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Guidelines for subtyping small B-cell lymphomas in bone marrow biopsies

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Abstract In this review, we summarise the patterns of bone marrow involvement by small B-cell lymphomas. Both our own experience and the literature reports on the subject show that each subtype of lymphoma can be recognised from a distinct combination of a suggestive growth pattern and a particular cytological composition. A predominantly paratrabecular infiltrate composed of centrocytes is characteristic of follicle centre cell lymphoma. In mantle cell lymphoma, prominent intertrabecular nodules, each consisting of a monotonous proliferation of small to intermediate-sized lymphoid cells with an irregular nucleus, are the most frequent finding. Marginal zone cell lymphoma displays similar intertrabecular nodules, but the infiltrates are rather loose and polymorphic, whereas the lymphoid cells exhibit monocytoid features. Diffuse infiltrates composed of small lymphocytes with clumped chromatin, of plasma cells with Dutcher bodies and of mast cells are observed in most cases of lymphoplasmacytoid lymphoma/immunocytoma. Although chronic lymphocytic leukaemia / small lymphocytic lymphoma can present with a comparable pattern of bone marrow involvement, an interstitial infiltrate of small lymphoid cells is usually observed. A comparable interstitial pattern also prevails in hairy cell leukaemia. This lymphoma subtype, however, can be readily identified by the abundant clear cytoplasm of the neoplastic cells, erythrocyte extravasation and associated abnormalities in the haematopoietic series.

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Introduction

As the importance of bone marrow (BM) biopsies in the staging, follow-up and diagnosis of non-Hodgkin's lymphoma (NHL) is beyond dispute, several studies have been undertaken to determine the incidence and the morphologic characteristics of BM involvement by these neoplasms. However, since at the time these studies were performed diagnostic haematopathology was dominated by the Kiel classification in Europe and the Working Formulation in the States, the investigators subtyped NHL according to these systems and used the corresponding terminology [3, 17, 19, 28, 41].

The introduction of the REAL classification involved the definition of several, often previously unrecognised, clinicopathological entities based on a combination of clinical, morphological, immunophenotypical and genotypical features [23]. Among these, a subset of neoplasms predominantly composed of small B-cells, comprising follicle centre cell lymphoma (FCCL), mantle cell lymphoma (MCL), marginal zone cell lymphoma (MZL), lymphoplasmacytoid lymphoma/immunocytoma (LPI), chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), and hairy cell leukaemia (HCL) can be discerned. Overall, these small B-cell neoplasms display a considerable incidence of BM involvement at diagnosis or during the course of the disease [19, 28, 41]. Moreover, the BM trephine may be the first tissue available for histological examination in HCL, CLL/SLL, MCL and LPI [4, 10, 11, 13, 33, 42].

Considering the significant diagnostic contribution of an adequate histopathological evaluation of a BM trephine displaying invasion by a small B-cell NHL on the one hand, and the lack of an integrated view on the exact morphological picture characterising the REAL entities on the other, we decided to review the histological characteristics of BM involvement by the various subtypes of

