A Cryptic t(11;14) Translocation in Mantle Cell Lymphoma Highlights the Importance of FISH

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Abstract

Mantle cell lymphoma (MCL) is a mature B-cell neoplasm composed of monomorphic small to medium-sized atypical lymphocytes arising from naïve mantle zone B-cells, with a generally aggressive and incurable clinical course. The t(11;14)(q13;q32) between *IGH@* and *CCND1* is present in almost all cases of MCL. Secondary cytogenetic abnormalities are common, and have been associated in some cases with clinical progression. Variant and cryptic t(11;14) translocations have been reported as well. Herein, we present the case of an 80-year old woman with classical MCL, and a cryptic t(11;14) translocation detected by fluorescence in situ hybridization (FISH), and not by conventional cytogenetics. FISH on previously G-banded metaphases showed a cryptic *CCND1-IGH@* fusion signal on a derivative chromosome 10, and another fusion signal on one of the abnormal copies of chromosome 11. Cases such as this highlight the importance of FISH studies as part of an algorithmic and multidisciplinary approach to diagnosis.

Key Words: Mantle Cell Lymphoma, cryptic t(11;14), FISH on previously G-banded metaphases

Introduction

Mantle cell lymphoma (MCL) is a mature B-cell neoplasm composed of monomorphic small- to medium-sized atypical lymphocytes arising from naïve mantle zone B-cells, with a generally aggressive and incurable clinical course (Swerdlow SH et al., 2008). It comprises 6 percent of all new cases of non-Hodgkin lymphoma (NHL) per year, with approximately 66,360 new cases of NHL in the United States yearly, and occurs more frequently in older adults, males, and Caucasians (Kahl B, 2012). Morphologic variants have been described, including the aggressive blastoid and pleomorphic variants, as well as small cell and marginal zone-like variants, an indolent subtype, and in situ lesions (Swerdlow SH et al., 2008; Hsi ED et al, 2014). Leukemic involvement is a common presentation in both classical and blastoid variant MCL.

The t(11;14)(q13;q32) involving *IGH@* and *CCND1* is present in almost all cases of MCL, causing an overexpression of Cyclin D1 and deregulation of the cell cycle (Swerdlow SH et al., 2008). Secondary cytogenetic abnormalities are highly common in MCL, including numerous recurrent aberrancies, and have been associated with disease progression and, in many cases, with poor prognosis. The cytogenetic picture is further complicated by rare cases of Cyclin D1 negative MCL, as well as cases with variant and/or cryptic t(11;14) translocations. Accurate cytogenetic studies are important in MCL for diagnosis and potentially classification, therapy, and prognostication, given the commonly seen complex cytogenetic abnormalities and generally irreversible clinical course. Molecular cytogenetic techniques serve as a highly useful, and even mandatory tool for difficult to classify cases, including those with a cryptic t(11;14) translocation.

Clinical Presentation

An 80-year-old woman presents with a history of a CD5+/CD20+ lymphoproliferative disorder, and new onset splenomegaly, thrombocytopenia, anemia, and elevated absolute lymphocyte count. A bone marrow biopsy was hypercellular for age (50 percent cellularity) with atypical aggregates of small- to medium-sized neoplastic B-cells expressing CD20, PAX5 and BCL1 by immunohistochemical staining. Flow cytometry of the bone marrow revealed a monotypic, kappa-restricted B-cell population comprising 37 percent of total cells and expressing CD5, CD19, CD20, CD22, FMC7 and CD38, and negative for CD10 and CD23. A diagnosis of mantle cell lymphoma was rendered.

Materials and Methods

Chromosome analysis was performed using standard cytogenetic techniques on the bone marrow and peripheral blood. Twenty metaphase cells were analyzed and karyotypes were prepared using the Applied Imaging CytoVision software (Applied Imaging, Genetix, Santa Clara, CA). Karyotypes were described according to the ISCN 2013 nomenclature (Shaffer LG et al., 2013).

Fluorescence in situ hybridization (FISH) was performed using the Vysis *CCND1-IGH (CCND1-IGH@)* dual-color, dual-fusion as well as the Vysis *TP53* (17p13.1)/ Cep17 (chromosome 17p11.1-q11.1) from Abbott Molecular (Des Plaines, IL) on interphase nuclei and on previously G-banded metaphases.

Results

Chromosome analysis reveals an abnormal complex female composite karyotype with multiple structural abnormalities in 6/20 metaphase cells analyzed including del(6)(q25), add(8)(p21), add(10)(p15), add(11)(q13);add(11)(q13),-14, tas(12;21)(pter;pter) and a marker chromosome. The remaining 14 cells are chromosomally normal. No t(11;14) was detected by conventional cytogenetics.

