Primary Digestive Richter's Syndrome

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The clinical and morphologic transformation of 3 to 5% of chronic lymphocytic leukemia (CLL) to diffuse large-cell lymphoma (DLCL) is commonly referred to as Richter's syndrome. Richter's syndrome occurs mostly in lymph nodes and may represent a second neoplasm or a transformation from the same clonal population. Clinical features in six patients with digestive Richter's syndrome were recorded. Paired samples of CLL and DLCL were investigated by immunohistological analysis (n = 6) and by polymerase chain reaction (PCR) for immunoglobulin heavy-chain gene rearrangement (n = 4). Histological examination revealed the involvement of the gastrointestinal tract by DLCL of B-cell phenotype (n = 6). The same monoclonal rearrangement between CLL and DLCL was demonstrated by PCR and sequencing analyses in two patients. The monoclonal rearrangement was different between CLL and DLCL in only one case. Median survival was 22 months for five patients receiving chemotherapy, suggesting that digestive Richter's syndrome has a better prognosis than nodal Richter's syndrome. Indeed, appropriate surgical resection combined with chemotherapy led to partial or complete remission in four patients.

KEY WORDS: CLL, Digestive Richter's syndrome, Gene rearrangement.

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Approximately 3 to 5% of cases of chronic lymphocytic leukemia (CLL) show evidence of morphologic transformation into diffuse large-cell lymphoma (DLCL; 1, 2) or Hodgkin's disease (3–8). This process is commonly referred to as Richter's syndrome (RS; 9, 10). RS is characterized by rapid lymph node enlargement, splenomegaly, hepatomegaly, fever, and weight loss and is associated with a rapid fatal outcome (1, 2, 9, 11, 12). Because patients with CLL have a greater tendency to develop secondary tumors, there has been a debate about the origin of the DLCL. Characterization of immunoglobulin heavy-chain (IgH) gene rearrangement has shown that DLCL may evolve from the original leukemia cell clone (8, 13–21) or may be a separate and independent neoplasm (19, 22–26). Extranodal involvement, especially of the gastrointestinal tract, is very rare. To our knowledge, only 10 cases have been reported (10, 21, 23, 27–30). Clonal relationship between CLL and digestive RS never has been established by molecular analysis. In one patient, this relationship has been suggested by immunostaining for light and heavy immunoglobulin chains (21). In four other cases, DLCL was not clonally related to the preexisting CLL, suggesting that digestive RS mainly represents a true secondary neoplasm (23). Therefore, we studied the clinicopathology and molecular features of digestive RS in six patients. Our study also suggests that digestive RS may have a better prognosis compared with nodal transformation.

MATERIAL AND METHODS

Patients

Six CLL-treated patients developed digestive RS. Samples were fixed in formalin (Cases 1, 2, and 5) or in Bouin's liquid (Cases 3, 4, and 6), embedded in paraffin, and stained with hematoxylin and eosin.

In all cases, the initial diagnosis of CLL was established on peripheral blood lymphocytes (PBL) and bone marrow (BM) examination and count. In four cases, lymph nodes (n = 4) or spleen (n = 1) examined during the CLL phase were reviewed and corresponded to CLL involvement. BM status was also checked at the time of the transformation.

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Immunophenotypic Characterization

Immunohistochemical analysis was performed either on 10% formalin-fixed paraffin-embedded sections with the biotin-streptavidin-peroxidase LSAB kit on an automated Chemate (DAKO, les Ullis, France) or by flow cytometry (Beckman Coulter XL, Hialeah, FL) of PBL. Primary antibodies were directed against the following antigens: CD3, CD10, CD20, CD23, CD43, Epstein-Barr virus (EBV) latency membrane protein (LMP1), cytokeratin (KL1), Ki67 (MIB1), P53, κ and λ immunoglobulin light chains (all from DAKO,) and CD5 (Novocastra, Le Perray, France). MIB1 immunostaining was interpreted by a semiquantitative method (31).