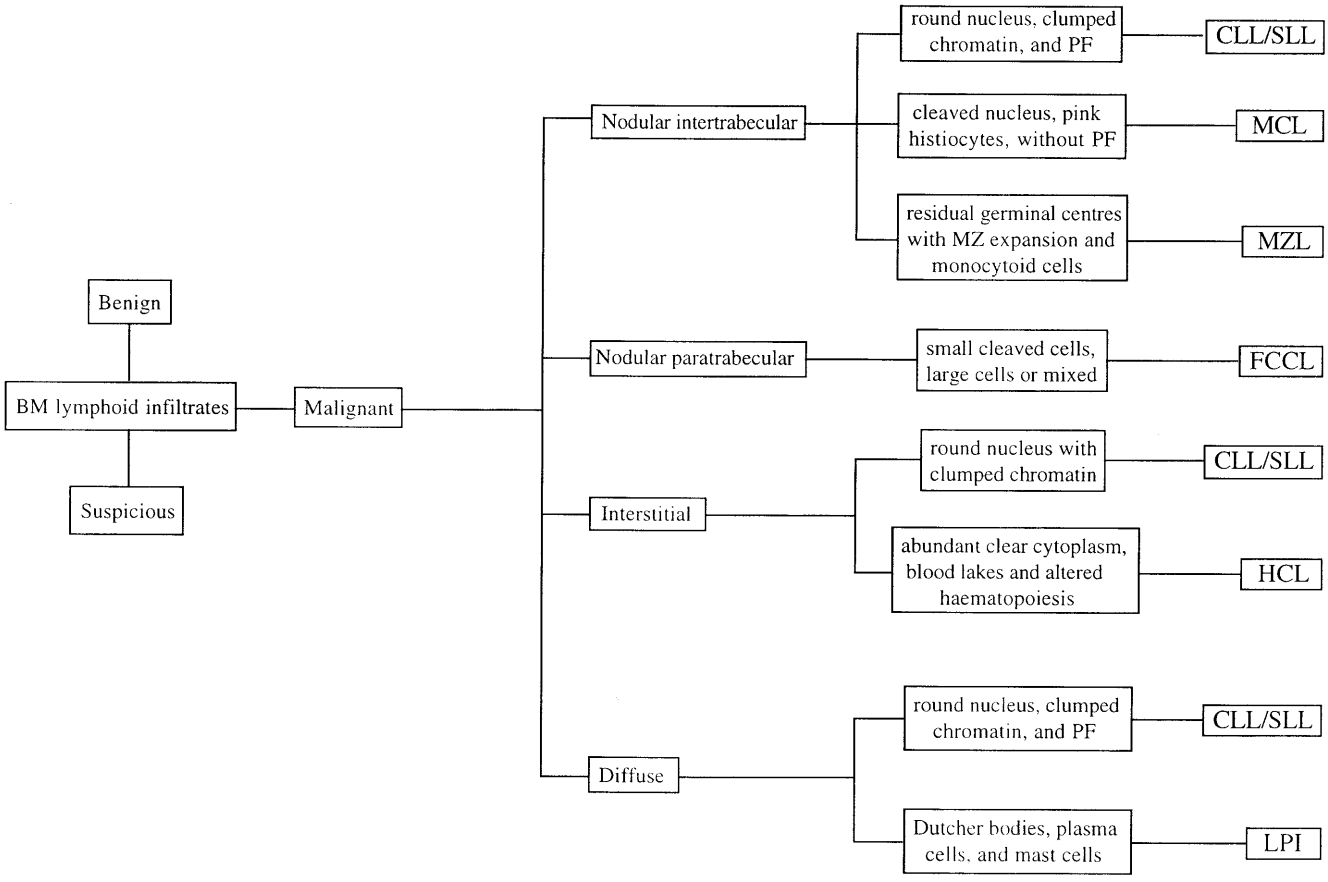

Fig. 1 Algorithmic approach to the subclassification of small B-cell lymphomas in bone marrow trephine biopsies (*FCCL* follicle centre cell lymphoma, *MCL* mantle cell lymphoma, *MZL* marginal zone cell lymphoma, *LPI* lymphoplasmacytoid lymphoma / immunocytoma, *CLL/SLL* chronic lymphocytic leukaemia / small lymphocytic lymphoma, *HCL* hairy cell leukaemia, *BM* bone marrow, *PF* pseudofollicles, *MZ* marginal zone)

small B-cell lymphomas as described in the REAL classification. We added our own findings on a substantial number BM biopsies involved by small B-cell lymphoma, collected in the Department of Pathology of the University Hospitals of Leuven over a 5-year period (1994–1998) to the previously published data. For FCCL, MCL, MZL and SLL, only cases with a clearly defined diagnosis established either in a lymph node or in an extranodal location were analysed. Biopsies showing involvement by LPI were included only if documented by the clinical syndrome of Waldenström's macroglobulinaemia, whereas CLL and HCL cases required a clinical and haematological picture fulfilling FAB classification criteria [6]. For each lymphoma category a limit of 50 cases was imposed.

This review allowed us to provide histological guidelines for the subclassification of these lymphoproliferative disorders in BM trephines, which are summarised in a practical algorithmic approach (Fig. 1).

The optimal fixation and embedding procedure for bone marrow trephines: one can have too much of a good thing. ...

While various fixatives and sophisticated (unusual) embedding media, including methylmetacrylate, have been claimed to be essential for a proper handling of BM biopsies, we obtain satisfactory results by using B5 fixation for a maximum of 3 h, followed by formic acid decalcification and subsequent processing for paraffin embedding. Not only does the latter simple technique provide adequate 3-µm-thick sections routinely stained with HE, it is also suitable for further immunohistochemical analysis and molecular genetic investigations.

Immunohistochemistry was recently introduced in the analysis of BM trephines, when several antibodies recognising their epitopes in paraffin-embedded material became freely available. Whereas a limited panel including CD3 and CD20 will be sufficient in almost all cases (Fig. 2), occasionally some additional immunostainings may be necessary. Among the latter, antisera detecting cytoplasmic immunoglobulin (IgM, IgG, kappa and lambda) and thus useful to identify a poly- or monotypic plasma cell proliferation, are particularly helpful. In addition, it can be worthwhile to stain for CD5 to support a diagnosis of MCL and CLL/SLL or to search for cyclin D1 immunoreactivity to distinguish between both subtypes of CD5-positive B-cell lymphomas. Nevertheless, it should be stressed that these particular antisera, espe-

