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The Natural History of Monoclonal Villous Lymphocytosis: A Chronic Lymphoproliferative Disorder of CD11c+ B Cells

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The long-term outcome of three asymptomatic subjects with isolated persistent lymphocytosis of monoclonal villous B-cells (MVL) is reviewed. After 7.5 years, evolution to a splenic lymphoma variant (SLVL) was documented in only one patient, accompanied by a loss of interleukin-1β autocrine production, confirming that MVL can be an early form of a malignant disorder. The clinical course was uneventful in the other two cases; a progressive lowering of lymphocyte count being noted in one. While the strict relationship of MVL to SLVL is confirmed, time to progression is unpredictable and the mechanisms by which it occurs still remain to be elucidated.

KEY WORDS: villous lymphocytosis evolution cytokines CD11c+ lymphocytosis

INTRODUCTION

We previously reported on three elderly patients with a monoclonal lymphocytosis of CD11c+ B-cells, showing peculiar diagnostic features as well as an indolent clinical course.[1] The morphologic and immunophenotypic properties of the expanded cell population closely resembled those found in the so-called splenic lymphoma with villous lymphocytes (SLVL).[2] This led us to speculate that monoclonal villous lymphocytosis (MVL) could represent an early form of SLVL. At that time, the patient follow-up was 3–7.5 years, and besides an absolute lymphocytosis there were no other clinical signs indicating SLVL. Having witnessed in subsequent years a rather heterogeneous and unpredictable course of these MVL cases, we now wish to update our original report in order to shed further light on the natural history of this rare disorder.

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CASE REPORTS

After a close observation period of 6–11.7 years, the three MVL patients showed three distinct evolutive patterns (Figure 1). Patient 1 progressed to a typical SLVL picture after about 7.5 years, as confirmed by the rise in circulating villous cells and the increasing spleen size. Because of a concomitant severe cardiac disease, splenectomy was not considered. The patient was instead managed with cyclic oral chlorambucil (10 mg/d for 2–6 weeks) and prednisone (50 mg/d), obtaining a partial lymphocyte response but only a transient control of splenomegaly. Eventually, he underwent splenic irradiation achieving a very good partial response lasting 12 months: the spleen size was reduced by approximately 75% and villous cells were no longer detectable in the blood smear (CD11c/CD20 double-positive cells below 1% by immunophenotypic analysis). A subsequent phase of progression was managed with oral cyclophosphamide (100 mg daily). Recently the patient died of his cardiac disease.

In this first case, a comparative evaluation of immunoglobulin (Ig) gene rearrangement and cytokine gene expression was carried out at presentation and progression. The molecular analysis of IgH gene rearrangement

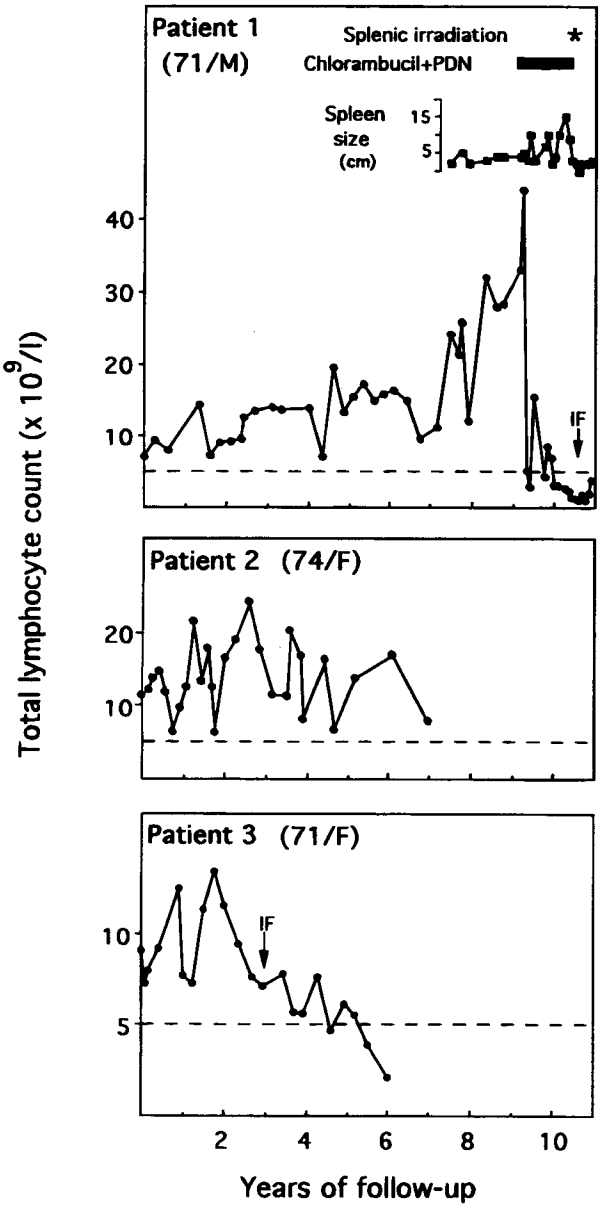

Figure 1 Absolute lymphocyte count and clinical course in MVL patients (age/gender). IF arrows denote immunophenotype study (see Text). Spleen size as measured below the costal margin. Horizontal dashed line denotes threshold of absolute lymphocytosis.

