [5]. Cyclin D1 overexpression (readily detectable by immunohistochemical analysis) is a highly specific molecular marker of MCL because it is expressed in virtually all of these tumors [6]. Recently, several reports have described cases of “in situ” MCL in which scattered cyclin D1+ cells were present within the mantle zones of reactive-appearing lymphoid follicles [7, 8]. Castleman’s disease (CD) is a benign lymphoid disorder first described by Dr. Benjamin Castleman in 1956. Microscopically, two distinct histological patterns have been described: (a) the hyaline vascular (HV), which comprises 90% of CD and mostly presents as a solitary lymphadenopathy, and (b) plasma cell (PC) type, mostly presents as multicentric disease, and sometime associated with Kaposi’s sarcoma herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), infection. We present a case of “in situ” MCL with a hyaline vascular Castleman disease (HV-CD)-like morphological findings.

**Patient, Methods and Results**

The patient was a 31-year-old woman presenting with a unique cervical lymphadenopathy.
Morphological findings

More than 80% of the lymph node biopsy section showed findings consistent with hyaline-vascular Castleman disease (HV-CD): follicular hyperplasia with atrophic germinal centers, hyaline vascular lesions, numerous high-endothelial venules in the paracortical areas (Figures 1 and 2); some follicle contain more than one germinal centre (“twinning”) (Figure 3).

Immunohistochemical findings

As several B-cell lymphomas, including MCL, may present a HV-CD aspect, manual immunohistochemical analysis for cyclin D1 (clone P2D11E11, Leica, UK, dilution 1:50) was carried out on paraffin-wax sections using peroxidase conjugated EnVisionTM Dual Link reagent (DAKO, Denmark). Scattered cyclin D1+ cells were detected within the mantle zones of three reactive-appearing lymphoid follicles (Figures 4 and 5). We performed immunostain for CD20 (clone L26, Leica, UK, dilution 1:50) and for CD5 (clone 4C7, Leica, UK, dilution 1:50), but we do not identify the corresponding cells cyclin D1 positive cells. We also performed cyclin D1 in other 27 cases of CD (13 HV-CD and 14 PC-CD) but the reported case was the only who associated “in situ” MCL.

Figure 1 – Hypoplastic germinal center, “onion skin” like disposition of mantle cells, high endothelial venules hyperplasia (HE stain, ob. 10×).

Figure 2 – Germinal centers hypoplasia, numerous high endothelial venules in the paracortical areas (HE stain, ob. 4×).

Figure 3 – “Twinning” lymphoid follicle (HE stain, ob. 4×).

Figure 4 – (A) and (B): Scattered cyclin D1 positive cells in the mantle zone, near the germinal center and within the periphery of the germinal center (cyclin D1 stain, ob. 20×).
**Discussion**

The MCL is an aggressive lymphoid neoplasm with a rapid clinical evolution, short responses to therapy, frequent relapses, and a median survival of three to four years [4]. MCL is characterized by enhanced cell proliferation, impaired cell death pathways and reduced response to DNA damaging agents, and is therefore difficult to treat [10]. Patients with MCL are usually treated aggressively, with intensive chemotherapy regimens, including hematopoietic stem cell transplantation [11]. The most important marker for MCL is the translocation (11;14)(q13; q32), resulting in a rearrangement of the gene loci for immunoglobulin heavy chain (IGH) on chromosome 14 and cyclin D1 (CCND1) on chromosome 11 [5]. However, some cases of t(11;14) positive CLL [12] and t(11;14) negative MCL have been reported [13].

The case reported in our study represents an extremely rare form of MCL, which may be classified in the group of “in situ” MCL, associated with HV-CD. Diagnosis in this case of “in situ” MCL is difficult because the lymph node architecture is preserved and the findings of HV-CD are prominent.

As cyclin D1 is not found in appreciable amounts in reactive lymphadenitis (only nuclei of reactive macrophages and stromal cells are consistently positive), this marker is very important in the diagnosis of “in situ” MCL.

Cyclin D1 is a cell cycle regulator usually transiently expressed in cells [14]. Cyclin D1, a D-type cyclin that is not expressed in normal B-lymphocytes, plays a key role in cell cycle regulation during the G1 to S-phase transition by binding to cyclin-dependent kinase 4 (CDK4) and CDK6, resulting in phosphorylation and inactivation of the retinoblastoma protein (RB) [15, 16]. Aberrant cyclin D1 overexpression is a highly specific molecular marker of MCL and leads to a high mitotic rate of the affected B-cells [14]. Cyclin D1 is expressed in virtually all of MCL but only in a few cases of aggressive chronic lymphocytic leukemia/small lymphocytic lymphoma (B-CLL/B-SLL) and multiple myeloma (MM) [6]. Cyclin D1 is not expressed in non-neoplastic T-cells or B-cells [17].

