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Mantle cell lymphoma, in leukaemic phase with prominent splenomegaly. A report of eight cases with similar clinical presentation and aggressive outcome

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Abstract Mantle cell lymphoma (MCL) is a well-defined peripheral B-cell lymphoma usually diagnosed upon peripheral lymph node biopsy. We report eight cases of peripheral B-cell leukaemia that demonstrate presumptive evidence of mantle cell characteristics. The patients had a median age of 68.5 years, and five were male. All presented with an enlarged spleen without any peripheral lymphadenopathies, and they were leukaemic at presentation (median lymphocytosis, 38×10^9/l). Morphological diagnosis of MCL was very difficult in five cases but easier in three because we were able to analyse either pre- or post-mortem lymph nodes and spleen. The immunophenotype of blood lymphocytosis using flow cytometry, the presence of a t(11;14)(q13;q32) and a cyclin D1 expression by leukaemic cells all fit with the diagnosis of MCL. All patients progressed and died with a median overall survival of 8 months. Multifocal areas of transformation in blastoid or large cell variants were observed in the three autopsied patients. In summary, one should consider the diagnosis of MCL at presentation in leukaemic phase even in the absence of peripheral adenopathies.

Keywords Mantle cell lymphoma · B-CLL · Leukaemia · Splenomegaly · Prolymphocytic leukaemia

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Introduction

Mantle cell lymphoma (MCL) [2] has recently been recognised as a distinct entity in the classification of B-cell non-Hodgkin's lymphomas [15]. It has previously been described as intermediate lymphocytic lymphoma [3, 37], centrocytic lymphoma [20] and mantle zone lymphoma [38]. The leukaemic phase of a non-Hodgkin's lymphoma initially diagnosed on a peripheral lymph node is well defined and usually associated with a poor prognosis, particularly in MCL [1, 27, 33]. An initial leukaemic presentation without significant peripheral lymphadenopathies does not usually lead to the diagnosis of mantle cell lymphoma. However, sporadic cases of MCL with an initial leukaemic phase have been described [14, 25, 29], and most of them were clinically aggressive.

Over a 6-year period (1992–1997), we identified eight cases which demonstrated presumptive evidence of MCL characteristics. These eight cases shared common clinical features, such as the absence of significant peripheral lymphadenopathy, an usually prominent splenomegaly and a very aggressive evolution. The phenotypic, cytogenetic and molecular data were all consistent with MCL. The differential diagnosis between MCL and B-cell chronic lymphocytic leukaemia (CLL) was very difficult upon cytological study of peripheral blood smears and on bone marrow (BM) biopsies. By contrast, the diagnosis of MCL based on histopathologic study of nodes or spleen was easier. Overall, our data suggest that MCL should always be considered when assessing the diagnosis of B-CLL, especially when patients present with massive splenomegaly and no peripheral lymphadenopathy. Our results underline the need of a multidisciplinary approach, combining morphology with flow cytometry immunophenotypic analysis, cytogenetics and cyclin D1 detection, all of which are important in the classification of peripheral B-cell lymphoma [9].

Materials and methods

Clinical analysis

All of the patients underwent staging, follow-up and treatment in the Department of Haematology. Staging procedures included a physical examination, chest, abdominal and pelvic computed tomography (CT) scan, complete blood count, flow cytometric analysis, BM aspirate and biopsy. An autopsy was possible in three patients. These patients were included in the retrospective study of chronic lymphoproliferative disorders recently published by Levy et al. [22].

Cyto- and histopathology

Cytological analysis was performed on peripheral blood films stained with May-Grünwald-Giemsa. Biopsies and post mortem samples were fixed in Bouin's solution or 10% buffered formalin and embedded in paraffin. Paraffin blocks were sectioned at a thickness of 3 µm and stained with hematoxylin and eosin, Giemsa and silver impregnation according to Gordon-Sweet. BM biopsy specimens were fixed in Bouin's solution, decalcified in RDO (Eurobio, France), processed and cut in the usual manner.

Immunohistochemical study

Immunohistochemistry was performed on paraffin-embedded tissue using a three-stage indirect immunoperoxidase technique or an alkaline phosphatase-antialkaline phosphatase (APAAP) method. The antibodies anti CD20 (L26, Dako), anti-CD3 (CD3, Dako), anti-CD5 (4C7, Novocastra), anti-Delta [immunoglobulin (Ig) D, Dako], anti-CD23 (MHM6, Dako), anti-CD10 (56C6, Novocastra), anti-kappa and anti-lambda (kappa, lambda, Dako), CNA42 (Delsol, Toulouse), anti-Ki67 (Mib-1, Immunotech) were used. Microwave pretreatment (750 W, three 5-min treatments) of slides in citrate buffer (10 mM, pH 6) was performed for all of the antigens except for the Ig light chains.