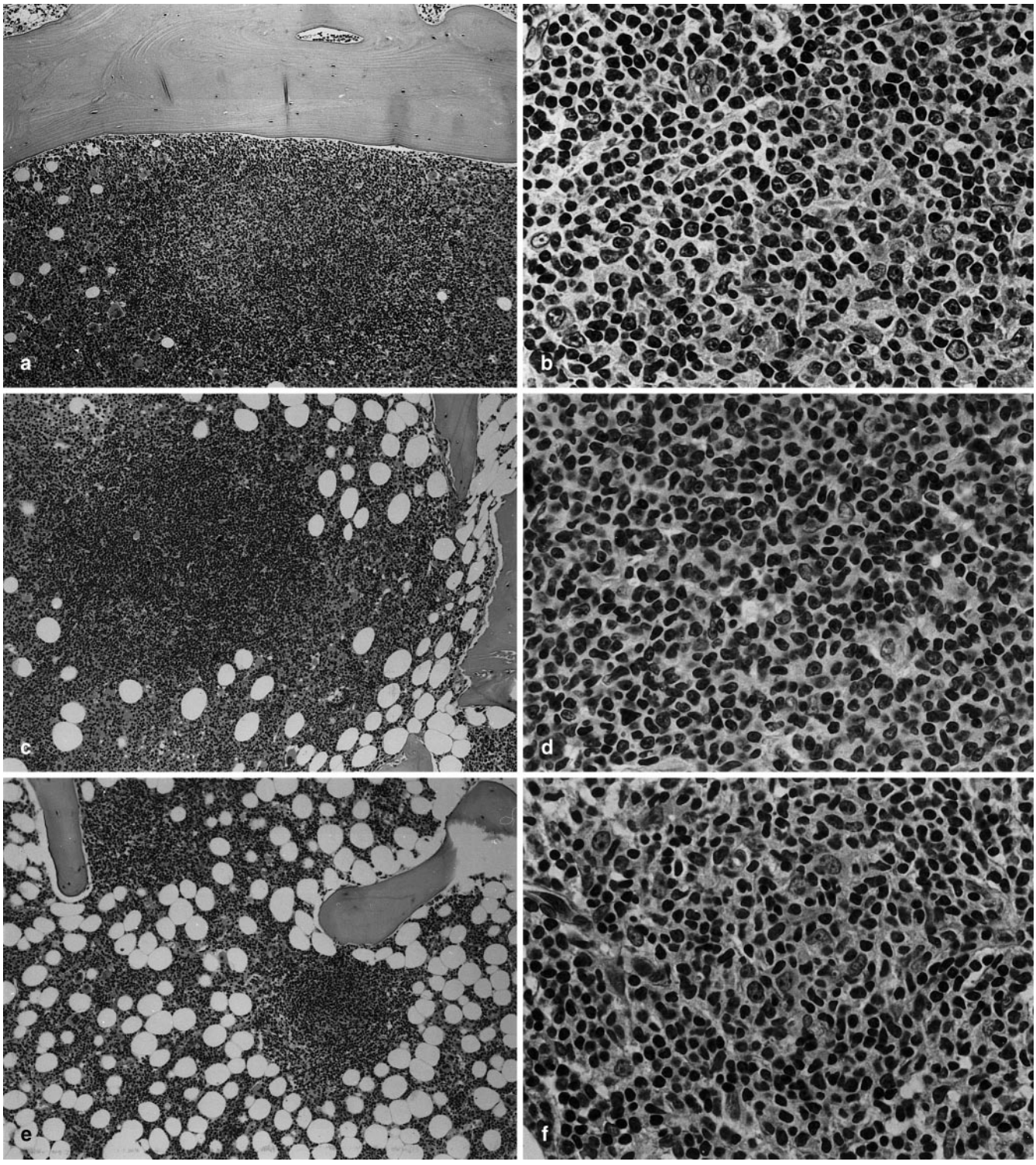

Fig. 2a–f Bone marrow involvement by nodular aggregates. **a**, **b** Follicle centre cell lymphoma (FCC): nodular aggregates, composed of loosely arranged small lymphoid cells with a cleaved nucleus, admixed with larger and follicular-dendritic-like cells, in a characteristic paratrabecular localisation. **c**, **d** Mantle cell lymphoma (*MCL*): small to intermediate-sized lymphoid cells with an irregular nuclear outline forming an intertrabecular nodule. Note the presence of ”pink” histiocytes. **e**, **f** Marginal zone cell lymphoma (*MZL*): follicle-like nodules in an intertrabecular localisation comprising small lymphoid cells with dispersed chromatin and a considerable amount of clear cytoplasm

cially the one immunoreacting with cyclin D1, lack perfect sensitivity, as exemplified by negative immunostaining results obtained in otherwise characteristic cases.

In a selected number of cases molecular techniques can be applied to DNA extracted from serial sections of the trephine to demonstrate clonal immunoglobulin heavy chain (IgH) and T cell receptor (TCR) gene rearrangements using a polymerase chain reaction (PCR) technique. Whereas classic PCR techniques are known to

Table 1 Patterns of bone marrow involvement in small-B-cell neoplasms as observed in a series of 151 cases, collected in the Department of Pathology, Leuven, expressed as number (%) of cases (*FCCL* follicle centre cell lymphoma, *MCL* mantle cell lymphoma, *MZL* marginal zone cell lymphoma, *LPI* lymphoplasmacytoid lymphoma/immunocytoma, *CLL/SLL* chronic lymphocytic leukaemia/small lymphocytic lymphoma, *HCL* hairy cell leukaemia)

Neoplasm	*n*	Nodular intertrabecular	Nodular paratrabecular	Interstitial	Diffuse
FCCL	35	7 (20%)	35 (100%)	1 (3%)	0 (0%)
MCL	22	19 (86%)	6 (27%)	4 (18%)	2 (9%)
MZL	12	12 (100%)	0 (0%)	6 (50%)	0 (0%)
LPI	16	3 (19%)	1 (6%)	4 (25%)	12 (75%)
CLL/SLL	50	22 (44%)	0 (0%)	40 (80%)	11 (22%)
HCL	16	0 (0%)	0 (0%)	15 (94%)	3 (19%)

have only limited sensitivity, it has been demonstrated recently that additionally investigating the rearranged kappa gene locus increases the success rate of the method from 60% to 90% [21]. Moreover, a similar approach to the analysis of TCR gene rearrangements also yields promising results (Inghirami, personal communication).

Specific histological features of each lymphoma entity

To adequately describe a lymphomatous BM infiltrate, several previously introduced terms appear very convenient [3, 33]. Therefore we suggest maintaining the established terminology defining nodular intertrabecular (centrally located lymphoid aggregates, occasionally touching the bone trabeculae), nodular paratrabecular (lymphoid infiltrates lining the bone trabeculae), interstitial (infiltration of the marrow in between the fat cells), and diffuse (obliteration of the intertrabecular area, with replacement of the adipocytes by the neoplastic cells) growth patterns. The incidence of each of these four patterns of BM involvement is illustrated by the results found in our material (Table 1).

To reach a final diagnosis, not only the characteristics of the infiltrate at low power should be evaluated; in addition the cytological features are very informative.

Follicle centre cell lymphoma

The hallmark of BM involvement by FCCL is undoubtedly the presence of nodular paratrabecular infiltrates, which vary in number and extent (Fig. 3a, b) [19, 34, 41, 46]. These infiltrates line the bone trabeculae over some distance, displacing both the myeloid precursors and the fat cells adjacent to it. The smaller ones may be barely perceptible on low power examination, prompting a high index of suspicion for their identification. While, in occasional cases, these aggregates extend into the intertrabecular area to form nodules recapitulating neoplastic follicles, a clear-cut interstitial pattern of involvement is extremely rare and a diffuse pattern is almost never found.

The infiltrates are predominantly composed of loosely aggregated small lymphoid cells, with scanty cytoplasm and a dark staining, cleaved nucleus (centrocytes). Interestingly, the cellular morphology displayed in the corresponding lymph node can be discordant, a phenomenon that we observed in four of our cases and which has also been reported in other series [5, 14, 19, 29]. It can be assumed that these different cytological presentations are merely an expression of the heterogeneity of FCCL, as they can also be noted in different lymph node specimens from the same patient, either simultaneously or sequentially [45].

Hypocellular and/or fibrotic paratrabecular foci have also been recorded in FCCL and were ascribed to multiple-drug chemotherapy [36]. This feature, whether therapy related or primarily associated with the lymphomatous infiltrate, has two major implications for diagnosis. It may impair the identification of neoplastic lymphoid cells in BM smears, since BM aspiration tends to sample the areas that offer less resistance and therefore stresses the importance of the trephine biopsy, particularly if a FCCL is suspected [15]. On the other hand, the presence of these foci should raise the suspicion of BM involvement by FCCL, and necessitates serial sectioning and/or immunohistochemical procedures to rule out the presence of malignant cells.

Mantle cell lymphoma

The majority of MCL cases are characterised by intertrabecular nodular infiltrates, variable in size and number and composed of densely packed small to medium-sized cells with an irregular nuclear outline (Fig. 3c, d). This distinctive cytological composition is consistently reported [2, 13, 39, 46] and indeed represents a diagnostic picture, particularly if, in addition, “pink” histiocytes are conspicuous [35]. Large transformed cells (paraimmunoblasts) or pseudofollicles are typically absent.

