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Correspondence

The t(11;14)(q13;q32)/*CCND1–IGH* translocation in chronic lymphocytic leukaemia/small lymphocytic lymphoma: an unusual genetic aberration during the natural clinical course

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Sir: Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) and mantle cell lymphoma (MCL) are both CD5+ B-cell lymphomas, but show distinct genetic profiles. Recurrent cytogenetic abnormalities in CLL/SLL include del(13q), trisomy 12, del(11q/*ATM*), and del(17p/*TP53*).[1] However, the t(11;14)(q13;q23)/*CCND1–IGH* translocation, which is the primary genetic event in >95% of MCL cases, is exceedingly rare in CLL/SLL.[2–5] Most cases reported were acquired post-chemotherapy, with only one case harbouring the translocation during the natural disease course.[5] Whether these cases represented secondary acquisition of t(11;14) by CLL/SLL, MCL transformation or composite CLL and MCL remained controversial.

Here, we report a 59-year-old man with no significant past medical history who presented with right cervical lymphadenopathy, mild leucocytosis (white blood cell count of 12.67 K/μl), and absolute lymphocytosis (3.12 K/μl). Excisional biopsy of the right cervical lymph node revealed monotonous-appearing, small-sized lymphoid cells with condensed/clumped chromatin and scant cytoplasm, with paler areas of proliferation centres containing higher numbers of prolymphocytes and paraimmunoblasts (Figure 1A). Flow cytometry demonstrated a single abnormal B-cell population with a typical CLL/SLL immunophenotype: expression of CD19, CD5, CD23, CD20 (dim), CD22 (dim), CD38 (subset), FMC7 (subset), and CD200 (bright), and lambda surface light chain restriction. On immunohistochemical staining, the neoplastic cells were positive for CD5, CD23, and LEF-1, but a subset also showed weak positivity for cyclin D1 (Figure 1A). A single-nucleotide polymorphism array detected multiple chromosomal arm level gains/losses, including deletion of 36 Mb in 11q14.1–23.2, a region containing the *ATM* gene. Next-generation sequencing (NGS)-based clonal *IGH* gene rearrangement studies showed a single clone with mutated *IGHV* (3.5%) and *IGHV* gene usage of V3-21 usage, which has been associated with an adverse prognosis in CLL/SLL independent of *IGHV* mutation status.[6] Despite the weak expression of cyclin D1, it was thought that the overall findings were most consistent with CLL/SLL.

The patient was followed in the clinic by observation without any treatment. However, 9 months later, he showed disease progression with worsening cytopenia and increasing peripheral adenopathy. Bone marrow and axillary lymph node were biopsied to assess interval disease changes. Both showed diffuse involvement by lymphoid cells with similar morphological and immunophenotypic features to those of the diagnostic cervical lymph node (Figure 1B–E). However, unexpectedly, cyclin D1 positivity was noted in the majority of the neoplastic cells in the marrow and in a subset of cells in the axillary lymph node, whereas SOX11 was negative in both. Chromosome analysis of the marrow aspirate showed a complex karyotype that included t(11;14). Retrospective fluorescence *in-situ* hybridisation (FISH) studies performed on the patient's initial, pre-treatment right cervical lymph node biopsy demonstrated t(11;14) in 30% of cells with *CCND1* break-apart probes and in 19% cells with *IGH*/*CCND1* dual-fusion probes, and del(11q/*ATM*) in 68% of cells. *CCND1* translocation and *ATM* deletion were also detected in the left axillary lymph node biopsy (22% and 73.3% of cells, respectively). In contrast, there were approximately equal percentages of cells harbouring *CCND1* translocation (48%) and *ATM* deletion (49%) in the marrow (Figure 2A–C). Although attempts were made to use *CCND1* and *ATM* FISH probes to confirm the coexistence of *CCND1* rearrangement and *ATM* deletion in the same cells, technical difficulties prevented a definite conclusion from being drawn. Targeted NGS-based mutation profiling on the marrow identified an *SF3B1* p.K700E (c.2098A>G) mutation, which is much more often associated with CLL/SLL than with *de-novo* MCL. Clonal *IGH* rearrangement studies performed on the marrow showed an identical clonal sequence to that in the pre-treatment right cervical lymph node, confirming their clonal relationship (Figure 2D,E).