Immunophenotypic analysis

For immunophenotyping, mononuclear cell suspensions of peripheral blood were prepared according to well-established methods. A direct antibody labelling technique was employed using mouse monoclonal antibodies, CD3, CD5, CD19, CD20, CD23 (Becton-Dickinson, San Jose, Calif.), goat polyclonal anti-Kappa and anti-lambda light chains (Tago, INC) and FMC7 (Immunotech), labelled with either phycoerythrin or fluorescein isothiocyanate. Specimens were analysed using Lysis II software on a fluorescence-activated cell sorter (Becton-Dickinson).

Cytogenetic studies

Peripheral blood cells were incubated at 37°C for 72 h in the presence of tetradecanoyl phorbol acetate (TPA) and lipopolysaccharide (LPS). Chromosome preparations were made using standard methods and were analysed with R- or G- banding. Karyotypes were described according to ISCN [17].

Cyclin D1 detection using western blot analysis

Mononuclear cell suspensions of peripheral blood were prepared according to well-established methods. Cells (10^7) were lysed in buffer [Tris 20 mM pH 8, 150 mM NaCl, 1% Triton X100, 5 mM ethylene diamine tetraacetic acid (EDTA), 1 mM Na orthovanadate, 10 mM NaF, 10 µg/ml leupeptin, 10 µg/ml aprotinin, 100 µg/ml phenylmethylsulfonyl fluoride (PMSF)] for 20 min at 4°C. Lysates were spun at 12,000 rpm for 15 min, and the supernatant was collected. Protein concentration was assessed using the Bio-rad assay method (Biorad laboratories, Richmond, Calif.). Protein extracts (100 µg) were separated using 12% sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis and transferred to Immobilon membranes (Millipore, Bedford, Mass.). Membranes were blocked for 1 h in 5% non-fat dry milk-PBS and incubated with anti-cyclin D1 antibody (clone H295, Santa Cruz Biotechnology, Calif.). Subsequently, filters were washed twice in Tris 10 mM pH 7.5, 200 mM NaCl and 0.05% Tween and incubated with a horseradish peroxidase-linked secondary antibody at a 1/10,000 dilution for 1 h. Membranes were washed three times with the same rinsing buffer and detection was perfor-med using an enhanced chemoluminescence protocol (ECL, Amersham, Buckinghamshire, UK) according to the manufacturer's instructions.

Results

Clinical features

The clinical features are summarised in Table 1. Five out of eight patients were male, and the median age was 68.5 years (range 48–85 years). All patients had an enlarged spleen from 2 cm to 10 cm below the costal margin, and none had significant peripheral lymphadenopathies. Four patients presented with B symptoms. CT scan revealed abdominal lymphadenopathies in two patients. Initial blood lymphocytosis ranged from 8×10^9/l to 320×10^9/l with a median of 38×10^9/l.

Treatment (Table 2) was heterogeneous from one patient to another and mainly consisted of alkylating agents, steroids, fludarabine monophosphate or multidrug regimens such as CHOP (adriamycin, cytoxan, vincristine, prednisone) or VAD (vincristine, adriamycin, dexamethasone). No complete response was observed, and the disease rapidly became refractory to chemotherapy. All patients died from disease progression, and the median overall survival was 8 months (range 2–60 months).

Table 1 Clinical characteristics. *AX* axillary, *RP* retroperitoneal, *asc* ascitis, *pleur* pleural effusion

Case	Age (years)	Gender	Spleen (cm below costal margin)	Lymph nodes	Additional clinical symptoms	Blood lymphocytosis (10^9/l)
1	71	Female	8	No		183
2	85	Male	7	AX 1 cm	B symptoms	38
3	71	Male	2	No	B symptoms	320
4	60	Male	6	RP		38
5	48	Female	2	No		24
6	66	Male	8	No	B symptoms	8
7	65	Female	8	No		117
8	75	Male	10	RP	B symptoms, asc, pleur	16

