Occasional articles

Bone marrow trephine biopsy in lymphoproliferative disease

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Introduction

Examination of bone marrow biopsy specimens is a valuable diagnostic procedure in patients with known or suspected lymphoproliferative disorders.¹ A bone marrow biopsy specimen may be diagnostic in patients without lymphadenopathy or when there is no conclusive histological evidence from other sites. In some conditions, such as hairy cell leukaemia,² it is the primary diagnostic procedure. Bone marrow biopsy is mandatory for staging lymphomas and useful in monitoring treatment.³ Valuable information on the state of haematopoiesis and changes in stromal components is also provided by trephine biopsy specimens.⁴ Bone marrow biopsy specimens are especially important in the staging of Hodgkin's disease, because pathology in the marrow indicates systemic disease and an unfavourable prognosis,^{5,6} and they are of confirmed value in histological staging and grading of multiple myeloma where histology has been shown to be more accurate than aspiration cytology for quantifying tumour cell burden.⁷

Methods

Detection of lymphoproliferative disorders in the marrow depends on the investigation of adequate material. Biopsy specimens consisting mainly of cortical bone and subcortical marrow should not be considered adequate for diagnosis. To avoid sampling errors only sections with at least five well preserved marrow spaces should be considered for definitive diagnosis. The size of the biopsy specimens is an important criterion in identifying marrow pathology because of the frequent focal involvement in lymphoproliferative disorders. Bilateral iliac crest bone marrow biopsy specimens have been shown to increase the detection rate of non-Hodgkin's lymphoma and to minimise sampling error,^{8,9} but their value is limited and they are indicated only in a selected group of patients.¹⁰

Proper evaluation of bone marrow biopsy specimens requires appropriate processing of the specimens. There is, however, some controversy as to which is the optimal technique for processing bone marrow biopsy specimens.¹¹⁻¹³ Several methods are in use: (1) paraffin wax embedding after decalcification;^{14,15} (2) resin embedding either in glycol-methacrylate, a water miscible plastic,^{16,17} or

preferably in methyl-methacrylate.¹⁸ Each of these methods has its advantages but also its disadvantages.

Paraffin wax embedding after formalin fixation and decalcification is the technique traditionally used in any diagnostic histopathology department because it requires no special equipment. Although some tissue shrinkage is unavoidable with this technique, with some extra care high quality sections of bone marrow can be obtained. Applying optimal fixation times and careful decalcification, routine histological stains such as haematoxylin and eosin (fig 1A) Perls's, Giemsa and reticulin, as well as enzyme histochemical stains (chloracetate-esterase) give excellent results. A major advantage is that immunoreactivity is well preserved.¹⁴ Using carefully prepared decalcified marrow sections, any antigen which can be shown in conventionally fixed and processed tissue should be detectable^{15,19} using immunoperoxidase or immunoalkaline phosphatase methods.²⁰

A variety of resins are available as alternatives to wax embedding.^{16,18,21} The use of methyl-methacrylate (MMA) provides excellent morphology (fig 1B) and sections can be processed and stained within 16-24 hours when rapid fixation is used. However, this method requires specialised equipment and does not preserve antigenic and enzymic reactivity.¹⁸ A comparison of well established methods for paraffin wax and MMA embedding is given in table 1.

Because MMA embedded material does not preserve antigenic and enzymic reactivity¹⁸ in many laboratories using this method, immunohistochemical phenotyping is performed on cryostat sections of bone marrow.^{18,22-24} Because the tissue in bone marrow is not homogeneous, a special supporting medium which does not disturb antigenic reactivity, such as Histocon (No. 0582, Polysciences,

Table 1 Comparison of methods for embedding bone marrow biopsy specimens

	MMA	Paraffin wax
Fixation	Carnoy (2-4 hours)	Unbuffered formalin (12-24)
Dehydration	Alcohol, methanol	Alcohol, methanol
Decalcification		Formic acid
Embedding	MMA	Paraffin wax
Polymerisation	35°-37°C (overnight)	
Sectioning	1-3µm (special microtome)	3-4µm (conventional microtome)

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Figure 1 Normal bone marrow. (A) paraffin wax; (B) methylmethacrylate; (C) frozen section; (A, B, C): haematoxylin and eosin.

Inc., Warrington, Pennsylvania, USA), should be used when cutting frozen sections.^{18 25} Frozen section technique offers excellent preservation of all cell surface and intracytoplasmic antigens but has the minor disadvantage of diminished cytological detail (fig 1C).

It is our experience that adequate morphology is obtained from formalin fixed, decalcified, and paraffin wax embedded trephine biopsy specimens and that this technique is of particular value for characterising and differentiating neoplastic lymphoid cell populations in the bone marrow using immunohistochemistry (fig 2). It is especially useful in distinguishing between reactive and neoplastic B lymphocytic aggregates and between minimal disease caused by multiple myeloma and reactive plasmacytosis (fig 3).

