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REVIEW ARTICLE

Recent advances in bone marrow biopsy pathology

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Abstract The second quarter of 2009 saw steady advances in bone marrow biopsy (BMB) pathology. The following publications are a personal selection of the highlights. Quality issues in diagnostic immunohistochemistry for BMB have largely been ignored in external quality assurance programmes, and this issue is highlighted. In other areas, publications reflecting advances in flow cytometry and aspirate morphology are discussed where translation to the BMB is possible. Classifications undergo constant change, and several publications address the redefinition of the cut off points between malignancy, benign, and normal. Lastly, current scientific research is presented where it is relevant to the understanding of BMB pathobiology.

Keywords Bone marrow biopsy · Immunohistochemistry · Leukaemia

Technical issues

With regard to immunohistochemistry (IHC), daily quality control/quality assurance measures and participation in external quality assurance (EQA) programmes are important in ensuring good laboratory practise and patient care and are standard practise in many subspecialties in histopathology laboratories. Bone marrow biopsy (BMB) has been generally excluded from EQA programmes for diagnostic IHC due to a lack of standards for tissue processing. The European Bone Marrow Working Group (EBMWG) has set up an EBMWG IHC Committee with the task of exploring the plausibility of an EQA programme for BMB IHC in Europe [1]. Twenty-eight laboratories participated in a web-based anonymous survey; 19 laboratories submitted a total of 109 slides stained for CD34, CD117, CD20, CD3, Ki-67, and a megakaryocyte marker of choice. Eight different fixatives and nine different decalcification methods were used. Only 21% of laboratories did not have any poor results. The CD117 and Ki-67 were the most problematic immunostains, while CD20 was the least problematic.

The EBMWG IHC Committee calls for a reduction in the tissue processing methods for BMB and establishment of an EQA programme for BMB IHC to help diagnostic IHC laboratories calibrate their tests according to expert recommendations. This is especially necessary in the light of recent introduction of IHC tests in BMB that may predict therapeutic response [1].

Myelodysplastic and related syndromes

The International Working Group on Morphology of Myelodysplastic Syndrome has attempted to establish morphological definitions so that monocytes, including immature monocytes, could be separated from the spectrum of monocyte precursors [2]. Cells from peripheral blood or bone marrow were selected to provide a large panel of normal and leukaemic cells at different maturational stages and were submitted to five experts who had previously reached a consensus on the basis of microscopy in defining four subtypes:

1. Monoblast;
2. Promonocyte;
3. Immature monocyte; and
4. Mature monocyte.

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They achieved a good concordance rate of 76.6% confirming that the criteria for defining the four subtypes could be applied consistently. The monocyte is still the most difficult cell to identify with confidence in the peripheral blood or in the bone marrow in healthy individuals, as well as in patients with infections and in those with leukaemic proliferations, and this study establishes useful morphological criteria. It has now to be established whether the monocyte subtypes thus defined correlate with immunological or molecular markers and can be translated into diagnostic categories in the BMB.

Ballmaier and Germeshausen have published a useful review of congenital amegakaryocytic thrombocytopenia (CAMT) [3], an extremely rare inherited bone marrow failure syndrome, usually presenting as a severe thrombocytopenia at birth due to ineffective megakaryocytopoiesis and no characteristic physical anomalies. Usually, the isolated thrombocytopenia progresses to pancytopenia during the first years of life.

The BMB in CAMT at time of diagnosis is usually normocellular with absent or severely reduced numbers of megakaryocytes but normal development of other lineages. Megakaryocytes are often small and immature. A few CAMT patients have been reported with normal megakaryocyte numbers in initial bone marrow samples. The progression to pancytopenia in most cases of CAMT is associated with the development of a hypocellular marrow and aplastic anaemia with a relative increase of lymphocytes.

Most of the cases of CAMT are caused by defective expression or function of the thrombopoietin receptor due to homozygous or compound heterozygous mutations in the gene *MPL*. The essential roles of thrombopoietin as a lineage specific regulator of platelet production and as a regulator of haematopoietic stem cell function are reflected in the haematological defects seen in affected individuals.