Table 2 Outcome under treatment. *CHOP* adriamycin, cytoxan, vincristine, prednisone, *FAMP* fludarabine monophosphate, *CPM* cytoxan, *Dexa* dexamethasone (high dose), *CLB* chlorambucil, *MDR* multidrug regimen other than CHOP, *VAD* vincristine, adriamycin, dexamethasone

Patient	Treatment	Time to death (months)
1	CHOP, FAMP, CPM+Dexa	30
2	CLB	7
3	CLB	2
4	CHOP, Splenectomy, MDR	27
5	CPM, CHOP, FAMP, Splenectomy CLB+Dexa	60
6	CHOP, CLB+Dexa	8
7	CLB+Dexa, VAD	10
8	CHOP, MDR	3

Cytological analysis of peripheral blood lymphocytes

At presentation, leukaemic lymphoid cells were very difficult to classify in all of the cases, particularly between B-CLL and leukaemic phase of peripheral B-cell lymphoma. For each case, more than one diagnosis was initially discussed: B-CLL in five cases, MCL in four cases, prolymphocytic leukaemia in two cases, lymphoplasmocytic lymphoma in two cases, atypical B-CLL in two cases and lymphoblastic leukaemia in one case (case 7).

Histological findings

BM biopsy findings

BM biopsies were obtained for each patient at presentation. For seven patients, lymphomatous involvement consisted predominantly of small lymphoid cells associated with rare medium-sized lymphoid cells. Pattern of infiltration was nodular and interstitial in six cases and tumour cells ranged from 5% to 80% of the total cell population. In one case (case 6), the pattern was paratrabecular and associated with a discrete interstitial infiltrate. The cell's nuclei were either round or slightly irregular, resembling B-CLL cells or sometimes larger with triangular, irregular nuclei, fine chromatin and small central nucleoli more closely resembling centrocytes (Fig. 1A). Centroblasts or immunoblasts were not present, and no residual germinal centres were found. The absence of proliferative centres was striking. Increase in reticulin fibres was observed in four cases and mast cell hyperplasia in two. The absence of intracellular Igs using immunohistochemistry argued against lymphoplasmacytic lymphoma and B-CLL with plasmacytoid differentiation.

In one case (case 7), there was a massive and diffuse infiltration by medium sized lymphoid cells looking like blast cells with fine chromatin and small nucleoli (Fig. 1B). The mitotic index was very high. The diagnosis of a blastoid variant of MCL was done, the differential diagnosis with lymphoblastic lymphoma being very difficult.

Spleen and hilar lymph nodes biopsies findings

Two patients (cases 4 and 5) underwent a splenectomy during the course of their illness. Histological study of the spleens showed a multimicronodular pattern due to the infiltration of the follicles that appear homogeneous and voluminous. No residual germinal centres could be disclosed. The nodules were infiltrated by a mixture of small lymphocytes resembling cells of B-CLL, prolymphocytes and centrocytes. Many scattered histiocytes with large clear cytoplasm without tingible bodies were present in homogenised follicles, giving a mottled pattern. Cords and sinuses were infiltrated by tumour cells. Many iron-laden macrophages were present with some Gandy-Gamna nodules.

Splenic hilar lymph nodes were completely effaced by small- to medium-sized lymphocytes in a diffuse and vague nodular pattern (Fig. 2A) without residual germinal centres. No proliferative centres were observed. A characteristic mottled pattern due to numerous scattered histiocytes was also observed (Fig. 2B, C). The nodular pattern coupled with the mottled pattern was highly suggestive of MCL.

Immunohistochemical studies on spleen paraffin sections showed expression of CD20, Delta heavy chain and CD5 and an absence of expression of CD23 by the tumour cells. In both cases, very few cells express intracytoplasmic monotypic lambda Ig. Some remnants of follicular dendritic cells, not well demarcated, were observed and in some areas, around 20–30% of cells express Ki-67.

Autopsy findings

Autopsies were performed in three patients (cases 1, 4 and 5), including the two patients who had had a splenectomy during the course of the disease. In all cases, there were numerous polyadenopathies in the mediastinum, retroperitoneum, mesentery and in one case, at the hepatic and splenic hilum. These adenopathies had a maximum diameter of 15 cm. The only spleen analysed at autopsy (1000 g) presented a multimicronodular pattern on section. In all of the cases, extranodal organs, particularly the kidneys, the liver, the gut, and in one case the brain, were involved by the tumour. In these organs, numerous white nodules measuring up to 8 cm in diameter were seen.