Molecular Genetic Studies

Genomic DNA was extracted from frozen tissues ($n = 5$), formalin-fixed tissues ($n = 2$) and PBL ($n = 3$) according to a standard phenol chloroform procedure. Analysis of IgH gene was performed as previously described (32). The monoclonal-dominant bands of both CLL and DLCL material of Cases 1, 2, and 5 were excised from the gel, eluted, and submitted to nucleotide sequencing analysis using the ABI PRISM Dye Terminator Cycle Sequencing Ready Reaction Kit (Perkin-Elmer Applied Biosystem, Foster City, CA). Nucleotide sequence data were analyzed using the Sequence Navigator Software (Perkin Elmer Applied Biosystem). Sequence comparisons were made with the Genbank-EMBL database using the Wisconsin Package (Genetics Computer Group, Inc, Madison, WI), and the BLAST program (33).

RESULTS

Clinical Results

Two males and four females were diagnosed for CLL (average age: 67 y). Blood cell counts are summarized in Table 1. At initial CLL diagnosis, all patients had blood and BM involvement but no lymphadenopathy. Splenectomy was performed in the single patient (Case 4) who presented splenomegaly and hemolytic anemia. After a variable follow-up period, patients were treated by chlorodeoxyadenosine on the basis of lymphocytosis >50,000 or tumoral lymphadenopathy or anemia and thrombopenia.

Digestive RS was revealed by recurrent gastric ulcer disease (Cases 1 and 3), upper (Case 4) or lower (Case 5) digestive-tract bleeding, intestinal obstruction (Case 2), or acute perforation (Case 6). At examination, a general alteration was observed, with weight loss and general weakness. The median interval between initial diagnosis of CLL and RS was 82 months (range: 24 to 158 mo).

TABLE 1. Blood Cell Count at Diagnosis

Case Number	White Cells	Lymphocytes (%)	Platelet	Hemoglobin (g/dL)
1	25,000	80	246,000	12.9
2	54,100	85	198,000	12.2
3	10,000	60	119,000	12.2
4	39,560	76	275,000	12
5	10,800	65	263,000	13.6
6	42,900	65	160,000	12.6

Morphologic and Immunophenotypic Characterization

The anatomic sites examined for pathologic evaluation are listed in Table 2, and the results of the immunophenotypic study of CLL and DLCL samples are summarized in Table 3. Whatever the anatomic site, CLL corresponded to small monomorphic lymphocytic cells with rare scattered blast cells. Indeed, MIB1 stained only few cells of CLL specimens (Fig. 3A). A typical B-CLL CD5+, CD20+, SIg+, CD23+, CD43+ phenotype was evidenced in all cases (Table 3).

Digestive DLCL was diagnosed on the presence of a dense, large lymphoid cell infiltrate of the digestive mucosa (Fig. 1). In five cases (Cases 1, 2, 3, 5 and 6), blastlike large cells had a vesicular nucleus with prominent nucleoli (Fig. 2A). In Case 4, lymphoma cells infiltrating the stomach mucosa had a uniform nucleus with a finely dispersed chromatin and small nucleoli (Fig. 2B). In all DLCL samples, the high mitotic rate was confirmed by the Ki67 (MIB1) staining (Fig. 3B). No lymphoepithelial lesion was found, either at the level of DLCL infiltration or adjacent mucosa, even after cytokeratin staining. The B-cell phenotype of DLCL is shown in Table 3. By comparison with the paired CLL samples, a loss of both CD5 and CD23 expression was found in four DLCL samples (Cases 3, 4, 5, and 6). A decrease in CD5 expression was observed in Case 1

TABLE 2. Clinical Data of Six Patients with RS

Case Number	Sex	Age (y)	Date of Diagnosis	Site[a]	Diagnosis
1	F	66	1994	LN/BM/PB	CLL
		69	1997	Stomach	DLCL
2	F	71	1994	LN/BM/PB	CLL
		73	1996	Rectum	DLCL
3	F	60	1990	LN/BM/PB	CLL
		64	1994	Stomach	DLCL
4	M	62	1983	Spleen/BM/PB	CLL
		76	1997	Stomach	DLCL
5	F	67	1988	PB/BM	CLL
		78	1999	Intestine	DLCL
6	M	76	1986	LN/PB/BM	CLL
		83	1994	Intestine	DLCL

LN, lymph node; PB, peripheral blood; BM, bone marrow; M, male; F, female.

