To the editor:

**Cyclin D1-negative mantle cell lymphoma with cryptic t(12;14)(p13;q32) and cyclin D2 overexpression**

Virtually all cases of mantle cell lymphoma (MCL) carry the t(11;14)(q13;q32) translocation, leading to the juxtaposition of the CCND1/CYCLIND1 gene to the immunoglobulin heavy chain (IGH) joining region, resulting in cyclin D1 mRNA and protein overexpression.¹-³ The existence of “true” MCL negative for cyclin D1 has been controversial but was recently substantiated by gene expression profiling.⁴ Fu et al reported 6 cases of cyclin D1-negative lymphomas with pathologic and clinical features otherwise typical of MCL, and a molecular signature similar to that of cyclin D1-positive MCL. In these cyclin D1-negative MCL, the tumor cells overexpressed instead either cyclin D2 or cyclin D3, but had no evidence of chromosomal aberration involving the corresponding CCND2 and CCND3 genetic loci. Subsequently, 2 additional cases of cyclin D1-negative/cyclin D2-positive MCL were reported to harbor a t(2;12)(p11;p13) fusing the CCND2 gene to the IGH locus.⁵

Here, we report a case of cyclin D1-negative MCL with strong nuclear expression of cyclin D2 and a cryptic t(12;14)(p13;q32), juxtaposing the CCND2 gene next to the IGH locus. This lymphoma occurred in a 52-year-old man with stage IV disease involving the bone marrow and gastrointestinal tract. The diagnostic lymph node biopsy showed morphologic and immunophenotypic features typical of MCL (CD20⁺, CD5⁺, CD10⁻, CD23⁻, CD43⁺, BCL-2⁺, BCL-6⁻), except for lack of cyclin D1 expression (Figure 1A-E). Conversely, most nuclei were positive for cyclin D2 (Figure 1F) and by competitive real-time–

![Figure 1](https://www.bloodjournal.org/content/111/3/1745/F1)

**Figure 1.** Histologic, immunohistologic, and cytogenetic features in a case of cyclin D1-negative lymphoma with CCND2-IGH fusion. (A,B) Hematoxylin and eosin-stained lymph node biopsy showing a vaguely nodular lymphoid infiltrate around an atrophic residual germinal center (A), composed of small cells with irregular nuclei admixed with scattered histiocytes (B). (C-F) Immunohistochemical findings: strong CD5 expression in the tumor cells around a negative residual germinal center (C), composed of small cells with irregular nuclei admixed with scattered histiocytes (D); lack of cyclin D1 expression in the tumor cells; note that reactive histiocytes exhibit moderate nuclear staining (E); cyclin D2 nuclear expression in the tumor cells detected by a polyclonal anti-cyclin D2 antibody (Cell Signaling) (F).

![FISH results](https://www.bloodjournal.org/content/111/3/1745/F2)

Hybridization of spread metaphases with LSI IGH Dual Color, Break Apart Rearrangement probe (Vysis) shows one chromosome 14 with a normal hybridization pattern (juxtaposed centromeric orange and telomeric green probes) and one chromosome 14 hybridizing only with the centromeric probe, indicating an IGH break (arrow); loss of the telomeric part of the probe precluded identification of the partner chromosome (G). A break apart FISH assay for CCND2 locus rearrangement (telomeric BAC clone: RP11-578L13; centromeric BAC clone: RP11-388F6) shows 2 chromosomes 12 with a normal hybridization pattern and hybridization of the telomeric green probe to 14q, indicating a cryptic t(12;14)(p13;q32) (H). The CCND2 rearrangement is confirmed in the lymph node sample by interphase FISH as the nuclei show 2 yellow (normal chromosomes 12) and one or 2 green (derivative 14) signals with the 2 BAC clones (I).
polymerase chain reaction (RT-PCR) cyclin D2 mRNA was overexpressed. Conventional cytogenetic analysis yielded 4 mitoses with a normal karyotype. Interphase FISH performed with LSI IGH/CCND1 Dual Color, Dual Fusion Translocation Probes (Vysis, Downer’s Grove, IL) was negative for the t(11;14)(q13;q32), but demonstrated rearrangement of the IGH locus. Q-banded karyotype established from a bone marrow sample was 43,XY,−1,der(8)t(8;8)(p23;q13),−11,−13,add(15)(p11),der(17)t[17]p22;12),add(21)(q22),-22,+mar[p2]/46,XY[17]. FISH performed on bone marrow cells with the LSI IGH Dual Color, Break Apart Rearrangement Probe (Vysis), showed a rearrangement of the 14q32 region (Figure 1G). Because of apparent cyclin D2 overexpression, the tumor cells were investigated for a CCND2 rearrangement, using a break apart FISH assay as previously described. A break in the CCND2 locus was clearly demonstrated, with the telomeric probe mapping to 14q32 (Figure 1H). The short arms of both chromosomes 12 were normal, demonstrating a derivative 14 through a cryptic t(12;14)(p13;q32) translocation. Interphase FISH confirmed a CCND2 rearrangement in the lymph node (Figure II).

This is the first description of a cyclin D1-negative MCL with a t(12;14)(p13;q32) and cyclin D2 overexpression. Of the 4 cyclin D1-negative/cyclin D2-positive MCL previously reported, 2 were found to harbor a genetic alteration of the CCND2 gene, due to a translocation to the IGK locus. Our findings in the current case confirm that CCND2 is recurrently targeted by chromosomal rearrangements in cyclin D1-negative MCL, and identify IGK as a previously undescribed translocation partner. By analogy to other translocations involved in B-cell lymphomas, one would have expected to find this translocation more often. Interestingly, the t(12;14)(p13;q32) translocation has, to date, not been described. This is likely due to the rarity of true cyclin D1-negative MCL with CCND2 alterations but also to the cryptic nature of this rearrangement.
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