Massive involvement of the large bowel by the tumour without features of lymphomatous polyposis was found in two cases. Ulceration of sigmoid by the tumour, extending to the peritoneum, was present in two cases and could easily explain the death of these patients from gram-negative bacilli septicaemia. One patient died from a massive temporal tumour of the brain in relation to the lymphoma.

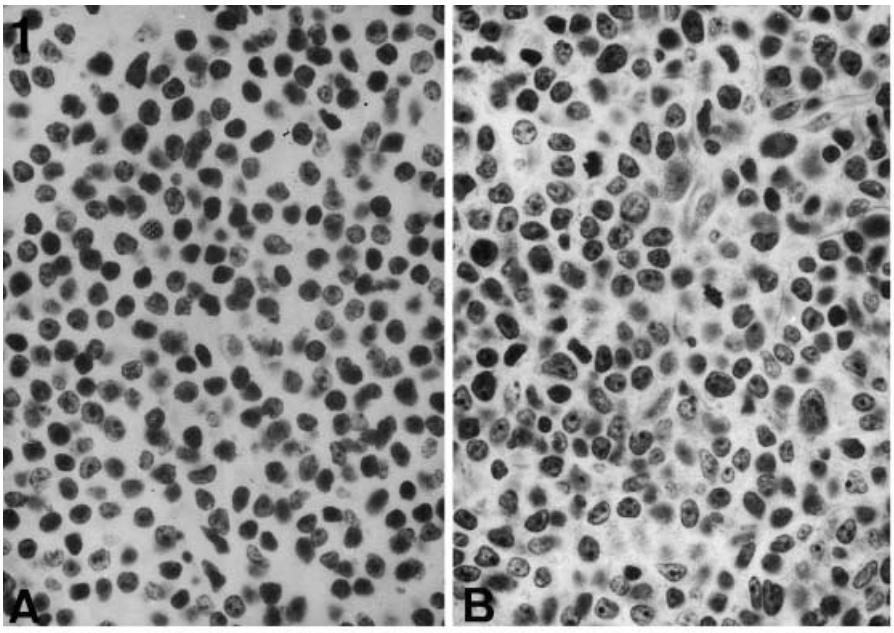


Fig. 1 Bone marrow biopsies, cytological pattern: **A** small and medium-sized cells (Giemsa, ×304). **B** medium-sized blastoid cells (Giemsa, ×228)