Myeloproliferative neoplasms (MPN)

Essential thrombocythaemia (ET) and primary myelofibrosis (PMF) overlap in clinical and pathological features but differ in biological behaviour and prognosis. The latest contributions to understanding the nature of these disorders have focused on bone marrow microenvironment remodelling and proliferative stress, recognising megakaryocytes (MKCs) as "key-cells" [4]. Florena et al. [4] investigated the apoptotic profile of ET and PMF MKCs in order to further characterise the biology of these disorders. Bone marrow biopsy from 30 patients with ET and 30 patients with PMF were studied immunophenotypically for the expression of pro-apoptotic (Fas, Fas-L, Bax, and Bad) and anti-apoptotic (Bcl-2, Bcl-XL, and human telomerase reverse transcriptase) molecules and the "executioner" molecule caspase-3. The fraction of MKCs undergoing apoptosis was assessed by deoxynucleotidyl transferase-mediated dUTP nick-end labelling. Only the mitochondrial pathway seemed to be involved in MKC apoptosis. The anti-apoptotic molecule, Bcl-XL, was predominantly found in ET MKCs while pro-apoptotic molecules, Bax and Bad, showed a prevalent expression in PMF MKCs. A significant fraction of PMF MKCs were committed to apoptosis according to caspase-3 expression and TUNEL while only a few ET cells were committed to apoptosis. hTERT was significantly more expressed in PMF in agreement with the proliferative nature of PMF [4]. The authors concluded that ET and PMF MKCs, while morphologically similar, are characterised by markedly different apoptotic profiles. The higher apoptotic fraction of PMF was consistent with the fibrotic nature of the disease, while the anti-apoptotic profile of ET cells was compatible with a "steady" maturative state [4].

The new World Health Organization (WHO) classification of MPN has been revised to include the Janus Kinase 2 (JAK2) mutation status, lower threshold of platelet values (450×10^9/L) in ET, and other advances in understanding [5]. To investigate any change of incidence of MPN, Girodon et al. [6] performed a retrospective study of a population-based registry in the Côte d'Or area, France, from 1980 to 2007. A total of 524 MPN were registered for the 1980–2007 period, including 135 PV, 308 ET, and 81 PMF. No change in the incidence of either PV or PMF was observed for the 2005–2007 period using the WHO 2008 criteria compared to 1980–2004. On the contrary, a pronounced increase in the incidence of ET was noted after 2005, mainly due to the use of JAK2 mutation screening and the lower platelet count threshold. The authors concluded that their study confirms the relevance of the new WHO diagnostic criteria particularly in allowing earlier diagnosis of ET.

Splanchnic vein thrombosis (SVT) is a severe complication of ET. No clear explanation has been given for the occurrence of thrombosis in this unusual site in patients with ET, but the existence of a specific association between unexplained SVT and the JAK2 mutation has been reported [7]. Allegra et al. [7] described SVT (portal and splenic vein) in a young woman as the first presenting symptom. Extensive screening for thrombophilia was negative. The patient did not fulfil the WHO diagnostic criteria for MPN and the initial platelet count was 310×10^9/l. Bone marrow biopsy, however, showed a prominent increase of large megakaryocytes. The reticulin pattern was normal. The diagnosis of ET was established and supported by the presence of JAK2 V617F mutation. After discharge, the number of platelets increased gradually to 610×10^9/l. The authors concluded that in patients with SVT, the detection of JAK2 V617F mutation is diagnostic for masked MPN as could be documented by

BMB histopathology. This paper shows the value of BMB even when the platelet count is below the WHO threshold.

In addition to the JAK2 mutation, the thrombopoietin receptor gene (MPL) mutation is a useful diagnostic marker in MPN. The MPL is expressed in megakaryocytes and exhibits the gain of function point mutation W515K/L in approximately 5% of patients with PMF, representing one subtype of MPN. Hussein et al [8] studied a series of primary and secondary acute myeloid leukaemias (AML) with megakaryoblastic phenotype and myelofibrosis unrelated to PMF which were analysed for the MPL W515K/L mutation by pyrosequencing. In three of 12 cases (25%), MPL W515L was found and in two of these a combination with trisomy 21 or the Philadelphia chromosome occurred. None of the four secondary AML cases evolving from pre-existing PMF showed MPL W515K/L. The authors concluded that MPL W515L occurs in a considerable proportion of acute megakaryoblastic leukaemias with myelofibrosis unrelated to PMF. As is the case of the JAK2 mutation, MPL W515L is not specific for particular types of MPN.

