Essentials of Diagnostic Pathology
Series Editor: Farid Moinfar

Christine Beham-Schmid
Annette Schmitt-Graeff

Bone Marrow Biopsy Pathology

A Practical Guide

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ISSN 2194-6256 ISSN 2194-6264 (electronic)
Essentials of Diagnostic Pathology
ISBN 978-3-662-60307-9 ISBN 978-3-662-60309-3 (eBook)
https://doi.org/10.1007/978-3-662-60309-3

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Preface

When I (C.B-S) was asked by Prof. F. Moinfar to write a book on bone marrow pathology, I was hesitant in view of the abundance of excellent textbooks on this topic. However, the fact that this book should be intended as a practical guide dominated rather by illustrations than by text, and the promise of Prof. Annette Schmitt-Graeff to act as a coauthor, at least encouraged me to start this project.

As a young internship doctor in the small public hospital in Oberndorf/Salzburg, I (C.B-S) was stimulated by Primarius Dr. K. Mittermayer to have a look on bone marrow aspirates. This resulted in my interest in hematology, which was deepened when I consecutively started a training in pathology with focus on hematopathology at the Institute of Pathology, Faculty of Medicine, University of Graz. During this time, I received intensive training in bone marrow biopsy pathology in Munich (Prof. Burkhardt) and Tel Aviv (Bertha Frisch) and in lymphoma diagnostics in London (P.G. Isaacson). Up to now, I have seen ten thousands of bone marrow biopsies and gained a lot of experience. Since the knowledge of clinical data is essential for exact pathohistological diagnosis of bone marrow biopsies, a close cooperation with the clinical colleagues is mandatory.

My (A.S-G) enthusiasm for bone marrow (BM) diagnostics dates back to my residency in hematology/oncology at the Departments of Internal Medicine, University Hospitals of Cologne and Essen, Germany. I was keen on evaluating blood and BM cytology. I also realized the impact of BM and lymph node biopsies on therapeutic strategies for our patients suffering from myeloid or lymphoproliferative neoplasms. This appreciation was the rationale to pursue a residency and a fellowship in anatomical pathology at the University Hospital Düsseldorf, Germany, where I established histologic BM assessment. My research activities were on the cytoskeleton including BM stroma with Prof. Dr. Dr. h.c. Giulio Gabbiani, University Hospital Geneva, Switzerland, where I assumed the position as consultant. There and at the Berlin Reference Center for Lymph Node Pathology of Prof. Dr. Dr. h.c. Harald Stein I was principally in charge of BM pathology including supervising residents in this field.

Later, I joined the faculty at the Medical Center, University Freiburg, Germany, where I was appointed Professor of Hematopathology and GI Pathology. My activities were focused on integrating morphological, immunophenotypic, and molecular aspects of hematological neoplasms and primary immunodeficiency disorders with the late Prof. Dr. Paul Fisch in close clinico-pathologic cooperation.

As previous president of the German Division of the IAP (GDIAP) and actual member of the General IAP and GDIAP Education committees, I have taught and directed numerous hematopathology courses of the IAP nationally and internationally. In the context of my active involvement in education and teaching, I am delighted to contribute to this textbook with a mix of basic information and challenging diagnostic cases.

This book is intended as a practical guide in the complex field of bone marrow pathology. We hope it will turn out helpful in the daily diagnostic work.

June 2020
Graz, Austria — Christine Beham-Schmid
Freiburg, Germany — Annette Schmitt-Graeff

Acknowledgments

I would like to thank my coauthor and friend Annette Schmitt-Graeff, without her support, my own contributions for this book would not have been possible.

Moreover, I am deeply indebted to Prof. Farid Moinfar for giving me the opportunity to write this book with my coauthor.

My special acknowledgment is also attributed to my teachers in hematology and hematopathology Prim. Dr. K. Mittermayer, Oberndorf/Salzburg, Prof. Dr. R. Burkhardt, Munich/Germany, Prof. Dr. B. Frisch, Tel Aviv/Israel, Prof. P.G. Isaacson, London/G.B., and Prof. Dr. J. Thiele, Cologne/Germany.

In addition, I would like to recognize the excellent work of the team of the laboratory of hematopathology and the photographers, Institute of Pathology, Medical University of Graz, Austria.

Last but not least, I am most grateful to my husband Alfred and my son Clemens for their never-ending patience and support during this project.

Christine Beham-Schmid

First, I would like to acknowledge the great dedication of my coauthor Prof. Dr. Christine Beham-Schmid, Graz, and the series Editor Prof. Dr. Farid Moinfar, Linz, Austria, to the project of our book.