[a] Anatomic sites' involvement based on pathologic evaluation.

TABLE 3. Immunophenotype of Paired CLL and DLCL Samples in Six Cases of RS

Phenotypic Marker	1		2		3		4		5		6	
	CLL	DLCL	CLL	DLCL	CLL	DLCL	CLL	DLCL	CLL	DLCL	CLL	DLCL
CD20	+	+	+	+	+	+	+	+	+	+	+	+
CD5	+	+/−	+	+	+	−	+	−	+	−	+	−
CD3	−	−	−	−	−	−	−	−	−	−	−	−
CD43	+	+	+	+	+	−	+	+	+	+/−	+	+
CD23	+	+	+	−	+	−	+	−	+	−	+	−
κ	NC	NC	+	+	+	+	NC	NC	NC	NC	NC	+
λ	NC	NC	−	−	−	−	NC	NC	NC	NC	NC	−
P53	+	+	+	+	−	−	+	+++	NC	+++	−	−
Ki67 (MIB1)	10%	80%	25%	80%	5%	NC	5%	95%	NC	80%	2%	60%

NC, noncontributive; +/−, weakly positive.

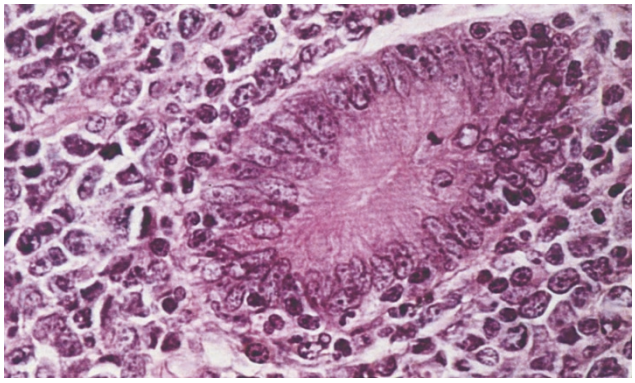

FIGURE 1. Diffuse infiltration of the intestine mucosa by large lymphoma cells (hematoxylin and eosin staining, ×400).

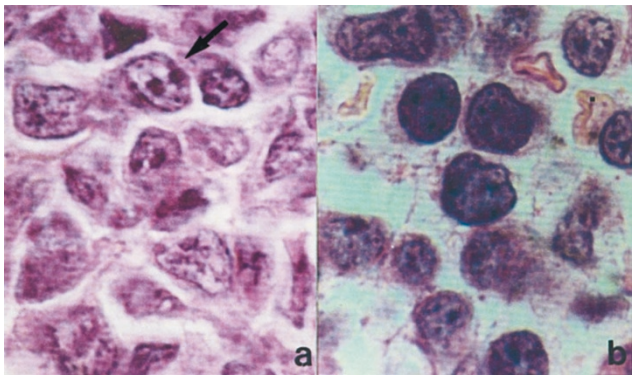

FIGURE 2. (**A**) Large lymphoma cells with prominent nucleoli (***arrow***; hematoxylin and eosin staining [HE], ×1000). (**B**) Large lymphoma cells with clear chromatin and smaller nucleoli in Case 4 (HE, ×1000).

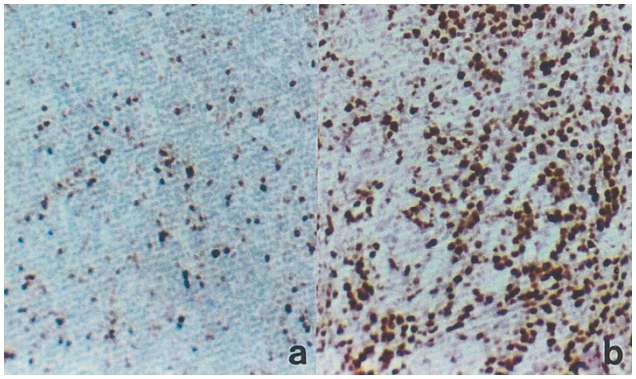

FIGURE 3. MIB1 staining in (**A**) chronic lymphocytic leukemia (5% of positive cells) and (**B**) in diffuse large-cell lymphoma (80% of positive cells).

and a loss of CD23 expression in Case 2. CD10 expression was negative in all cases except Case 4. A strong p53 expression was observed in DLCL cells in two cases (Cases 4 and 5). Staining for EBV (LMP1) was negative in all cases. At DLCL diagnosis, bone marrow examination showed only CLL cells in all patients except one with infiltration by the DLCL cells (Case 4).