Lymphocytes in normal bone marrow

Normal bone marrow may contain up to 25% of lymphocytes which are either diffusely dispersed or in the form of nodular aggregates.²⁶ Benign lymphocytic aggregates²⁷ are a relatively common finding and are increased according to sex, age, and certain diseases.²⁸ If reactive lymphocytic aggregates are very large (> 0.6 mm in diameter) or numerous (more than four in a standard 1 cm trephine), the term "nodular lymphoid hyperplasia" is used.²⁹ Recognition of benign lymphocytic aggregates is frequently possible as they are usually small and contain a polymorphous cell population within a delicate network of reticulin fibres. They have well defined borders and are distributed at random in the marrow.³⁰ Lymphocytic nodules of various sizes are suspicious for lymphoma especially if they are peritrabecular, located around a large sinus, or contain fat cells.³¹ However, a clear distinction between reactive lymphocytic aggregates and lymphocytic lymphoma, or even between leukaemia and lymphoma, may not always be possible by morphology alone (fig 4), and immunohistochemical investigations are required for definitive diagnosis.^{31 32}

Non-Hodgkin's lymphoma

A considerable range of positive staging biopsy

Figure 2 (A), (B), (C). High grade malignant non-Hodgkin's B cell lymphoma. (A) paraffin wax haematoxylin and eosin; (B) tumour cell reactivity with anti-κ (peroxidase.); (C) no reactivity of tumour cells with anti-λ (peroxidase.); (D) megakaryoblastic leukemia (note morphological similarities to "A"). Paraffin wax haematoxylin and eosin; (E) reactivity of tumour cells with FVIII-related antigen (peroxidase).

Figure 3 Multiple myeloma with minimal bone marrow disease. (A) plasma cells showing κ light chain restriction. (B) no reactivity of plasma cells with anti- κ (peroxidase).

specimens in lymphoproliferative disorders has been reported (16–75%).^{33–35} This variation might be due to inclusion of unequal proportions of patients with early and advanced disease as well as inconsistency in histological subtypes of lymphoma because the incidence

of bone marrow pathology varies greatly according to the histological subtype,^{30 35} with low grade lymphomas showing a much higher incidence of marrow pathology compared with high grade lymphomas.³⁶ This is borne out by our own experience in terms of the incidence of bone marrow pathology in lymphoproliferative disorders (table 2).

In Europe the updated Kiel classification³⁷ is widely accepted and is applicable to non-Hodgkin's lymphoma in the bone marrow.³⁸ Although divergences between the histology of the lymph node and bone marrow have been described^{39–41} subtyping of NHL in the bone marrow is, in most cases, clinically relevant.⁴⁰ Not only the subtype but also the growth pattern is of important prognostic value.^{1 42 43} Non-Hodgkin's lymphoma may manifest one, or a mixture, of the following growth patterns: nodular; interstitial; paratrabecular; patchy; and dense (packed marrow) (fig 5). Certain subtypes of lymphoma, such as centrocytic (CC), show a predilection for a paratrabecular pattern of marrow disease, which is a helpful diagnostic feature. Centroblastic-centrocytic (CB–CC) lymphoma in most cases show a nodular pattern which is often combined with formation of germinal centres. Our experience of growth patterns in the various subtypes of non-Hodgkin's lymphoma is summarised in table 3. While an increase in reticulin fibres may be seen in all subtypes of non-Hodgkin's

Table 2 Incidence of bone marrow pathology in lymphoproliferative disorders at time of initial diagnosis (authors' experience)

Diseases (Kiel classification)	No of cases	Bone marrow affected	Bone marrow not affected
Low grade non-Hodgkin's disease	490	311 (64%)	179 (36%)
High grade non-Hodgkin's disease	199	30 (15%)	169 (85%)
Multiple myeloma	157	141 (90%)	16 (10%)
Hodgkin's disease	158	14 (9%)	144 (91%)
Total	1004	496 (49.5%)	508 (50.5%)

Figure 4 Nodular lymphocytic aggregates in the bone marrow. Methylmethacrylate (haematoxylin and eosin) A and C are neoplastic (lymphocytes could be shown to be light chain restricted). B and D are benign lymphocytic aggregates (immunohistochemical stains showed a polytypic cell population).

Figure 5 Growth patterns of non-Hodgkin's lymphomas in the bone marrow: (methylmethacrylate, haematoxylin and eosin.) (A) nodular; (B) paratrabeular; (C) patchy; (D) interstitial/dense.

lymphoma, the most noticeable increase is seen in hairy cell leukaemia.⁴⁴

The extent of tumour cell burden is also of important prognostic value.¹ Without regard to subtype, the median survival in patients with less than 20 volume per cent non-Hodgkin's lymphoma metastasis in the marrow is 73 months; it decreases to 24 months with more than 50 volume per cent.⁴⁵ The extent of tumour burden in our series is shown in table 4.