I express my deep appreciation to many experts who inspired me with their devotion to hematopathology and hematology. In particular, I want to mention Prof. Dr. Dr.hc Harald Stein, Berlin, and Prof. Dr. Juergen Thiele, Cologne/Hannover, Germany, and Prof. Dr. Kristin Henry, London, G.B. Special thanks go to Prof. Dr. Rüdiger Hehlmann who founded the European LeukemiaNet (ELN). I would also like to acknowledge Prof. Dr. Attilio Orazi, El Paso, and Prof. Dr. Daniel A. Arber, Chicago, USA, for their exciting investigations and teaching in hematopathology.

I am especially indebted to Prof. Dr. Robert Zeiser, Dr. Dietmar Pfeifer, Dr. Milena Pantic, and Dr. Justina Rawluk, Department of Hematology and Oncology, Medical Center, University Freiburg, Germany, for their support and helpful contribution to molecular analyses, cytogenetics, and cytology of myeloid neoplasms.

Lastly, I would like to thank my mother Margret Gräff, my husband Eberhard Schmitt, our son Rafael J. P. Schmitt, and my daughter-in-law Zelda Othenin for their patience and love.

Annette Schmitt-Graeff

Contents

Normal Bone Marrow

1

Abbreviations

BBL	Berlin blue iron stain
BCR-ABL	Breakpoint cluster region and Abelson tyrosine kinase
BMB	Bone marrow biopsy
CML	Chronic myeloid leukemia
H&E	Hematoxylin and eosin stain
HPF	High power field
IHC	Immunohistochemistry
ITP	Idiopathic thrombocytopenia
MDS	Myelodysplasia
MGG	May–Grünwald Giemsa stain
MPO	Myeloperoxidase
PCR	Polymerase chain reaction
B-PLL	B-cell prolymphocytic leukemia

1.1 Introduction

Histological investigation of bone marrow biopsy is an integral examination method for diagnosis of various hematological and also non-hematological diseases [1]. Since sampling of bone marrow biopsies (BMB) from newborns as well as geriatric patients can easily be performed, the indications for retrieving BMB have increased, especially in hematology, internal medicine, oncology, but also osteology [2]. Various fixatives and different methods are described for preparation of bone marrow biopsy sections; however, each hematopathologist prefers his own technique used in his laboratory. Therefore, it is not our intention to persuade the investigating pathologists to use a special method, but the need for well-fixed and well-stained thin sections cannot be emphasized enough.

As the name "bone marrow" implies, histological examination includes bone structure as well as marrow. In adults, normal bone marrow consists of fatty tissue and hematopoiesis, which is present in skull, sternum, clavicle, scapula, vertebrae, ribs, pelvic bone, and proximal sections of hollow bone [3]. The term "marrow cellularity," used by hematologists and hematopathologists, refers to the actively producing compartment and does not include fatty tissue. Thus, aplastic marrow or hypoplastic marrow shows complete or partial replacement by fat cells. Usually, bone marrow biopsies are taken from the posterior iliac crest [2]. Preferably, bone marrow examination should be done in conjunction with clinical data (including question and/or indication for examination, previous illnesses, drugs) and complete blood count data and, ideally with bone marrow aspirate imprints or smears (in our experience, only in rare cases cytology is available for the investigating hematopathologist; thus, this book focuses on histology, immunohistochemistry and, if necessary, molecular pathological methods of bone marrow biopsies). A bone marrow biopsy containing at least five intertrabecular spaces (excluding subcortical spaces containing mainly fatty tissue) is considered adequate for diagnosis. All biopsy specimens should have sections routinely stained with hematoxylin and eosin (H&E), May–Grünwald Giemsa (MGG) or Giemsa, BBL and reticulin stain (e.g., Gomori's stain). Metachromatic stains (e.g., MGG) give additional information, which are not available in routinely H&E stained sections. For example, identification of eosinophils, plasma cells, and mast cells is facilitated; furthermore, differentiation of proerythroblasts and myeloblasts is easily possible. Iron stains (e.g., Prussian blue) should be done from each bone marrow biopsy; however, one has to be aware that decalcification might remove iron. Therefore, the report should state "iron stain is negative" and not "there is absence of storage iron."