These results were described as:

44-45,XX,del(6)(q25),add(8)(p21),add(10)(p15),add(11)(q13);add(11)(q13),-14, tas(12;21)(pter;pter),+mar[cp6]/46,XX[14].

FISH studies using a *CCND1-IGH@* dual-color, dual-fusion probe on interphase nuclei showed fusion signals in 23% (46/200) of nuclei examined (Figure 1A). These results were described as:

nuc ish(*CCND1,IGH@*)x3(*CCND1* con *IGH@*x2)[46/200]
nuc ish(*TP53*,D17Z1)x2[200]

FISH performed on previously G-banded metaphase nuclei confirmed an unbalanced rearrangement of chromosome 10 involving a complex, unbalanced translocation of chromosomes 11 and 14 (Figure 1B, Figure 3).

Based on these results, the karyotype was characterized as (Figure 2):

44-45,XX,del(6)(q25),add(8)(p21),der(10)(11q25->11q13::14q32->14pter::10p15->10qter),der(11)t(11;14) (q13;q32),add(11)(q13),-14,tas(12;21)(pter;pter), +mar[cp6]/46,XX[14]

Discussion

The t(11;14)(q13;q32) translocation juxtaposes the proto-oncogene *CCND1* at 11q13 to the immunoglobulin heavy chain alpha (*IGH@*) at chromosome 14q32 (Jares P et al., 2012). This results in overexpression of the Cyclin D1 protein, and progression from the G1 to the S phase of the cell cycle (Swerdlow SH et al., 2008; Jares P et al., 2012). This translocation is present in the majority of MCL cases, and is considered the primary genetic event, although Cyclin D1 negative cases have been reported (Swerdlow SH et al, 2008; Jares P et al., 2012), and t(11;14) has been detected in healthy patients without MCL (Hirt C et al., 2004). These and other studies suggest that secondary cytogenetic abnormalities drive progression of MCL, and may be important in classification, therapy and prognosis (M'kacher R et al., 2003; Zhang L et al., 2006). However, the (11;14) translocation has also been seen in other B-cell derived neoplasms (Huret, JL et al., 1998; Mitelman F et al., 2014) with different clinical behavior than MCL, emphasizing the need for correct diagnosis using a multidisciplinary and algorithmic approach.

Our case highlights a cryptic t(11;14) translocation not detected by conventional cytogenetics, as well as multiple secondary cytogenetic abnormalities. Cryptic t(11;14) translocations have been reported in MCL, including cases featuring the use of multicolor FISH (M-FISH) and cases where M-FISH lacked the resolution to detect the cryptic t(11;14) (Mohamed AN et al., 2002; M'kacher R et al., 2003; Maravelaki S et al., 2004; ; Aamov HV et al., 2006; Gazzo S et al., 2006; Zhang L et al., 2006; Salaverria I et al., 2008). Array CGH was of use in many cases as well. These molecular cytogenetic methods have improved sensitivity and can overcome limited mitotic indices of leukemic cells in culture / overgrowth by normal karyotypes, and complex rearrangements masking t(11;14) by karyotype (Mohamed AN et al., 2002).

MCLs feature the highest number of cytogenetic alterations among lymphoid neoplasms, and most MCL cases have complex karyotypes with high numbers of structural and numerical alterations (Salaverria I et al., 2007). MCL seems not to have recurrent translocations other than t(11;14), but shows multiple recurrent chromosomal rearrangements frequently involving chromosomes 1, 8, and 10 (Salaverria I et al., 2007), as featured in this case. Numerous breakpoints and imbalances have been reported as well (Wlodarska I et al., 1999; Salaverria I et al., 2007), including some seen in this case such as 6q-. These loci appear to be nonrandom, and may contain target genes relevant in the progression of the disease (Salaverria I et al, 2007). The exact