All three biopsies showed morphological, immunophenotypic and FISH (del11q/*ATM*) findings suggestive of CLL/SLL, other than cyclin D1 expression and t(11;14) in a subset of cells (Table 1). Together with the flow cytometric finding of a single clonal population with a similar immunophenotype in each

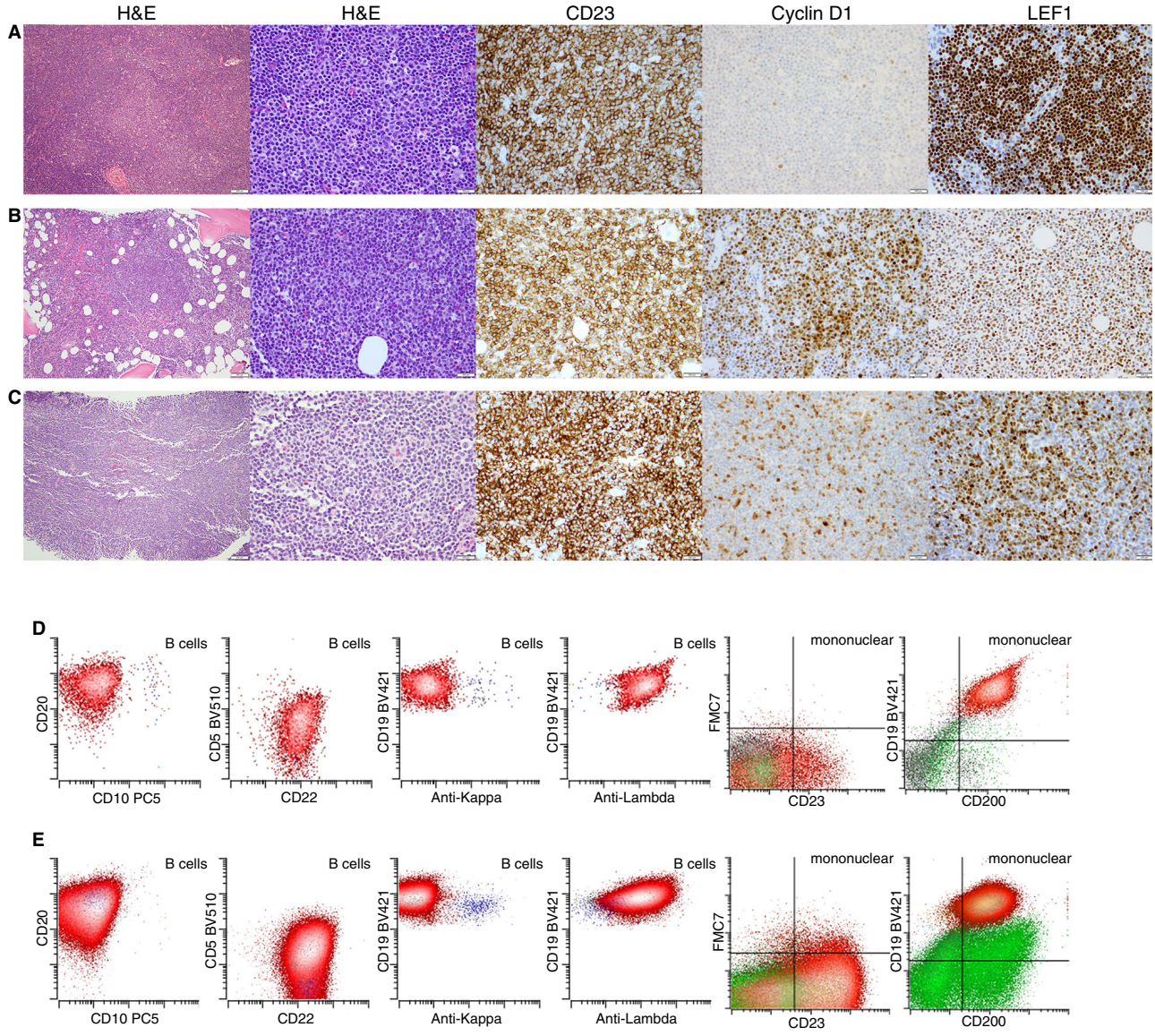

Figure 1. Morphological features of the right cervical lymph node (**A**), bone marrow (**B**), and left axillary lymph node (**C**), and flow cytometric findings of a single abnormal B-cell population in the bone marrow (**D**) and left axillary lymph node (**E**).