The most important and indispensable information for diagnosis of bone marrow biopsies is the knowledge of the patient's age (without knowledge of the patient's age, bone marrow diagnosis is not accurate and always incomplete). This knowledge helps to avoid pitfalls in histological

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C. Beham-Schmid, A. Schmitt-Graeff, *Bone Marrow Biopsy Pathology*,
Essentials of Diagnostic Pathology, https://doi.org/10.1007/978-3-662-60309-3_1

diagnosis, for example, recognition of normally present subcortical hypoplasia or non-representative tangentially retrieved BMB. It is also important to recognize and report changes in hematopoietic cells due to inadequate fixation, decalcification, or staining procedures.

1.1.1 Bone Components (Fig. 1.1)

Representative bone marrow biopsies show cortical bone (cortex, compact bone) and trabecular bone (trabeculae, cancellous bone, ossicles) (Fig. 1.1a, b) with appendant bone

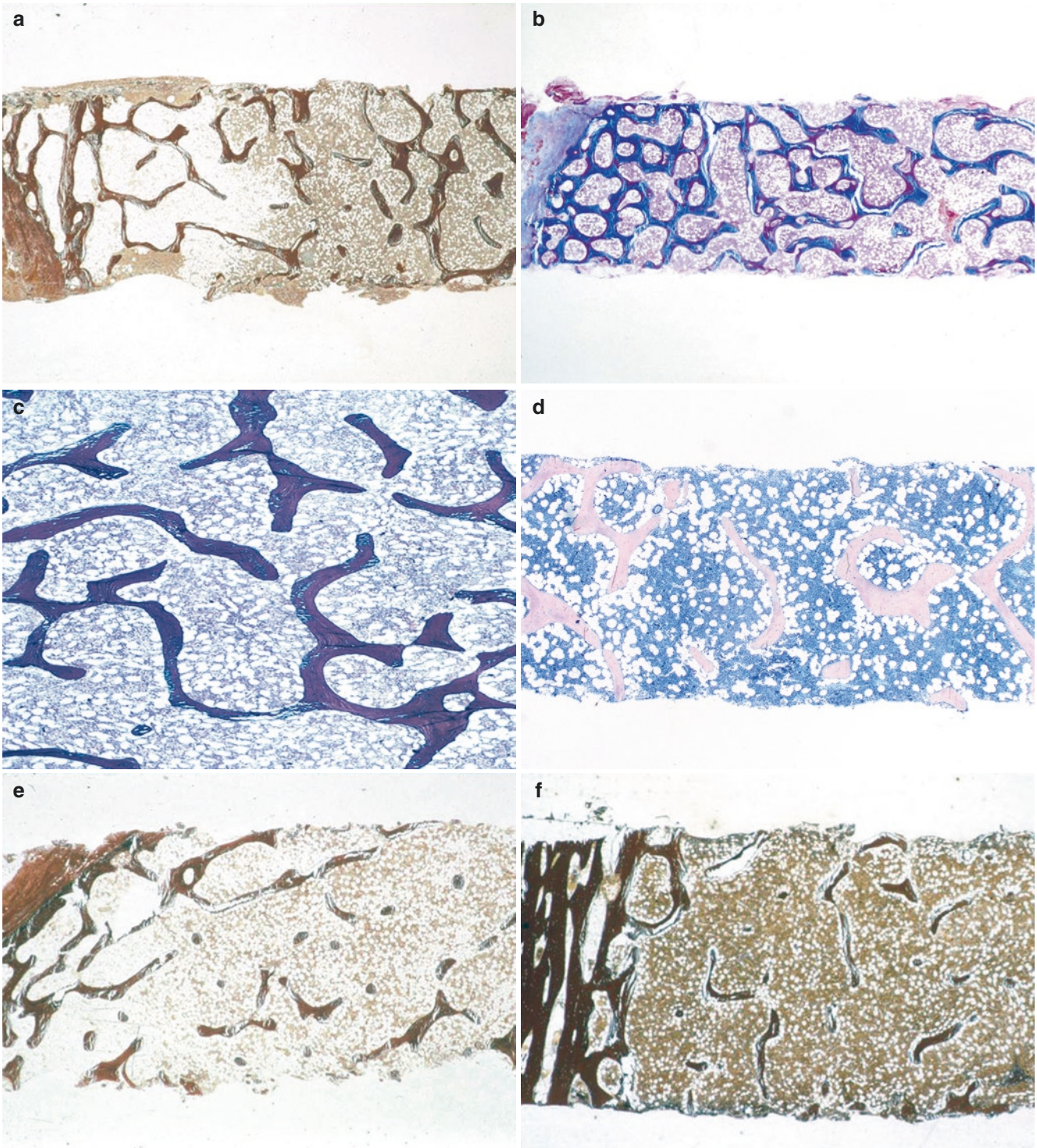

Fig. 1.1 (**a**, **b**) Low magnification of representative BMBs with cortical bone (left side) and trabecular bone (left biopsy: Gomori's stain, right biopsy: Ladewig). (**c**) Higher magnification of (**b**) showing trabecular bone constituting the honeycomb of bone. (**d**) Normal bone structure (MGG) of a 50-year-old female. (**e**) BMB of a 52-year-old female with rarefication of trabecular bone (Gomori's stain). (**f**) A 48-year-old female showing rarefication of trabecular bone (Gomori's stain). (**g**) Severely thickened cancellous bone of a 60-year-old male (Gomori's stain). (**h**) BMB of a 73-year-old male with marked osteosclerosis (Gomori's stain)

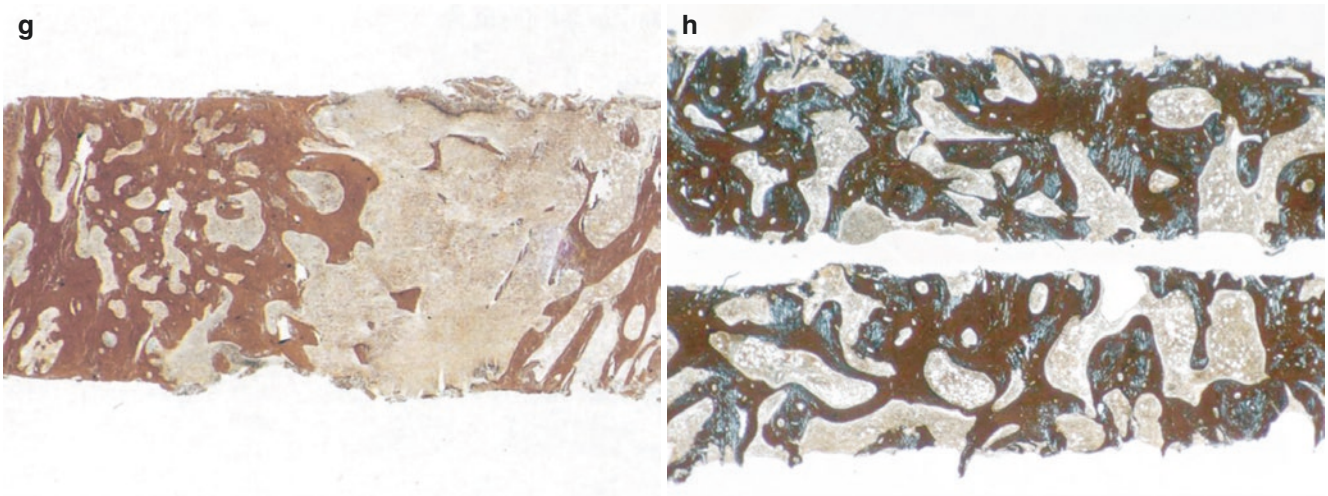