Data on angiogenesis in the bone marrow of BCR-ABL1-negative MPN patients suggest an increase of the microvessel density (MVD) and vascular endothelial growth factor (VEGF) expression, but the relationship to the JAK2-V617F status remains controversial [9]. Medinger et al. [9] performed immunohistochemical studies of MVD and VEGF expression in 100 MPN, including 24 ET, 46 PV, 26 PMF, 4 MDS/MPN, and 20 control reactive bone marrow cases, and correlated these findings with biological and clinical data and the JAK2-V617F status. A significantly increased MVD was found, particularly that assessed by CD105 and VEGF expression in MPN compared to controls (PMF>PV>MDS/MPN>ET). Stronger association was observed between CD105-MVD and VEGF expression, fibrosis, and JAK2 V617F mutant allele burden compared to CD34-MVD. Microvessel density was strongly increased in MPN with high JAK2 V617F mutant allele burden. The authors concluded that the study highlighted the importance of newly formed CD105+ vessels in the bone marrow of MPN patients and indicates that assessment of CD105-MVD better reflects angiogenic activity in MPN.

Systemic mastocytosis (SM) is a stem cell disorder characterised histologically by the presence of multifocal compact aggregates of mast cells in at least one extracutaneous organ with or without evidence of skin lesions. The mast cell aggregates are accompanied by fibrosis, which is often prominent, but is nevertheless, poorly understood. Chiu et al. [10] evaluated the composition of the fibrotic mast cell aggregates by studying eight BMB and two spleens involved by SM and compared the findings with those observed in other fibrotic bone marrow disorders, such as PMF and metastatic malignancy (MM). It was found that all cases showed marked reticulin and collagen fibrosis. However, unlike PMF and MM, which are usually associated with increased low-affinity nerve growth factor receptor positivity, its expression was low in all cases of systemic mastocytosis. Myofibroblastic differentiation was only focally detected in two of eight bone marrow biopsies. In all cases, the systemic mastocytosis lesions were largely devoid of type IV collagen and laminin. The latter findings were in contrast with those seen in cases of PMF and MM where smooth muscle actin, collagen IV, and laminin were expressed in most cases. In contrast with the other two conditions, only minimal vascularity was detectable within the fibrotic mast cell lesions. The authors concluded that systemic mastocytosis exhibits a distinct pattern of stromal change and suggested that the fibrogenetic mechanism in systemic mastocytosis is most likely different from that of other bone marrow neoplasms, which are also associated with fibrosis. [10]

Clinical phenotype in SM is markedly variable, complicating prognostication and therapeutic decision making. The WHO classification recognises indolent (ISM), and aggressive (ASM), SM with associated clonal haematologic non-mast cell lineage disease (SM-AHNMD), and mast cell leukaemia (MCL) as major categories [11]. In a retrospective study of 342 consecutive adult patients with SM seen at the Mayo Clinic between 1976 and 2007, Lim et al. [12] classified the cases according to the WHO as ISM in 46%, SM-AHNMD in 40%, ASM in 12%, and MCL in 1%. KITD816V was detected in bone marrow-derived DNA by allele-specific polymerase chain reaction in 68% of 165 patients evaluated (ISM, 78%; ASM, 82%; and SM-AHNMD, 60%); JAK2 V617F was detected in 4%, all in SM-AHNMD. The life expectancy in ISM was not significantly different from that of the age- and sex-matched US population. In addition to non-ISM classification, multivariable analysis identified advanced age, weight loss, anaemia, thrombocytopenia, hypoalbuminaemia, and excess bone marrow blasts as independent adverse prognostic factors for survival. The authors concluded that their study validates the prognostic relevance of the WHO subclassification of SM and provides additional information of value in terms of both risk stratification and interpretation of clinical presentation and laboratory results.

Chronic basophilic leukaemia (CBL) is a rare and poorly characterised entity that was not listed as a diagnostic entity in the 2008 WHO classification of tumours of haematopoietic and lymphoid tissues [13] and must as a result be classified as an MPN, unclassifiable. Few cases have been described in detail. Tang et al. [14] reported a patient who presented with fatigue, weight loss, leukocytosis, persistent prominent basophilia, and mild eosinophilia. The bone marrow showed features characteristic of a myeloproliferative neoplasm with a marked increase in maturing

basophils. The basophils exhibited nuclear hypersegmentation, abnormal granulation, and abnormally low CD38 expression. Conventional karyotyping revealed t(5;12)(q31;p13). ETV6, but not PDGFRB rearrangement, was detected by fluorescence in situ hybridization. The authors conclude that CBL is a very rare form of MPN but that increased recognition, as well as additional molecular/genetic studies might permit better classification of CBL, which does appear to have distinct clinicopathologic features that distinguish it from other unclassifiable MPNs.