Few cases of cyclin D1-negative MCL were reported [18, 19]. These cases also lacked the characteristic IGH/CCND1 fusion by FISH analysis and were negative for cyclin D1 protein expression by immunostains [18]. Nevertheless, all of the cases exhibited the characteristic pathologic features of MCL and, more importantly, shared the characteristic MCL gene expression profile by microarray analysis [18]. Overexpression of either cyclin D2 or D3 was observed in all cases of cyclin D1-negative MCL, indicating an important substitute role for these cyclins in the pathogenesis of cyclin D1-negative MCL [18].

Another marker, SOX11, with nuclear expression, may be useful for “in situ” MCL diagnosis. The SRY (sex determining region Y)-box 11 (SOX11) transcription factor was recently discovered as a new marker in mantle cell lymphoma (MCL), expressed in both cyclin D1 positive and negative cases [20]. SOX11, located on chromosome 2p25, is a member of the SOX gene family and was discovered in 1995 [21]. Nuclear Sox11 may not only be a valuable marker for diagnosing cyclin D1-positive and -negative MCL but may also be expected to have a functional role in the development and/or survival of the tumor cells [20]. Recent studies have identified a group of patients diagnosed with MCL, SOX11 negative, that show an indolent clinical course and a long survival of more than 7 to 10 years, some of them not even requiring chemotherapy for long periods [22–24]. MCL with an indolent clinical evolution may correspond to a distinctive clinical and biological subtype of the disease. These patients usually had an asymptomatic, non-nodal, and leukemic disease, and the tumors carried predominantly hypermutated IGVH genes and noncomplex karyotypes, and the tumor is more frequently CD5 negative [24]. The translocation t(11;14)(q13;q32) and cyclin D1 overexpression are also present in indolent MCL [24]. This clinical presentation and SOX11 negativity identify patients with MCL that do well without aggressive chemotherapy [24]. Reported cases of “in situ” MCL appear to have a long time until appearance of the signs and symptoms of conventional MCL; after the initial clinical staging (flow cytometry of the peripheral blood, bone marrow biopsy, TAC, PET SCAN), the patient with only “in situ” MCL will be monitored, without treatment. All suspicious sites require careful morphological and phenotypic examination (including cyclin D1 stain) for a conventional MCL diagnosis. “In situ” MCL is different for “early” (“in situ”-like) MCL, with a pure or true mantle zone growth pattern, and with a distinct clinical feature (frequently limited stage I/II Ann Arbor). The patients with “early” MCL require standard chemotherapy [8].

The relation of “in situ” MCL and monoclonal B-cell lymphocytosis (MBL) non-CLL-like require further investigation. The problem consists in the very few numbers of “in situ” MCL and the rarity of non-CLL MBL. MBL is characterized by the presence of <5×10^9 clonal B-cells/L in peripheral blood (PB) in otherwise healthy subjects, in the absence of symptoms and signs of a B-cell chronic lymphoproliferative disorder [25]. An overall frequency of MBL between 3.5% and 14% of adults older than 40 years has been reported, depending on the sensitivity of the assay and population age [26, 27]. Non-CLL-like MBL has generally been subdivided into two major groups: CD5 negative and CD5 positive MBL cases [26]. Nieto WG et al. (2010) describe for the first time CD5 positive MBL cases, which both phenotypic and genetic features that are highly characteristic of MCL cells; the three cases remain without any symptoms or signs of disease after two years of follow-up [28].

In lymph node involved by lymphoma, focally histological changes resembling Castleman disease can be present and the term “Castleman-like” is preferred [29]. In the reported case, large amounts of histological...
section presented findings of HV-CD, a very unusual feature. Patients with HV-CD have a minimally increased risk of developing simultaneous or subsequent lymphoma [30]. Because all others studied cases of CD were cyclin D1 negatives, we suppose an incidental association of these two diseases in our case.

Conclusions

“In situ” MCL is a very rare event and can be present many years before a diagnosis of symptomatic MCL, as “in situ” follicular lymphoma (FL), “in situ” MCL cases were sometimes incidentally identified in a staging lymph node for other malignancies (carcinoma/ melanoma). As cyclin D1 is not found in appreciable amounts in reactive lymphadenitis (only nuclei of reactive macrophages and stromal cells are consistently positive), this marker is very important in the diagnosis of “in situ” MCL. The pathologists should be aware of the existence of an “in situ” MCL, and demand an adequate immunohistochemical panel, including a marker for cyclin D1, to differentiate this neoplasm from follicular hyperplasia. The HV-CD morphology can dissimulate an “in situ” MCL, as presented case.

References

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Received: July 10th, 2011

Accepted: November 25th, 2011