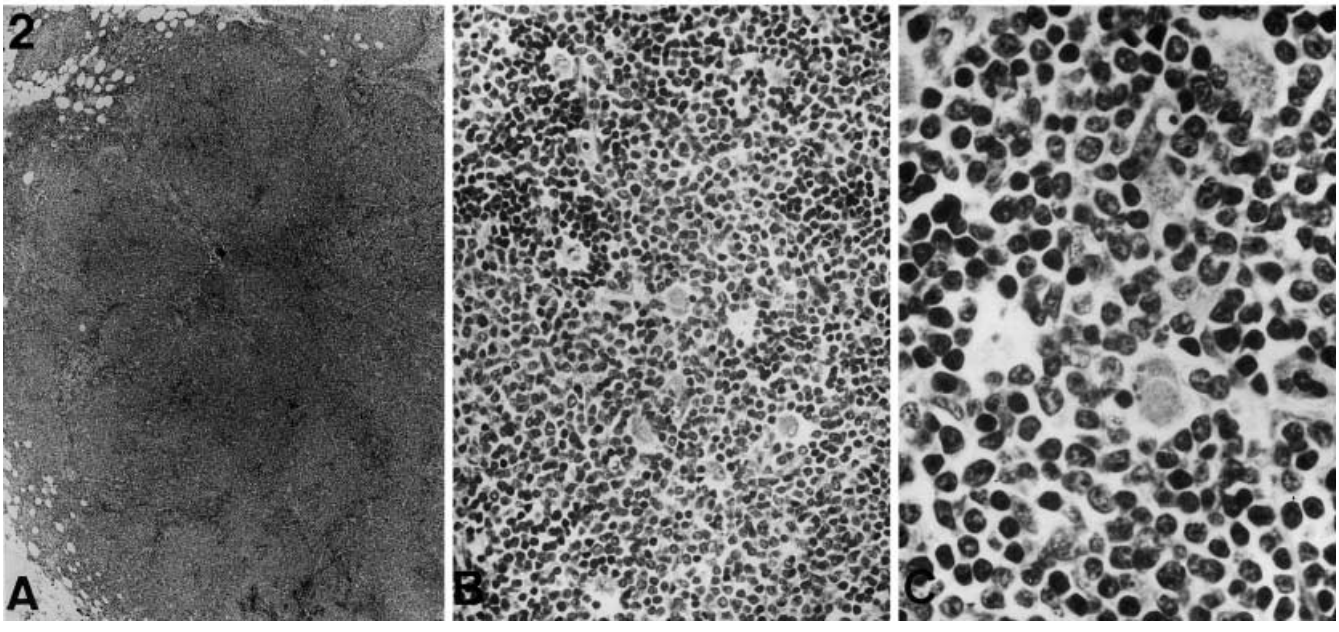
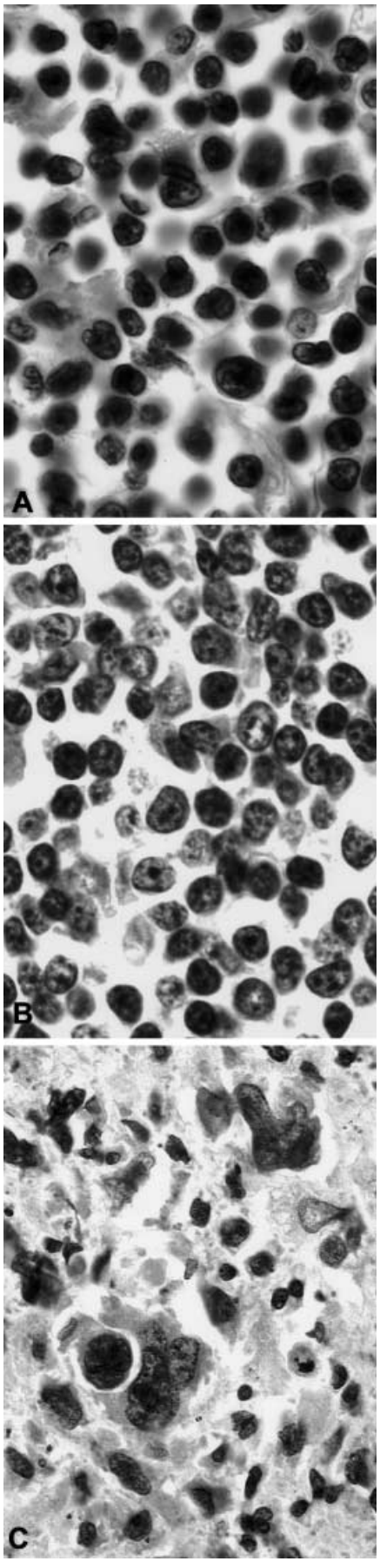


Fig. 2 Lymph node biopsies: **A** nodular pattern, (haematoxylin and eosin, ×32); **B** mottled pattern (Giemsa, ×152); **C** mantle cells (Giemsa, ×304)

Table 3 Flow cytometry data of peripheral blood lymphocytes. CD22 staining was evaluated as weak (w), moderate (m) or strong (s); *ND* not done, *IgS* immunoglobulin surface expression

Case	CD5+CD20+	Bright IgS	CD23+	CD22	FMC7+	Matutes Score[b]
1	97%[a]	Yes	8%	ND	56%	1/4
2	9%	Yes	7%	m	2%	1/5
3	97%	Yes	6%	s	14%	2/5
4	95%	Yes	16%	ND	25%	1/4
5	56%	Yes	6%	m	6%	2/5
6	78%	Yes	0%	s	74%	1/5
7	92%	Yes	0%	m	75%	1/5
8	33%	Yes	14%	w	48%	2/5

[a] The percentage indicates the percentage of CD20 cells expressing CD5, CD23, or FMC7 staining
[b] The score was calculated according to Matutes et al. [22]



Histological analysis disclosed in the three cases a histological pattern of the lymph nodes suggestive of MCL (vague nodular pattern, numerous scattered histiocytes). Immunohistochemical staining of tumour cells found an expression of CD2O, CD5, δ heavy chain expression, and an absence of expression of CD10 and CD23. Infiltration of the BM was diffuse and massive in two cases, and nodular in one.