Focal paratrabecular nodules, usually smaller than the intertrabecular aggregates, are quite common, but exclusively paratrabecular BM involvement seems to be very rare in MCL, although one such case has been reported previously [39]. In the series of cases we reviewed, we did recognise paratrabecular infiltrates in addition, but these were certainly not as prominent and extensive as those observed in FCCL, and they never outweighed the

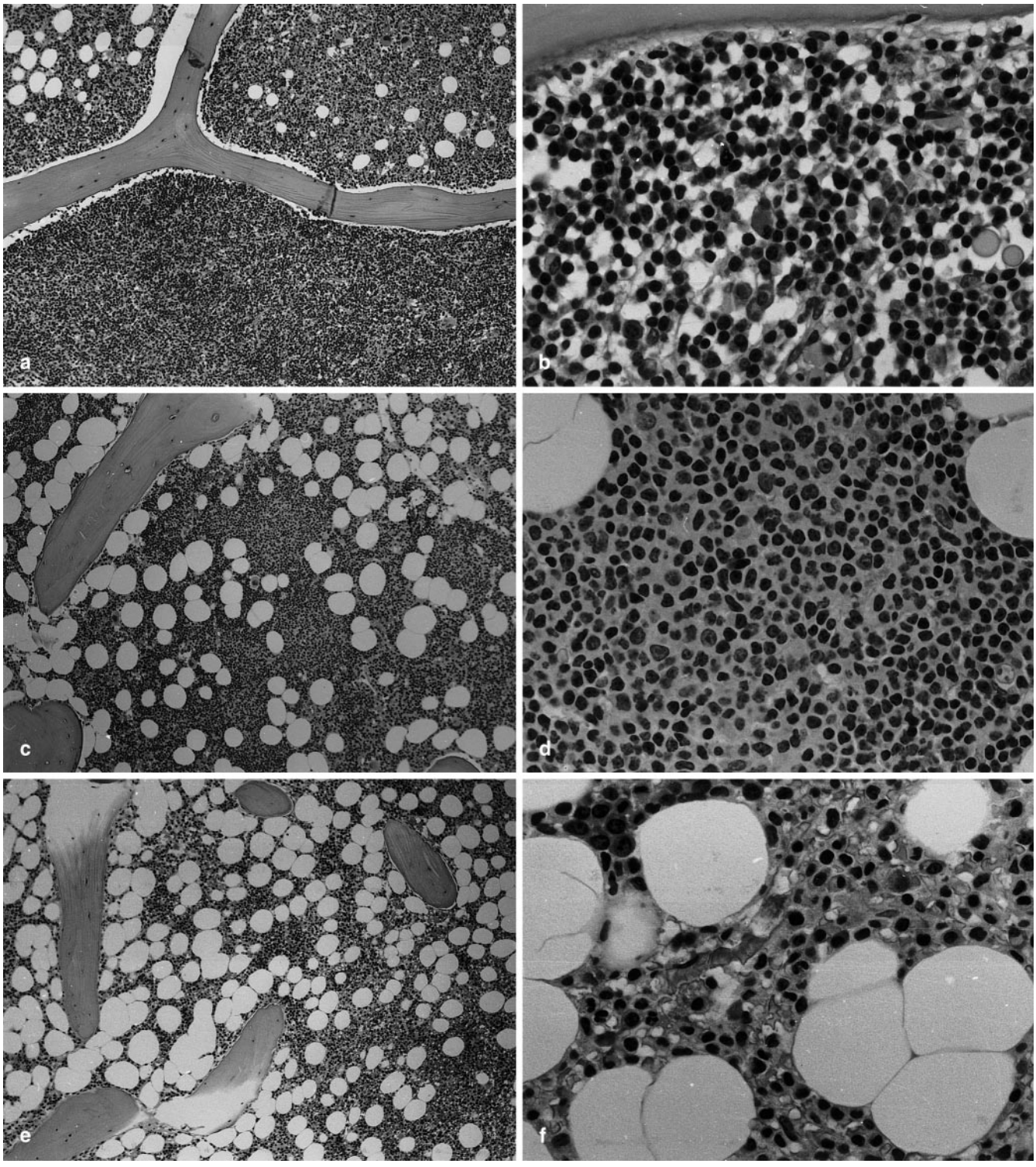

Fig. 3a–f Diffuse and interstitial patterns of bone marrow involvement. **a**, **b** Lymphoplasmacytoid lymphoma/immunocytoma (*LPI*): a diffuse infiltrate, sparing residual haematopoietic elements, that consists of small lymphoid cells with a round nucleus and a small, centrally located nucleolus. Note the admixture of plasma cells. **c**, **d** Chronic lymphocytic leukaemia/small lymphocytic lymphoma (*CLL/SLL*): bone marrow involvement by an interstitial infiltrate, accompanied by some smaller nodular aggregates. Small lymphocytes with a round hyperchromatic nucleus predominate. A pseudofollicle with larger cells (prolymphocytes and paraimmunoblasts) is shown. **e**, **f** Hairy cell leukaemia (*HCL*): small to intermediate-sized lymphoid cells with abundant clear cytoplasm infiltrate in between the fat cells. Note the megaloblastoid features of the erythroid series

nodular intertrabecular pattern. This peculiar paratrabecular involvement may even be helpful as a means of distinguishing between MCL and other lymphomas, such as CLL/SLL, that share the tendency to present primarily as nodular intertrabecular aggregates and/or interstitial infiltrates but never display paratrabecular nodules.

Larger tumour nodules tend to coalesce, simulating a diffuse pattern of involvement, but a truly diffuse proliferation is exceptional. Infrequently, tumour cells are scattered throughout the interstitium, but occasional small clusters are invariably present.

However, entirely diffuse and/or interstitial patterns are uncommon and, as they are suggestive of BM involvement by CLL/SLL, they should prompt a search for prolymphocytes and/or paraimmunoblasts [13, 46].

Evaluation of the cytological features is equally important, to distinguish cases of MCL displaying nodular intertrabecular and/or interstitial infiltrates from MZL.