performed by the polymerase chain reaction using consensus primers of CDR2 and JH regions[3] showed a consistent rearrangement pattern, excluding a clonal evolution heralding or accompanying the onset of SLVL. A concurrent cytogenetic study performed with QFQ-banding revealed a normal 46XY male karyotype in 20 metaphases analyzed. The results obtained by studying the mRNA expression[4,5] for interleukin-1β (IL-1β), tumour necrosis factor-α (TNFα), and interleukin-6 (IL-6) are reported in Table 1. Interestingly, the constitutive production of IL-1β documented at diagnosis of isolated benign MVL was lost at the time of clinical progression.

Differing from the first case, the two other MVL patients showed no clinical or laboratory evidence of SLVL during a follow-up period greater than 6 years, nearly as long as that documenting the evolution to SLVL in the former case. In patient 2 the lymphocyte count varied cyclically without a recognizable period. The patient was otherwise well and received no treatment. In patient 3 a steady though slow lymphocyte decrease occurred from the third year of follow-up onwards. The immunophenotypic analysis showed a lower percentage of CD20/CD11c double-positive cells (35%) than at baseline.[1] The patient's clinical condition remained stable an no treatment was necessary throughout the follow-up period.

DISCUSSION

Taken together, these findings imply that long-term outcome of MVL patients may be unpredictable on clinical grounds, and that a spontaneous attenuation of the phenomenon is possible as well as a progression to a typical, symptomatic SLVL.[2] The time frame of our study indicates that an isolated benign MVL can run a very prolonged course before posing therapeutic problems or showing any significant clinical change. Data from other studies are very scanty, perhaps reflecting the diagnostic difficulty in identifying isolated MVL cases. In a series of 50 cases from the Royal Marsden Hospital (London, UK), one of two patients presenting with an isolated villous lymphocytosis developed an overt SLVL after 18 months of follow-up.[6]

The practical implications from our report are that the natural history of an isolated MVL is heterogeneous and hardly predictable in individual subjects in the short-term, although the reassuring possibility exists that MVL may remain an indolent process for a long while. In view of the benign evolutive patterns and the fluctuation of some clinical parameters observed in patients 2 and 3, the funda-

Table 1 Cytokine mRNA expression in a case of MVL progressing to SLVL.

	mRNA expression		
Disease status	*IL-1β*	*TNFα*	*IL-6*
Chronic MVL	+	–(weak)	+
Progressive SLVL	–	–	+

[1]total cellular RNA extracted by Cs-chloride gradient ultracentrifugation and hybridized with specific cDNA probes as previously detailed (ref. 5)

mental question as to whether chronic MVL is to be invariably regarded as an early form of SLVL still remains open. The exact biologic mechanisms by which a stable moderate MVL may sometimes evolve much later into an aggressive disease are unknown. The description of frequent, multiple karyotypic abnormalities in SLVL prompts an early cytogenetic analysis of MVL cases, followed by a periodic reassessment, to point out links with the malignant counterpart.[7]

In our first patient we had no evidence of cytogenetic abnormalities, nor the comparative study of IgH gene rearrangement indicated phenomena of clonal evolution. However, the analysis of cytokine gene expression was more informative. Although no change in both TNFα and IL-6 gene expression was documented, the patient's villous cells lost their ability of expressing IL-1β when SLVL was diagnosed requiring therapeutic intervention. This latter cytokine is constitutively expressed by most chronic-phase B-cell leukaemias,[5] whereas an autocrine IL-6 production has been reported in both indolent and aggressive B-cell neoplasms.[4,5,8] Recently, low concentrations of endogenous IL-1β were found in progressive B-cell chronic lymphocytic leukaemia as opposed to higher values in stable disease.[9] The shift from an IL-1β^{+}/–6^{+} to IL-1^{-}/–6^{+} profile occurring at progression is therefore consistent, in this case, with the development of a biologically more aggressive disease, and is one characteristic differentiating MVL from SLVL.

Further insights on the mechanisms leading to SLVL could emerge by investigating the interactions of clonal B-villous cells with the regulatory natural killer cell system and by studying their expression of apoptosis-related genes. In this respect, the rare patients with a long-standing, isolated and asymptomatic MVL represent the setting in which investigate the immunobiologic changes underlying the evolution of a pre-clinical condition towards an overt lymphoproliferative malignancy.

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