Molecular Biology

PCR followed by electrophoresis and nucleotide-sequencing analyses demonstrated the same monoclonal IgH rearrangement between CLL and DLCL in two patients (Cases 1 and 2 Fig. 4). In Case 1, a biallelic monoclonal rearrangement was observed at CLL stage, whereas only one monoallelic rearrangement was conserved at DLCL stage. In Case 3, a monoallelic clonal pattern was evidenced in CLL, whereas no monoclonal pattern was found in DLCL, also suggesting allelic loss. In Case 5, two different clonal bands were detected in CLL and DLCL. The CLL band was also barely seen in the DLCL DNA analysis (Fig. 4), suggesting the presence of some residual CLL cells in the RS sample. Sequencing analysis of the dominant bands of CLL and DLCL revealed no homology between the two rearranged junctional regions. Moreover, BLAST and BESTFIT analyses revealed that the JH-joining region of the CLL monoclonal allele was identical to human JH6 gene, whereas the JH region of the DLCL allele matched to the JH1 gene (34). In two patients (Cases 4 and 6), neither frozen nor formalin-fixed digestive tissue was available for PCR analysis.

Treatment and Survival

A surgical resection of the tumor was performed in five patients (Cases 1, 2, 3, 5, and 6). One patient died during the postsurgical period (Case 1). Five patients (Cases 2, 3, 4, 5, and 6) were treated by

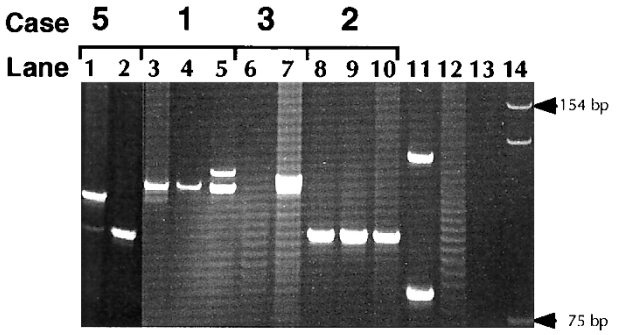

FIGURE 4. Comparison of immunoglobulin heavy-chain gene (IgH) rearrangement in chronic lymphocytic leukemia (CLL) and digestive Richter's syndrome. An identical monoclonal rearrangement was evidenced between CLL and digestive Richter's syndrome (RS) in Case 1 (CLL, ***Lane 5*** and RS, ***Lanes 3 and 4***) and Case 2 (CLL, ***Lanes 9 and 10*** and RS, ***Lane 8***). The identity of the IgH rearrangement was confirmed by sequencing analysis. In Case 1, an allele of the initial CLL (***Lane 5***) is lost in RS (***Lanes 3 and 4***). For Case 3, a monoclonal rearrangement was found in CLL (***Lane 7***) but not in RS (***Lane 6***). In Case 5, a different monoclonal rearrangement was detected in CLL (***Lane 2***) and in RS (***Lane 1***). A minor clone, identical to the CLL rearrangement, was also found in RS (***Lane 1***). ***Lanes 11 to 13*** correspond to monoclonal, polyclonal, and negative controls, respectively.

systemic chemotherapy. One patient received adjuvant radiotherapy (Case 2). After transformation of CLL into RS, the median survival concerning patients treated by chemotherapy was 22 months (range, 5 to 48 mo). The five patients who died presented with disease. The single living patient (Case 5) presented with lymphocytosis at only 5000 at last examination (see Table 4).