Marginal zone cell lymphoma

MZL involving BM biopsies typically consists of ill-delineated intertrabecular nodules, varying in size and number, that occasionally touch the bone trabeculae and can be accompanied by an interstitial infiltrate (Fig. 3e, f). The larger ones mimic lymphoid B follicles, with a residual germinal centre surrounded by an expanded marginal zone. Loosely arranged small lymphoid cells displaying a slightly or moderately indented nucleus with dispersed chromatin and a fair amount of clear cytoplasm constitute the neoplastic cell population. Among these a few large, activated lymphoid cells, plus some follicular dendrite-like cells and a variable number of plasma cells are found admixed.

Germinal centres occur only very sporadically in BM trephines and, even so, are preferentially observed in young patients or associated with inflammatory or autoimmune disorders [9, 18]. Owing to the intrinsic rarity of MZL, the investigation of these nodular structures may be neglected and they may be automatically ascribed to the aforementioned benign conditions. On the other hand, a significant number of MZL arise in the setting of autoimmune diseases, such as Sjögren's syndrome and Hashimoto's thyroiditis [1, 25–27]. As the latter conditions are associated with an increased lymphoid BM infiltration, they may prompt a high index of suspicion of MZL, especially for the pathologist familiar with the typical picture of BM involvement by MZL.

Lymphoplasmacytoid lymphoma/immunocytoma

In LPI the BM biopsy frequently represents the first diagnostic tissue available. A variety of growth patterns is observed, including interstitial, nodular intertrabecular and diffuse infiltrates [3, 24, 41], but paratrabecular involvement seems quite rare (Fig. 4a, b) [8].

Whereas the obvious architectural heterogeneity does not allow immediate recognition of these cases at lower magnification, LPI can easily be distinguished through its characteristic cytological aspect. The small lymphoid cells constituting the bulk of the neoplastic infiltrates display a round or slightly irregular nucleus, with clumped chromatin and a small, central nucleolus. A varying proportion of the cells shows evidence of plasmacytoid differentiation, either in their typically eccentrically located nucleus (plasmacytoid lymphocytes) or in the presence of notable intranuclear inclusions (Dutcher bodies). Genuine mature plasma cells are always numerous, but never aggregate to form cell clusters as featured by plasmacytomas. In addition, variable numbers of mast cells and somewhat larger lymphoid cells with a more open chromatin pattern and a conspicuous central nucleolus (prolymphocytes) are scattered throughout the infiltrates.

Considering the architecture of the tumoral infiltrate and the admixture of prolymphocytes, a correct distinction between LPI and CLL/SLL constitutes a major differential diagnostic problem. Overall, CLL/SLL infiltrates grow much more cohesively and never evidence Dutcher bodies or mast cells. However, the only finding that essentially excludes a diagnosis of CLL/SLL is the presence of paratrabecular foci. In selected cases, CD5 immunostaining may be necessary despite these useful morphological guidelines [43].

Chronic lymphocytic leukaemia / small lymphocytic lymphoma

CLL/SLL almost invariably presents with BM involvement for which it, considering its relatively high incidence among lymphoid neoplasms, can be regarded as the prototype lymphoma to be diagnosed based on a BM trephine. Except for nodular paratrabecular involvement which has never been described, CLL/SLL can take on any growth pattern (Fig. 4c, d) [3, 17, 19, 20, 40, 41]. Nodular infiltrates are uncommon and only occur in cases of atypical CLL, where they are invariably accompanied by an interstitial component [7].

Cytologically, small lymphoid cells with a round nucleus and scarce or even indistinct cytoplasm predominate. Overall, the infiltrates have a characteristic dark appearance owing to the clumped nuclear chromatin that obscures the nucleolus. However, various paler-staining cells, such as several equally small lymphocytes displaying some nuclear irregularity and a more dispersed chromatin pattern, and also some larger prolymphocytes are detected. Moreover, small clusters of large cells characterised by an abundant cytoplasm and a clear nucleus with a large, distinct nucleolus (paraimmunoblasts) are evident and compose conspicuous areas termed pseudofollicles. Although in our own experience these pseudofollicles, which we detected in about 50% of the cases, constitute the hallmark lesion in CLL/SLL, others state that these structures appear infrequently in BM biopsies