Interestingly, in these three cases, there were multifocal cytological transformation of the lymphoma. This transformation was prominent in the liver nodules in two cases, and in the brain tumour and spleen in one case. The cytological types of transformation were often blastoid, with fine dusty chromatin and inconspicuous nucleoli. However, in the three cases analysed, other atypical types of transformation were found: large cell multilobated representing, in some areas, 30% of the tumour cells in case 1, large cell associated with mantle cells in case 4 and anaplastic large B cell in case 5 (Fig. 3A–C).

Immunophenotypic findings

Immunophenotyping using flow cytometry was performed from peripheral blood in all eight cases. Results are shown in Table 3. A phenotype, highly suggestive of MCL (CD5+CD20+, bright surface Ig, CD23–) was present in six cases. FMC7 positivity was very heterogeneous. The majority of cells were CD5– in only two cases. Although CD22 was not analysed in two cases, all of the scores according to Matutes [23] range from 1 to 2.

Cytogenetic and molecular findings

Cytogenetic studies performed on peripheral blood cells showed a translocation t(11;14) (q13;q32) in all of the cases. Additional abnormalities were always present. The only recurrent abnormality was del (1)(p22 p32) in two cases (case 1 and case 6).

Protein extracts from peripheral blood mononuclear cells were performed, and a strong expression of cyclin D1 was found in all cases using western blot analysis. Immunohistochemistry for cyclin D1 could not be performed because the BM biopsies were fixed in Bouin's liquid and decalcified.

Discussion

We report eight cases of peripheral B cell lymphoma in leukaemic phase, whose classification, based on a multidisciplinary approach, is highly suggestive of MCL.

Fig. 3 Large cell variant of mantle cell lymphoma: **A** multilobated large cell (haematoxylin and eosin, ×506); **B** large cell mixed with mantle cell (Giemsa ×608); **C** anaplastic large cell (Giemsa, ×608)

These patients exhibit striking similarities in clinical presentation and course. All but one are above 60 years old and presented with marked splenomegaly, no significant peripheral adenopathies and an important peripheral blood lymphocytosis with a median of 38 10^9/l, mimicking a B-CLL. This disorder carries a poor prognosis. All patients rapidly died from disease progression with an 8-month median overall survival with whatever treatment.

Cytological analysis of peripheral blood and BM histopathological study disclosed neoplastic cells quite heterogeneous in appearance with a broad morphological spectrum [39]. On bone marrow (BM) sections, the infiltrate is more often nodular and interstitial, although sometimes paratrabecular or massive. Such findings have been previously reported in MCL [10, 35]. The neoplastic cells on BM sections may look like B-CLL or lymphoplasmacytoid cells. Indeed, although very precise cytological analysis of leukaemia MCL has been described on blood films [30], the neoplastic mantle cells have a broad morphological spectrum [39] and may resemble small mature lymphocytes (B-cell CLL) [9, 15] or atypical CLL or prolymphocytes [29]. However, most authors are in agreement today with the fact that a diagnosis of MCL should not be based on the examination of peripheral blood or BM biopsy alone, due to the lack of precise criteria for such a diagnosis [9, 36]. In some other cases, the differential diagnosis on the BM biopsy between lymphoblastic lymphoma and MCL in blastoid transformation was almost impossible on a pure morphologic criteria and requires additional staining, such as TdT and CD5. In the spleen, the precise classification of such small B-cell lymphomas on morphology alone may be very difficult with splenic marginal zone lymphoma (SMZL). The absence in our cases of a well defined biphasic pattern of a prominent plasmacytic differentiation and of monocytoid like B-cells are not in favour of a SMZL. However, rare cases of MCLs may resemble SMZL presenting with large cell and biphasic cytology [24], and some SMZL may express CD5 [32] and therefore require a multidisciplininary approach for optimal classification. Immunological and molecular studies in all of the cases and lymph node histological studies in three cases allowed us to diagnose the mantle cell origin of neoplastic cells.

Architectural pattern and cell morphology in lymph node involvement by MCL has been studied for a long time. The nodular architecture of the proliferation, the presence of numerous scattered histiocytes with large pale cytoplasms and a mantle zone pattern when it is observed, are hallmarks of this histologically defined disease [15, 36, 40]. These features and the absence of pseudo-follicles or proliferative centres easily allow the differential diagnoses from B-CLL or atypical B-CLL. The presence of intracellular Igs in neoplastic mantle cells has been described for a long time [20], and the diagnosis of lymphoplasmacytic lymphoma should not be assessed if all of the other criteria of MCL are present, as in our three cases. The post-mortem data were important in our series, allowing us to recognise a MCL on the lymph nodes and foci of large cell transformation. Although the majority of cells at death were mantle cell or blastoid mantle cell, our series supports the fact that large cell transformation, rarely occur in such lymphomas [15, 36, 40] or only at a very late stage.