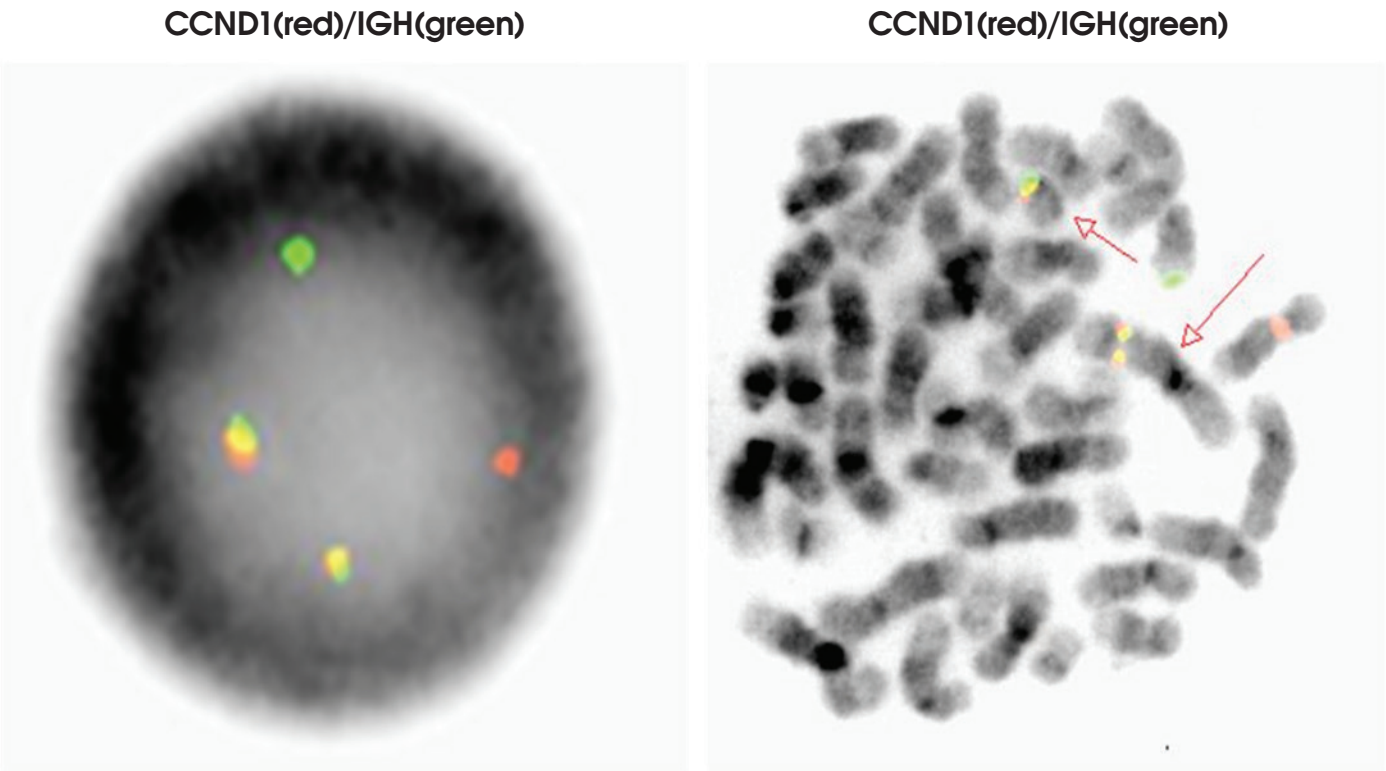

Figure 1A (left). FISH on interphase nuclei showing CCND1/IGH fusion signals.
Figure 1B (right). FISH on previously G banded metaphase showing *CCND1-IGH@* fusion signal on a derivative chromosome 10.