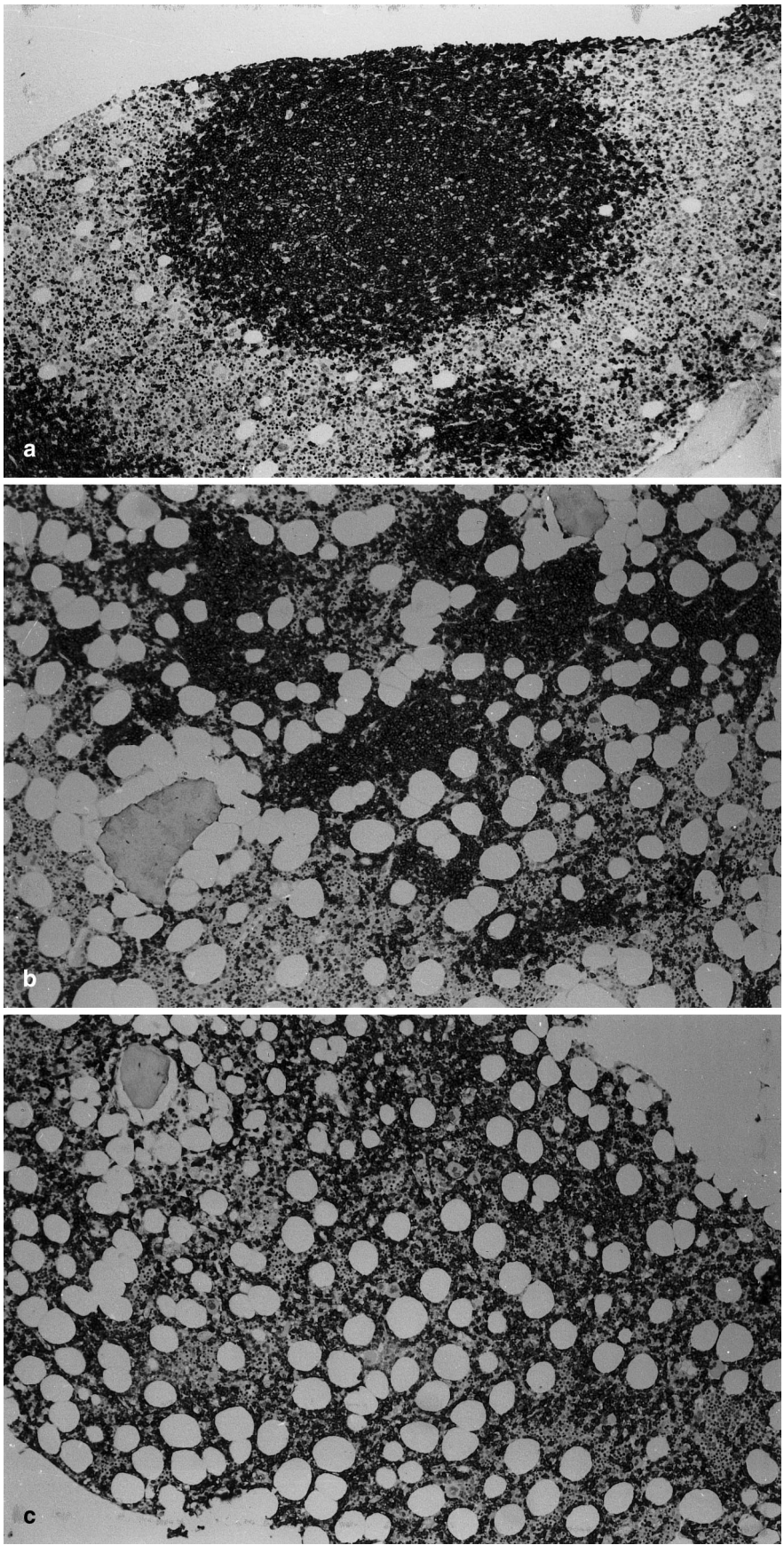

Fig. 4a–c Immunohistochemical staining for CD20 can be useful to highlight the neoplastic B-cell infiltrate. **a** The neoplastic cells of a FCC occasionally extend into the intertrabecular area to form nodules that resemble neoplastic follicles found in lymph nodes. **b** A combination of interstitial type involvement with nodular intertrabecular aggregates is observed in most cases of CLL/SLL. **c** Scattered neoplastic cells in a case of HCL are accentuated by CD20 immunostaining

[33]. Occasionally paraimmunoblasts occur as isolated cells admixed with the regular small neoplastic lymphocytes. In contrast with LPI, evidence of plasmacytoid differentiation is almost invariably lacking.

As indicated above, a reliable distinction between CLL/SLL and MCL is often very difficult to establish, in particular in trephines involved by a predominantly interstitial lymphoid infiltrate. Usually, a close examination of the cytological characteristics of the neoplastic cells suffices for a final diagnosis. However, rare cases show a tumoral proliferation displaying significant nuclear irregularity but lacking all morphological evidence to definitely assign it to one of both lymphoma subtypes [7, 16, 32, 46]. Therefore, the use of a selected panel of antibodies, detecting cyclin D1 [44, 47] and/or CD23 [30] can be useful in these cases.

Hairy cell leukaemia

The histological features characterising BM involvement by HCL are highly specific and allow an accurate identification of this entity in nearly every case (Fig. 4e, f) [4, 11, 12, 37]. This small B-cell lymphoma displays either an interstitial growth pattern, which predominates, or a diffuse pattern. Nodular infiltrates, intertrabecular nor paratrabecular, have never been described [3, 4, 11, 12, 38].

The typical cytological appearance of the hairy cells with their abundant clear cytoplasm imparting a loose appearance to the neoplastic infiltrate, substantially facilitates its recognition among other small B-cell neoplasms displaying a similar growth pattern. The nuclear morphology of these hairy cells varies, comprising round to elongated forms, as well as some slightly irregular nuclei and even cells showing more marked nuclear grooving. Within the usually open nuclear chromatin, an inconspicuous nucleolus is occasionally apparent. In some cases a distinct spindle cell component can be noticed. Since such fusiform elements are consistently lacking in other small B-cell malignancies, these may be useful to establish a diagnosis of HCL.

As contrasted with all the other subtypes of small B-cell lymphoma considered so far, HCL is accompanied by distinct alterations in the haematopoietic series. A moderate to severe decrease in the three normal haematopoietic cell lines associated with the occurrence of dysplastic features is usually observed. In addition, a variable degree of reticulin fibrosis and prominent erythrocyte extravasation can be noted [4, 12, 38].

The hypocellular or cell-poor HCL cases [12, 31] may raise problems in differential diagnosis against aplastic or hypoplastic anaemia and against hypocellular myelodysplastic syndrome, not only because of the reduced cellularity but also because of the presence of noticeable aggregates of plasma cells. In this setting, a careful examination of the residual cellular areas between the adipocytes and immunostaining using anti-B-cell markers is mandatory [22].

Finally, MZL infiltrates also containing cells with moderately abundant clear cytoplasm (monocytoid B-cells) can be distinguished from HCL on the basis of their growth pattern, which is usually at least partly nodular.

Can a subclassification of small B-cell neoplasms be accomplished in bone marrow trephine biopsies?

Based both on our own experience and on previously published data, we conclude that a reliable identification of the subtype of small B-cell lymphoma involving the trephine is feasible in a significant number of cases. Our findings enabled us to propose an algorithmic approach, which requires identification of the growth pattern of the lymphoid infiltrate, followed by a careful evaluation of the cytological features of the neoplastic cells (Fig. 1).

When a predominantly nodular intertrabecular pattern is observed, MCL, CLL/SLL and MZL appear to be the main diagnostic candidates. The identification of pseudofollicles will allow a confident diagnosis of CLL/SLL. In their absence, the detection of pink hystiocytes and distinct nuclear irregularities points to MCL in this setting. Moreover, the simultaneous presence of small paratrabecular nodules strongly favours MCL and rules out CLL/SLL. A diagnosis of BM involvement by MZL relies on the identification of typical follicle-like structures entrapped within an expanded marginal zone featuring monocytoid B-cells.

A typically paratrabecular involvement, in contrast, is strongly suggestive of FCCL. Whereas small foci of paratrabecular involvement do occasionally occur in MCL and LPI, their presence virtually excludes a diagnosis of CLL/SLL and HCL.