sample, we believe that the three biopsies represented the same lymphoid neoplasm. Mutation profiling on the bone marrow biopsy demonstrated *SF3B1* p.K700E, which also favours a diagnosis of CLL/SLL. The demonstration of a single, identical clonal *IGH* rearrangement in the right cervical lymph node and marrow biopsies provides further evidence of a single neoplastic process. Therefore, we believe that it is best to classify this case as a CLL/SLL harbouring both *ATM* deletion and t(11;14), the latter possibly as a secondary chromosomal aberration, rather than MCL transformation or composite MCL and CLL. Most of the rare reported CLL/SLL cases with acquisition of t(11;14) occurred after treatment with alkylating agents,[2–5] with the exception of one case in which t(11;14) was detected in a patient without any treatment.[5] To our knowledge, this is the second reported case of a highly unusual CLL/SLL harbouring t(11;14) during the natural clinical course. In the case reported by Arai *et al.*, the MCL showed pleomorphic morphology with prominent nucleoli, whereas, in our case, neoplastic cells with and without cyclin D1 expression

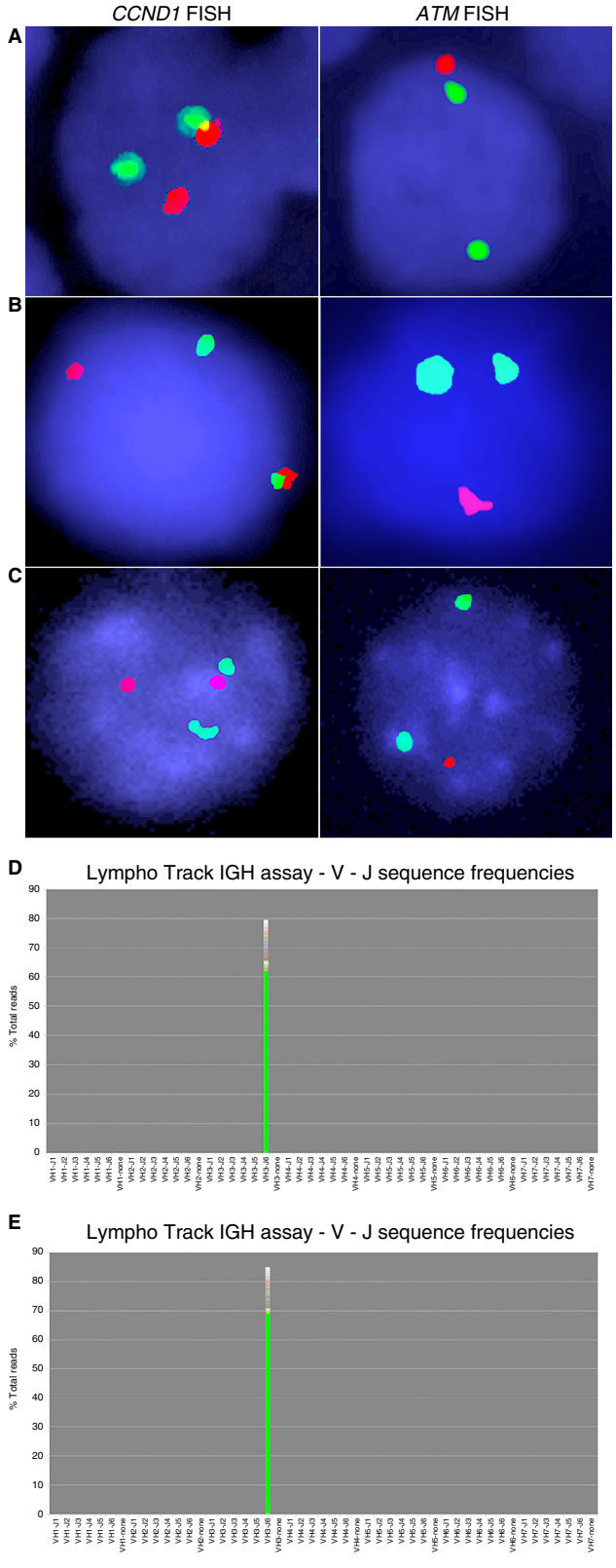

Figure 2. Fluorescence *in-situ* hybridisation (FISH) analysis of the right cervical lymph node (**A**), bone marrow (**B**), and left axillary lymph node (**C**), and clonal *IGH* rearrangement studies using a next-generation sequencing-based assay of the right cervical lymph node (**D**) and bone marrow (**E**). FISH probes: *CCND1* break-apart probes: 5′-*CCND1* is labelled in green, and 3′-*CCND1* is labelled in orange. *ATM* and CEP11 (centromere of chromosome 11) probes: CEP11 is labelled in green, and *ATM* is labelled in orange.

were all small in size with condensed chromatin, and were morphologically indistinguishable from each other. Clinically, our patient's disease was controlled after the initiation of ibrutinib therapy, with complete resolution of lymphadenopathy, systemic symptoms, and cytopenias. However, whether the presence of t (11;14) would predict a more aggressive long-term clinical outcome remains to be determined. Although extremely rare, our case illustrates that CLL/SLL with t (11;14) can pose diagnostic challenges, particularly if the clinical history is unclear. Integration of clinical, morphological, immunophenotypic, cytogenetic and molecular findings is necessary for accurate diagnoses.