Flow cytometry data analysing cell surface expression (S) of CD5, CD22, CD23, FMC7, and intensity of IgS of tumour cells have been used very successfully to eliminate a diagnosis of B-CLL [23]. In our cases, the absence of CD23 and the strong IgS orientates against a B-CLL. The association with CD5 expression is highly suggestive of MCL and our score, according to Matutes classification [23], was calculated between 1 and 2, as in 85% of MCL and 2% of typical or atypical B-CLL. Nevertheless, CD5 negativity may be seen in MCL in some series representing 30% of the cases [23], and the negativity for CD5 in the majority of B cells for two of our cases does not argue against the diagnosis. FMC7 staining, usually positive in MCL, is very heterogeneous in this series and should not be considered for the differential diagnosis between these lymphoproliferative disorders.

The t(11;14) (q13;q32) was observed in all of the cases and is associated with cyclin D1 strong expression by tumour cells as demonstrated using western blot assays. These two features are the molecular hallmark of MCL. Although this translocation has been seen in very rare B-CLL [6, 16] or atypical CLL [8, 11, 12, 13], the morphological features of the lymph nodes in three out of eight cases in our series and the flow cytometry data argued against B-CLL or atypical B-CLL. A recent study [5] analysing lymph nodes, histopathological features of atypical B-CLL diagnosed by means of cytology, found pseudofollicles in all of the cases. These were never observed in our cases. Interestingly, it was shown previously that the B-CLL with translocation to 14q32 had one of the worst outcomes of all of the B-CLLs [18] and that the atypical CLL with t(11;14) were sometimes very aggressive with a blastoid transformation [31].

It would be very interesting to get some histopathological data from these patients to be sure that they cannot be considered as having MCL in leukaemic phase. Moreover, in a recent series classified as atypical CLL, 14 out of the 57 cases had a t(11;14)(q13; q32) and were reclassified in MCL [4]. There were many additional chromosomal abnormalities in MCL, and the only other recurrent abnormality in our series is the deletion of chromosome 1, del(1) (p22 p32) described in 5 out of 13 patients with MCL [21].

The similar clinical presentation and outcome of our series are strongly in favour of a single entity. It may represent a genuine primary splenic MCL as reported by Pittaluga et al. [28]. In MCL, a leukaemic phase at presentation has been shown to have a very poor prognosis with a median overall survival of less than 2 years [1, 27] as the presence of splenomegaly [7]. The median age of our series (68 years) is very similar to that described in MCL, whether or not it is leukaemic at presentation [1, 27, 34, 37]. A clinical presentation, such as that ob-

served in our cases with leukaemic features and prominent splenomegaly without adenopathies, has been rarely reported in MCL and, from a clinical point of view, is close to prolymphocytic leukaemia. Although a diagnosis of prolymphocytic leukaemia was not established in any of our cases, a t(11;14)(q13;q32) has been reported in 20% of prolymphocytic leukaemia [8]. Median age and poor outcome are similar to those of MCL [19]. Moreover, immunological phenotype is very similar despite the fact that CD5 is positive in 70% of MCL and in 32% of prolymphocytic leukaemia (PLL) [23]. It seems interesting to consider the percentage of PLL CD5 positive with a t(11;14) translocation. Moreover, it has been reported that PLL may have a mantle zone pattern in lymph nodes [26]. Therefore, it appears that this series of mantle cell leukaemia may share important features with t(11;14) PLL and further analysis and comparison of these leukaemic processes should be addressed, particularly focusing on histopathological data.

In summary, the remarkably similar clinical presentation and outcome of our series may suggest that it represents a clinical variant of MCL. The histopathological study of the lymph nodes in three of these patients are clearly in favour of a mantle cell origin of tumour cells, and the autopsy data further demonstrate the existence of large cell transformation in a few areas. The extreme difficulty of diagnosing this entity using only peripheral blood analysis and BM biopsy strengthens the need for a multidisciplinary approach for the diagnosis of peripheral B-cell lymphoma. Moreover, it indicates that a MCL in leukaemic phase should be discussed, even in the absence of any peripheral adenopathy, particularly when the presentation is marked by an important lymphocytosis associated with large splenomegaly.

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