Multiple myeloma (MM)

Multiple myeloma can be divided into low,

intermediate, and high grade malignancy according to the cytological detail of the plasma cells.^{7,46} The grade of malignancy, along with the extent of infiltration, have been shown to be of significant prognostic value,³⁴ whereas fibrosis, which can be detected in about 10% of patients with multiple myeloma, is of no prognostic value.⁴⁷ Multiple myeloma may involve the marrow in a nodular, interstitial, nodular/interstitial, patchy or dense form.^{7,48} A significant correlation has been found between osteoclastic activity, the presence of lytic bone lesions, and the extent of the plasma cell infiltrate.⁴⁹ In cases with minimal involvement differential diagnosis from exu-

Table 3 Growth pattern of non-Hodgkin's disease (in %): low grade, n = 311; high grade, n = 30 (authors' experience)

Growth pattern	Low grade							High grade			
	NC	Ly	IC	CBCC	CC	HCL	pT	LB	IB	CB	pT
Nodular	27	14	21	72	10	0	61	0	14	33	50
Nodular/interstitial	20	20	18	0	0	0	0	0	0	0	0
Interstitial	30	41	27	0	6	0	0	15	0	0	0
Paratrabeular	0	0	0	12	67	0	0	0	0	0	0
Patchy	9	0	0	6	0	72	0	15	43	17	0
Dense	14	25	34	10	17	28	39	70	43	50	50
Total No of cases	66	76	71	32	30	18	18	13	7	6	4

Key: NC = not further classified; Ly = lymphocytic lymphoma (B-CLL); IC = immunocytic; CBCC = centroblastic-centrocytic; HCL = hairy cell leukaemia; pT = peripheral T cell; LB = lymphoblastic; IB = immunoblastic; CB = centroblastic.

Table 4 Extent of tumour cell burden (volume percentage) in non-Hodgkin's lymphoma (in %): low grade, n = 311; high grade, n = 30 (authors' experience)

%	Low grade							High grade			
	NK	Ly	IC	CBCC	CC	HCL	pT	LB	IB	CB	pT
< 20	5	14	15	34	20	28	28	0	0	34	25
21-50	40	26	30	38	50	33	28	7	57	16	25
> 50	55	60	55	28	30	39	44	93	43	50	50
Total No of cases	66	76	71	32	30	18	18	13	7	6	4

berant reactive plasmacytosis in patients with other diseases⁵⁰⁻⁵¹ may be extremely difficult and requires immunohistochemical investigation (fig 3).⁵²⁻⁵³ In both instances plasma cells may be located around blood vessels and diffusely dispersed among haematopoietic cells. Plasma cells in a paratrabecular position, however, are more indicative of multiple myeloma. It is important not to be too reliant on quantitative amounts of plasma cells in making the diagnosis of multiple myeloma, because minimal pathology with less than 15% can be seen. The cytological characteristics of plasma cells are not diagnostic for multiple myeloma or reactive plasmacytosis, but pleomorphism, multinuclearity, prominent nucleoli and nucleocytoplasmic asynchronism are suspicious for malignancy.⁵⁴

Hodgkin's disease

For the initial diagnosis of Hodgkin's disease in the bone marrow the presence of Reed-Sternberg cells together with the characteristic cellular environment (lymphocytes, plasma cells, eosinophils, epithelioid cells, reticulin fibres) is mandatory. When Hodgkin's disease has already been diagnosed elsewhere, mononuclear Hodgkin cells within a characteristic background are considered sufficient evidence for disease.⁵⁵ Subclassification of Hodgkin's disease in the bone marrow is not possible.⁵⁶ The infiltration pattern in Hodgkin's disease ranges from the presence of solitary to numerous granuloma-like structures, small paratrabecular foci, to large intertrabecular areas or complete replacement of the bone marrow.³⁴ The amount of fibrosis, vasculature, osseous remodelling and cellular composition in the infiltrated areas vary enormously.⁵⁷

Bone marrow biopsy specimens after treatment

After treatment of patients with lymphoproliferative disorders with chemo- or radiotherapy all components of the bone marrow may show varying degrees of damage. The resulting lesions seem to be independent of the applied agents.⁵⁸ Changes in cellularity range from hypocellularity to complete aplasia; alternatively, hyperregeneration of haematopoietic cells may be seen. Pronounced stromal reaction with focal or dense fibrosis, patchy oedema, distortion of sinusoids and capillaries, and appositional bone formation as well as focal necrosis may be present. Proliferation of histiocytes, plasma cells, and eosinophils may occur and granulomas may be present.⁵⁸⁻⁵⁹ Difficulties in the evaluation of residual disease may arise, especially in cases of centrocytic lymphoma with a prior paratrabecular growth pattern. After treatment such foci have been shown to become fibrotic, hypocellular, or even acellular in areas adjacent to the bone. In these cases it is important to cut serial sections, because residual tumour cells may be noted on deeper sectioning.⁶⁰ In most instances bone marrow lesions after chemo- or radiotherapy are reversible.⁵⁸

Conclusions

In too many histopathology laboratories the bone marrow trephine biopsy specimen is the Cinderella of histology specimens. Poor fixation and thick sections render them worthless either for evaluation of haematological disease or as an aide to the diagnosis and management of lymphoproliferative disorders. Bone marrow trephine biopsy specimens are an integral part of the diagnosis, staging, and follow up of patients with lymphoproliferative disorders. To obtain optimal value from this procedure good morphology and the availability of immunohistochemical techniques are essential.

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