Author contributions

Y. Liu and C. Ho conceived the study and wrote the manuscript. M. Roshal, W. Xiao and A. Dogan performed morphological evaluation and interpreted flow cytometric data. Y. Zhang and U. Aypar interpreted the cytogenetics studies. M. Arcila, C. Moung and C. Ho interpreted the molecular tests. J. Park collected clinical patient data. W. Yu and K. Nafa provided technical support for the molecular assays. All authors have reviewed and contributed to the manuscript.

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Conflicts of interest

M. Arcila has served as a consultant and received honoraria from Invivoscribe, Inc. C. Ho has received

Table 1. Summary of immunophenotypic, cytogenetic and molecular features of three biopsies from the patient

	Right cervical lymph node (Biopsy date: 16 March 2017)	Bone marrow (Biopsy date: 27 December 2017)	Left axillary lymph node (Biopsy date: 12 January 2018)
Immunophenotype			
CD5/CD23 coexpression	Positive	Positive	Positive
LEF1	Positive	Positive	Positive
Cyclin D1	Weakly positive/small subset	Positive/major subset	Positive/subset
SOX11	Negative	Negative	Negative
Others (flow cytometry)	CD20+ (dim), CD22 (dim), CD200+ (bright), CD38+ (subset), FMC-7 (subset), lambda light chain restriction	CD20+ (dim), CD22 (dim), CD200+ (bright), CD38+, lambda light chain restriction	CD20+ (dim), CD22 (dim), CD200+ (bright), CD38+, lambda light chain restriction
Cytogenetic analysis			
t(11;14)/*IGH–CCND1*	Present in 30% of cells	Present in 48% of cells	Present in 22% of cells
Del11q22.3 (*ATM*)	Present in 68% of cells	Present in 49% of cells	Present in 73.3% of cells
Others	Gain (two extra copies) of 2p, gain of 22q11.23–q13.33	del(2p), i(2p), del(10p), loss of chromosome 8, marker chromosomes	NA
Molecular analysis			
IGHV clonal rearrangement	*V3-21 J6*, mutated (3.5%)	*V3-21 J6*, mutated (3.5%)	NA
Others	NA	*SF3B1* exon 15 p. K700E	NA

NA, Not available.

honoraria from Invivoscribe, Inc. M. Roshal has served as a consultant for BD Biosciences, Agios, and Celgene, as well as receiving contract research funding from Agios, Roche, BMS, and Bayer. A. Dogan has received compensation from Roche, Novartis, Celgene, Seattle Genetics and Corvus Pharmaceuticals for consulting/advisory activities. The other authors declare no relevant conflicts of interest.

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