DISCUSSION

In approximately 3 to 5% of cases of CLL, the disease progresses to a large-cell lymphoma or Hodgkin's disease (2, 5–7, 35). Histological progression to large-cell lymphoma also corresponds to a general clinical alteration, as observed in our patients (1, 2, 12). Transformation occurs in lymph nodes, bone marrow, spleen, or other tissues (1, 2, 12). The prognosis for RS is very poor, with a median survival of 5 months (1, 2). Primary gastrointestinal involvement has been rarely reported (10, 21, 23, 27–30, 36). Clinical gastrointestinal manifestations during the CLL phase are rare and should lead to suspect transformation (36). Histologically, the main differential diagnosis remains the DLCL of MALT type, especially at the stomach level. Careful search for low-grade lymphoma component, lymphoepithelial lesions, and immunohistological analysis allowed us to rule out such possibility in our patients. Indeed, DLCL of MALT-type exhibit lymphoepithelial lesions composed of either small or large lymphoid cells (37, 38). MALT-type lymphoma cells usually express a CD5−, CD23− phenotype, whereas DLCL of RS type have an immunophenotype that usually resembles that of the original CLL (CD5+, CD23+, CD43+). However phenotypic changes may be observed (17), as in our patients with digestive RS with a loss of either or both CD5 or CD23. Immunoglobulin light-chain expression between CLL and DLCL may be different even though CLL and DLCL are clonally related (8, 14, 20). Because of this discordance, immunoglobulin gene rearrangement by Southern blot or PCR is the most appropriate analysis for study of the clonal relationship between CLL and DLCL. Such analysis has provided evidence for the same clonal origin for CCL and DLCL in most patients with nodal RS (8, 13–20). In other patients, an independent cellular clone was found at the DLCL phase (19, 22–26). When investigated, no clonal relationship between CLL and DLCL was previously established in digestive RS (23). Alternatively, we have demonstrated a common clonal origin at least in two out of four cases tested. In the DLCL of Case 1, only one of the two bands of the CLL was detected, suggesting allelic loss. This was also observed in Case 3. Finally, in only one case (Case 5), a different IgH gene rearrangement pattern was found between CLL and DLCL. Because IgH gene somatic mutation and/or reiterative rearrangements may in some instances modify the rearranged complementarity-determining Region 3 (17), sequencing analysis showed in this case that the two clonal populations were not related.

Specific oncogene or tumor-suppressor gene alterations involved in the morphologic transformation and clinical progression of CLL to DLCL have not been yet described. p53 has not been involved in the transformation of CLL (19) but may play a role in the development of a second malignancy (19, 39–41). Indeed, only two cases were strongly positive in the DLCL phase, whereas weak or negative p53 expression was found in the others. The EBV infection has been implicated in the progression of CLL to Hodgkin-like lymphomas (4, 5, 42). In our series, EBV immunodetection was negative in all cases of digestive RS.

TABLE 4. Treatment and Response in Patients with Digestive RS

Case No.	Regimen	Response	Duration (mo)	Last Follow-Up
1	Surgery	NR	1	Dead
2	CHVP, XRT	CR	24	Dead
3	CVPA	CR	36	
	Mini-CHOP[a]	PR	12	Dead
4	CEOP	NR	5	Dead
5	CEOP	CR	17	Alive
6	CVP	PR	16	Dead

mini-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHVP, cyclophosphamide, doxorubicin, vincristine, prednisone; CEOP, cyclophosphamide, epirubicine, vincristine, prednisone; CVPA, cyclophosphamide, vincristine, prednisone, adriamycine; CVP, cyclophosphamide, vincristine, prednisone; XRT, radiation; CR, complete response; PR, partial response; NR, no response; Dead, dead with disease.

[a] After relapse.

Median survival after transformation into RS was 22 months for patients treated by chemotherapy in our series. This differs from the 5 months' term outcome of nodal RS (39 patients; 1). One patient (Case 4) had a poor prognosis (5 months of survival) but was the only one characterized by DLCL bone marrow involvement.

Primary digestive RS seems to be of better prognosis than nodal RS, as previously suggested (21, 36). Indeed, an appropriate surgical resection, followed by chemotherapy led to complete remission for years in four patients.

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