Lymphoid lesions in the bone marrow

Monoclonal B cell lymphocytosis (MBL) is an asymptomatic monoclonal expansion of circulating chronic lymphocytic leukaemia (CLL)-phenotype B cells which, since the publication of the International Workshop on CLL (IWCLL) guideline in 2008 [15] has been defined as of $<5{\cdot}0\times10^9$/l circulating B cells in the peripheral blood rather than the absolute lymphocyte count. The relationship between the newly defined MBL and Rai 0 CLL and the impact of biological risk factors on MBL prognosis are unknown. Rossi et al. [16] examined 460 B cell expansions with CLL-phenotype. One hundred twenty-three clinical MBL (cMBL) were compared to 154 Rai 0 CLL according to clinical and biological profile and outcome. Clinical MBL had better humoral immune capacity and lower infection risk, lower prevalence of del11q22-q23/del17p13 and TP53 mutations, slower lymphocyte doubling time, and longer treatment-free survival. Despite these favourable features, all cMBL were projected to progress, and lymphocytes $<1{\cdot}2\times10^9$/l and $>3{\cdot}7\times10^9$/l were the best thresholds predicting the lowest and highest risk of progression to CLL. Multivariate analysis identified the presence of +12 or del17p13 as the sole independent predictor of treatment requirement in cMBL. The authors concluded that the newly defined cMBL has a more favourable clinical course than Rai 0 CLL and may influence management [16]. The revised criteria are likely to affect the diagnosis of CLL-phenotype infiltrates in the BMB, and haematopathologists should be aware of the new criteria when diagnosing low level infiltrates.

The IGHV mutational status and ZAP-70 or CD38 expression have been shown to correlate with the clinical course in CLL. The three markers may be discordant, and there is as yet no consensus on their combined use in clinical practise. Morabito et al. [17] studied 262 Binet stage A patients for the three markers. Sixty patients were profiled with HG-U133A gene expression chips. Disease progression was determined by time from diagnosis to treatment (TTT). The probability of being treatment-free at 3 years was significantly shorter in patients with un-mutated IGHV genes, ZAP-70 positive, or CD38-positive cells All three markers had an independent predictive value for TTT of similar power. A prognostic system based on presence of none (low-risk), 56%; one (intermediate-risk), 23%; or two or three (high-risk) markers, 21% was generated with a significant different clinical outcome. Specific transcriptional patterns were significantly associated with risk groups. Both ZAP-70 and CD38 should, therefore, be a routine part of assessment of the BMB in CLL.

Familial clustering of the precursor condition monoclonal gammopathy of undetermined significance (MGUS) has previously been reported in case reports and in small studies. Using population-based data from Sweden, Landgren et al. [18] identified 4,458 MGUS patients, 17,505 population-based controls, and 14,621 first-degree relatives of patients and 58,387 controls. Compared with relatives of controls, relatives of MGUS patients had increased risk of MGUS (2.8) multiple myeloma (MM, 2.9); lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia (WM, 4.0); and chronic lymphocytic leukaemia (2.0). Relatives of patients with IgG/IgA MGUS had a 4.0-fold, 2.9-fold, and 20-fold elevated risk of developing MGUS, MM, and LPL/WM, respectively. Relatives of IgM MGUS patients had 5.0-fold increased CLL risk and non-significant excess MM and LPL/WM risks. The results were very similar when assessed by type of first-degree relative, age at MGUS (above/below 65 years), or sex. Risk of non-Hodgkin lymphoma or Hodgkin lymphoma was not increased among MGUS relatives. Among first-degree relatives of a nationwide MGUS cohort, we found elevated risks of MGUS, MM, LPL/WM, and CLL. The authors concluded that their findings support a role for germline susceptibility genes, shared environmental influences, or an interaction between both.

In a similar study, Vachon et al. [19] examined whether MGUS is increased in first-degree relatives of MM or MGUS patients. Probands were recruited from a population-based prevalence study (MGUS) and the Mayo Clinic (MM). By electrophoresis, MGUS was detected in 6% relatives, and immunofixation identified 28 additional relatives for an age- and sex-adjusted prevalence of 8.1%. The prevalence of MGUS in relatives increased with age. Using similar MGUS detection methods, there was a 2.6-fold higher risk of MGUS in relatives compared with the reference population. The increased risk was seen among relatives of MM (2.0) and MGUS probands (3.3). The authors concluded that the increased risk of MGUS in first-degree relatives of MGUS or MM patients implies shared environment and/or genetics.