Predominantly interstitial or diffuse growth patterns constitute the most intricate problem in differential diagnosis, as they can be regarded as characteristic of both CLL/SLL and HCL, it is not uncommon for them to occur in LPI and they may even be found in some cases of MCL. Considering its high incidence compared with the other subtypes, CLL/SLL is always the first candidate to be borne in mind when such infiltrates are identified.

In general, the characteristic cytological picture displaying prominent stromal changes (extravasation of red blood cells and reticulin fibrosis) associated with peculiar abnormalities in the haematopoiesis will allow a diagnosis of HCL.

When pseudofollicles are noticed within a diffuse infiltrate, a diagnosis of CLL/SLL can be established with certainty. In the absence of these distinct structures, MCL should also be considered, despite the restricted number of MCL cases presenting with a diffuse pattern of BM involvement. However, the cytology of the infiltrating lymphoid cells usually distinguishes CLL/SLL (small lymphocytes with a regular nucleus and clumped chromatin) from MCL (small- to intermediate-sized cells with a cleaved nucleus and a less mature nuclear chromatin pattern).

Finally, the identification of LPI is prompted by the presence of Dutcher bodies, monotypic plasma cells and an admixture of mast cells.

Concluding remarks

Each subtype of small B-cell lymphoma shows a rather characteristic pattern of BM involvement as well as a distinct cytological composition. The recognition of and the familiarity with these architectural and cytological features will definitely be helpful in identifying BM involvement during staging procedures. Although the spectrum of variation within each category results in some degree of overlap between the various lymphoma entities, a critical morphologic evaluation of BM trephine biopsies should allow the correct subtyping of small B-cell lymphomas in very well defined settings.

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References

1. Anscombe AM, Wright DH (1985) Primary malignant lymphoma of the thyroid – a tumour of mucosa-associated lymphoid tissue: review of seventy-six cases. Histopathology 9: 81–97
2. Argatoff LH, Connors JM, Klasa RJ, Horsman DE, Gascoyne RD (1997) Mantle cell lymphoma: a clinicopathologic study of 80 cases. Blood 89:2067–2078
3. Bartl R, Frisch B, Burkhardt R, Kettner G, Mahl G, Fateh Moghadam A, Sund M (1982) Assessment of bone marrow histology in the malignant lymphomas (non-Hodgkin's): correlation with clinical factors for diagnosis, prognosis, classification and staging. Br J Haematol 51:511–530
4. Bartl R, Frisch B, Hill W, Burkhardt R, Sommerfeld W, Sund M (1983) Bone marrow histology in hairy cell leukemia. Identification of subtypes and their prognostic significance. Am J Clin Pathol 79:531–545
5. Bartl R, Hansmann ML, Frisch B, Burkhardt R (1988) Comparative histology of malignant lymphomas in lymph node and bone marrow. Br J Haematol 69:229–237
6. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C (1989) Proposals for the classification of chronic (mature) B and T lymphoid leukaemias. French-American-British (FAB) Cooperative Group. J Clin Pathol 42: 567–584
7. Bonato M, Pittaluga S, Tierens A, Criel A, Verhoef G, Wlodarska I, Vanutysel L, Michaux L, Vandekerckhove P, Van den Berghe H, De Wolf Peeters C (1998) Lymph node histology in typical and atypical chronic lymphocytic leukemia. Am J Surg Pathol 22:49–56
8. Brunning RD (1989) Bone marrow. In: Rosai J (ed) Ackerman's surgical pathology. Mosby, St Louis, pp 1379–1453
9. Brunning RD, McKenna RW (1979) Bone marrow manifestations of malignant lymphoma and lymphoma-like conditions. Pathol Annu 14:1–59
10. Brunning RD, McKenna RW (1994) Bone marrow lymphomas. In: Brunning RD, McKenna RW (eds) Atlas of tumor pathology. Tumors of the bone marrow. Armed Forces Institute of Pathology, Washington, pp 369–408
11. Burke JS (1978) The value of the bone-marrow biopsy in the diagnosis of hairy cell leukemia. Am J Clin Pathol 70:876–884
12. Burke JS, Rappaport H (1984) The diagnosis and differential diagnosis of hairy cell leukemia in bone marrow and spleen. Semin Oncol 11:334–346
13. Cohen PL, Kurtin PJ, Donovan KA, Hanson CA (1998) Bone marrow and peripheral blood involvement in mantle cell lymphoma. Br J Haematol 101:302–310
14. Conlan MG, Bast M, Armitage JO, Weisenburger DD (1990) Bone marrow involvement by non-Hodgkin's lymphoma: the clinical significance of morphologic discordance between the lymph node and bone marrow. Nebraska Lymphoma Study Group. J Clin Oncol 8:1163–1172
15. Criel A, Pittaluga S, Verhoef G, Wlodarska I, Meeus P, Mecucci C, Van Orshoven A, Van den Berghe H, Boogaerts M, De Wolf Peeters C (1996) Small B cell NHL and their leukemic counterpart: differences in subtyping and assessment of leukemic spread. Leukemia 10:848–853
16. Criel A, Verhoef G, Vlietinck R, Mecucci C, Billiet J, Michaux L, Meeus P, Louwagie A, Van Orshoven A, Van Hoof A, Boogaerts M, Van den Berghe H, De Wolf Peeters C (1997) Further characterization of morphologically defined typical and atypical CLL: a clinical, immunophenotypic, cytogenetic and prognostic study on 390 cases. Br J Haematol 97: 383–391
17. Dick F, Bloomfield CD, Brunning RD (1974) Incidence cytology, and histopathology of non-Hodgkin's lymphomas in the bone marrow. Cancer 33:1382–1398
18. Farhi DC (1989) Germinal centers in the bone marrow. Hematol Pathol 3:133–136
19. Foucar K, McKenna RW, Frizzera G, Brunning RD (1982) Bone marrow and blood involvement by lymphoma in relationship to the Lukes-Collins classification. Cancer 49:888–897
20. Geisler CH, Hou Jensen K, Jensen OM, Tinggaard Pedersen N, Hansen MM, Hansen NE, Holm M, Christensen BE, Drivsholm A, Nielsen JB, Thorling K, Andersen E, Larsen JK, Anderson PK (1996) The bone-marrow infiltration pattern in B-cell chronic lymphocytic leukemia is not an important prognostic factor. Danish CLL Study Group. Eur J Haematol 57:292–300
21. Gong JZ, Zheng S, Chiarle R, De Wolf-Peeters C, Palestro G, Frizzera G, Inghirami G (1999) Detection of immunoglobulin kappa light chain rearrangements by polymerase chain reaction: an improved method for detecting clonal B-cell lymphoproliferative disorders. Am J Pathol 155:355–363
22. Hakimian D, Tallman MS, Kiley C, Peterson L (1993) Detection of minimal residual disease by immunostaining of bone marrow biopsies after 2-chlorodeoxyadenosine for hairy cell leukemia. Blood 82:1798–1802
23. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JKC, Cleary ML, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC, Grogan TM, Isaacson PG, Knowles DM, Mason DY, Muller-Hermelink H-K, Pileri SA, Piris MA, Ralfkier E, Warnke RA (1994) A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 84:1361–1392
24. Huang JC, Finn WG, Goolsby CL, Variakojis D, Peterson LC (1999) CD5 small B-cell leukemias are rarely classifiable as chronic lymphocytic leukemia. Am J Clin Pathol 111:123–130
25. Hyjek E, Isaacson PG (1988) Primary B cell lymphoma of the thyroid and its relationship to Hashimoto's thyroiditis. Hum Pathol 19:1315–1326
26. Isaacson PG (1991) B cell lymphomas of mucosa associated lymphoid tissue (MALT). Bull Cancer 78:203–205
27. Isaacson PG, Spencer J (1987) Malignant lymphoma of mucosa-associated lymphoid tissue. Histopathology 11:445–462
28. Juneja SK, Wolf MM, Cooper IA (1990) Value of bilateral bone marrow biopsy specimens in non-Hodgkin's lymphoma. J Clin Pathol 43:630–632
29. Kluin PM, van Krieken JH, Kleiverda K, Kluin Nelemans HC (1990) Discordant morphologic characteristics of B-cell lymphomas in bone marrow and lymph node biopsies. Am J Clin Pathol 94:59–66