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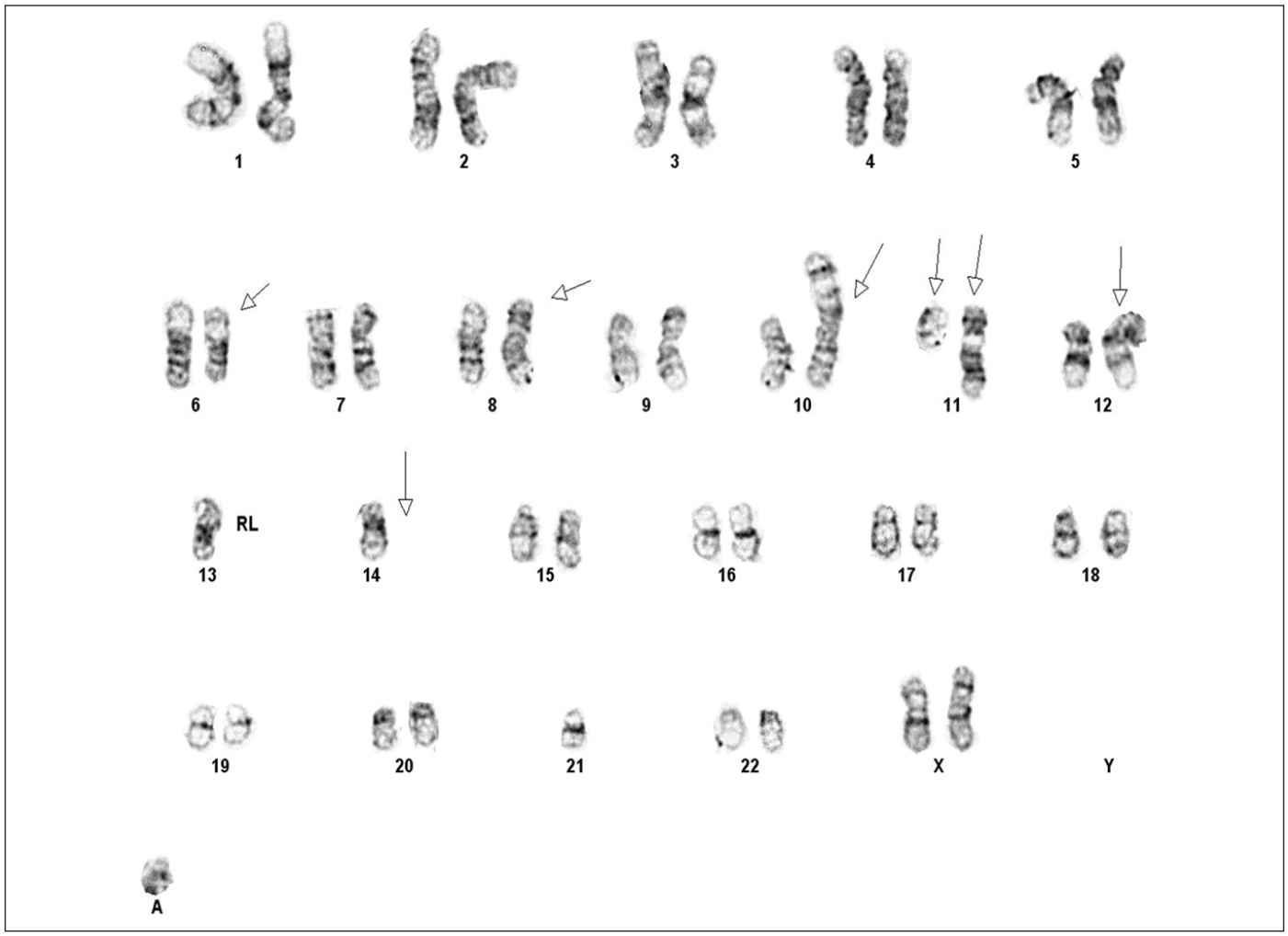

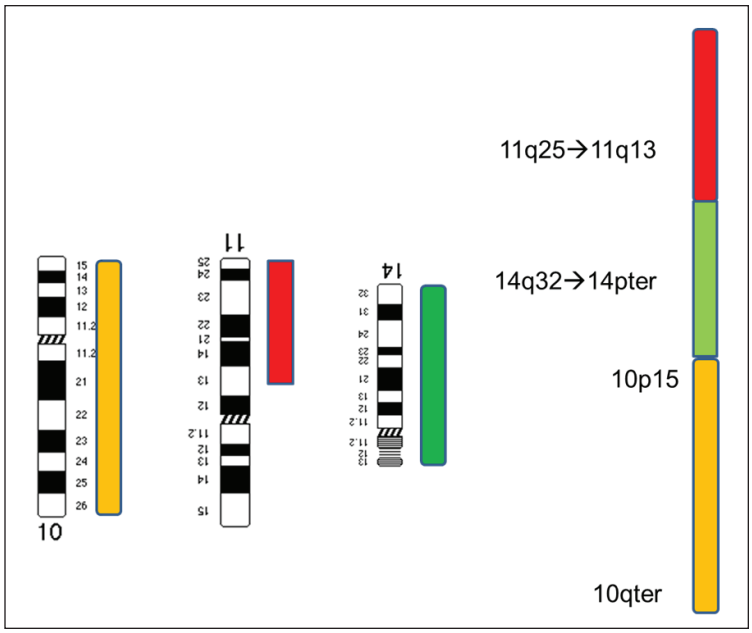

Figure 2 (above). Chromosome analysis showing abnormal female complex karyotype with multiple structural and numerical abnormalities.

Figure 3 (left). Diagram showing complex t(11;14) rearrangement on a derivative chromosome 10 (ISCN 2013).

prognostic significance imparted by our patient's cryptic t(11;14) and complex secondary cytogenetic abnormalities is unclear.

Cryptic t(11;14) translocations in MCL confirm the need for molecular cytogenetic techniques, including FISH on interphase nuclei and previously G-banded metaphases, in making an accurate diagnosis. This is important given the generally aggressive clinical course of MCL.

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