Lymphoplasmacytic lymphoma is a low-grade B cell malignancy exhibiting a cytological spectrum of plasmacytic differentiation ranging from small lymphocytes to true plasma cells and, including cells with features intermediate

between these two, referred to as plasmacytoid lymphocytes. Lymphoplasmacytic lymphoma characteristically has an associated monoclonal serum immunoglobulin M (IgM) paraprotein, although, it is indistinguishable from other lymphoma types. In a subset of lymphoplasmacytic lymphoma patients, the paraproteinemia is associated with distinctive clinical findings such as serum hyperviscosity, cryoglobulinemia, autoimmune phenomena such as peripheral neuropathy, and amyloidosis termed Waldenström's macroglobulinemia. As lymphoplasmacytic lymphoma infrequently involves the lymph nodes or other extramedullary sites, bone marrow biopsy is often the first and only diagnostic tissue obtained, but the diagnosis is often difficult and the presence of Waldenström's macroglobulinemia unpredictable.

To address these issues, Morice et al. [20] studied marrow histology, IHC, and flow cytometry from 35 lymphoplasmacytic lymphoma cases that had comprehensive clinical assessment for Waldenström's macroglobulinemia. Both IHC and flow cytometry were useful in identifying the lymphoid and plasmacytic disease components. In 19 cases, IHC revealed an earlier unrecognised pattern of plasma cell infiltration in which they were physically separate from the lymphoid infiltrates. By cytometry, approximately half of monotypic cells were CD5 and/or CD23 positive, although, none had features of chronic lymphocytic leukaemia. In 20 cases, the pattern of cytoplasmic CD38 and CD138 co-expression detected by cytometry was identical to that seen in plasma cell malignancies such as multiple myeloma. However, in 18 of these 20 cases, these plasma cells were CD19 positive, distinguishing them from those of true plasma cell neoplasms, which are CD19 negative. The two lymphoplasmacytic lymphoma cases with CD19-negative plasma cells had an IgG isotype serum paraprotein. Apart from this, no other pathological correlates of the clinical or laboratory features of symptomatic Waldenström's macroglobulinemia were identified [20].

Amyloid light chain amyloidosis (ALA) is a form of plasma cell dyscrasia characterised by overproduction of immunoglobulin light chains that form characteristic abnormally folded and aggregated insoluble fibrillar deposits in various organs causing organ damage. Deshmukh et al. [21] studied 36 well-documented cases of ALA. In all cases, presence of amyloid deposits had been documented by a congo red stain in the BMB and/or in other tissues. Bone marrow biopsies showed varying degrees of plasma cell (PC) infiltration. In eight cases with associated myeloma, the mean percentage of PCs was 18%, while in the remaining, it was 4%. Expression of CD20, CD79a, CD56, cyclin D1, and EMA was noted in 42%, 86%, 50%, 53%, and 83% of cases, respectively. Aberrant antigen expression in the form of CD56 and/or cyclin D1 expression was seen in 79% of cases. Nine of 10 cases with small lymphocyte-like PCs were positive for CD20, and all the 10 cases were positive for cyclin D1. Among cases lacking small lymphocyte-like morphology, CD20 and cyclin D1 expression was seen in only six of 26 and eight of 26 cases, respectively, CD20 expression correlated with cyclin D1 expression. Cytological atypia/pleomorphism was predictive of associated myeloma. The authors concluded that BMB involvement by neoplastic PCs in ALA can be identified by their aberrant antigen expression apart from light chain restriction.

CD123 is useful marker of plasmacytoid dendritic cells and is expressed in these cells in chronic myelomonocytic leukaemia and blastic plasmacytoid dendritic cell neoplasms amongst others. B lymphoid blasts from acute lymphoblastic leukaemia (ALL) have been shown to express functional CD123, and CD40 ligand stimulates proliferation of precursor-B ALL by up-regulating CD123 expression. [22] However, the prevalence of CD123 expression in ALL is not clear. Djokic et al. [22] evaluated CD123 expression in 95 paediatric and 24 adult ALL patients and compared the results with the CD123 expression in normal B cell precursors. Early B cell precursors were negative, while intermediate precursors and mature B cells showed weak CD123 expression. Leukemic blasts in 31% of precursor-B ALL samples exhibited strong expression of CD123; 61% had moderate CD123 expression and 8% were negative; and 81.5% of ALL with hyperdiploid karyotype (≥ 52 chromosomes) showed strong CD123 overexpression. In contrast, cases with ETV6/RUNX1 rearrangement had weak CD123 expression. The authors concluded that overexpression of CD123 is an aberrant phenotype present in a subset of precursor-B ALL with hyperdiploid genotype and that it represents an additional marker of good prognosis in paediatric precursor-B ALL. Aberrant CD123 expression in ALL may, therefore, be a good marker for monitoring of minimal residual disease.

Conflict of interest The author declares no conflict of interest.

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