30. Kumar S, Green GA, Teruya Feldstein J, Raffeld M, Jaffe ES (1996) Use of CD23 (BU38) on paraffin sections in the diagnosis of small lymphocytic lymphoma and mantle cell lymphoma. Mod Pathol 9:925–929
31. Lee WM, Beckstead JH (1982) Hairy cell leukemia with bone marrow hypoplasia. Cancer 50:2207–2210
32. Matutes E, Oscier D, Garcia Marco J, Ellis J, Copplestone A, Gillingham R, Hamblin T, Lens D, Swansbury GJ, Catovsky D (1996) Trisomy 12 defines a group of CLL with atypical morphology: correlation between cytogenetic, clinical and laboratory features in 544 patients. Br J Haematol 92:382–388
33. McKenna RW, Hernandez JA (1988) Bone marrow in malignant lymphoma. Hematol Oncol Clin North Am 2:617–635
34. McKenna RW, Bloomfield CD, Brunning RD (1975) Nodular lymphoma: bone marrow and blood manifestations. Cancer 36: 428–440
35. Medeiros LJ, Jaffe ES (1995) Low-grade B-cell lymphomas not specified in the Working Formulation. In: Jaffe ES (ed) Surgical pathology of the lymph nodes and related organs. Saunders, Philadelphia, pp 221–251
36. Osborne BM, Butler JJ (1989) Hypocellular paratrabecular foci of treated small cleaved cell lymphoma in bone marrow biopsies. Am J Surg Pathol 13:382–388
37. Paoletti M, Bitter MA, Vardiman JW (1988) Hairy-cell leukemia. Morphologic, cytochemical, and immunologic features. Clin Lab Med 8:179–195
38. Pittaluga S, Verhoef G, Maes A, Boogaerts MA, De Wolf Peeters C (1994) Bone marrow trephines. Findings in patients with hairy cell leukaemia before and after treatment. Histopathology 25:129–135
39. Pittaluga S, Verhoef G, Criel A, Maes A, Nuyts J, Boogaerts M, De Wolf Peeters C (1996) Prognostic significance of bone marrow trephine and peripheral blood smears in 55 patients with mantle cell lymphoma. Leuk Lymphoma 21:115–125
40. Rozman C, Montserrat E, Rodriguez Fernandez JM, Ayats R, Vallespi T, Parody R, Rios A, Prados D, Morey M, Gomis F, et al (1984) Bone marrow histologic pattern – the best single prognostic parameter in chronic lymphocytic leukemia: a multivariate survival analysis of 329 cases. Blood 64:642–648
41. Schmid C, Isaacson PG (1992) Bone marrow trephine biopsy in lymphoproliferative disease. J Clin Pathol 45:745–750
42. Schwonzen M, Pohl C, Steinmetz T, Wickramanayake PD, Thiele J, Diehl V (1992) Bone marrow involvement in non-Hodgkin's lymphoma: increased diagnostic sensitivity by combination of immunocytology, cytomorphology and trephine histology. Br J Haematol 81:362–369
43. Thaler J, Dietze O, Denz H, Demuth R, Nachbaur D, Stauder R, Huber H (1991) Bone marrow diagnosis in lymphoproliferative disorders: comparison of results obtained from conventional histomorphology and immunohistology. Histopathology 18:495–504
44. Vasef MA, Medeiros LJ, Koo C, McCourty A, Brynes RK (1997) Cyclin D1 immunohistochemical staining is useful in distinguishing mantle cell lymphoma from other low-grade B-cell neoplasms in bone marrow. Am J Clin Pathol 108: 302–307
45. Warnke RA, Weiss LM, Chan JCK, Cleary ML, Dorfman RF (1995) Malignant lymphoma, follicular. In: Warnke RA, Weiss LM, Chan JCK, Cleary ML, Dorfman RF (eds) Tumors of the lymph nodes and spleen. (Atlas of tumor pathology) Armed Forces Institute of Pathology, Washington, pp 63–118
46. Wasman J, Rosenthal NS, Farhi DC (1996) Mantle cell lymphoma. Morphologic findings in bone marrow involvement. Am J Clin Pathol 106:196–200
47. Zukerberg LR, Yang WI, Arnold A, Harris NL (1995) Cyclin D1 expression in non-Hodgkin's lymphomas. Detection by immunohistochemistry. Am J Clin Pathol 103:756–760