Fig. 1.1 (continued)

cells, which are flat endothelial cells, lining trabecular and subcortical surface, osteoblasts, osteoclasts, and osteocytes.

The cortex is a solid layer of compact bone of various thickness, on the outside periosteum, on the inside the endosteum, a single layer of cells, are attached. The cortex mainly consists of lamellar bone, but some woven bone is also present. There is constant remodeling of the bone. In adults, remodeling of the bone mainly takes place in the subcortical regions. A new layer of bone is added by osteoblasts, while the osteoclasts resorb other areas of the bone. Up to 20–25% of the bone surface may be covered by osteoid.

Trabecular bone constitutes the honeycomb of bone (Fig. 1.1c, d) and is enclosed by the cortical bone. A rarefication of trabeculae (osteopenia) results in enlargement of marrow cavities (Fig. 1.1e, f). A thickening of cancellous bone, osteosclerosis, causes a decreased size of marrow spaces (Fig. 1.1g, h). Semi-automatic and/or computerized quantification systems for bone and bone marrow structures are not generally required for the diagnosis and interpretation of bone marrow biopsy sections. For routine diagnosis, subjective assessment by naked eye of the components of the biopsy sections in a number of fields in the light microscope, or, if requested by the clinicians, assessment by use of a graticule in the ocular is recommended [3] (Fig. 1.2).

Osteoblasts with a diameter from 20 to 50 µm produce the bone matrix, osteoid, which gets subsequently ossified [4]. Osteoblasts line the surface of the cancellous bone and if these cells are activated, they become cuboidal (Fig. 1.2a, b). After mineralization of bone, some osteoblasts are trapped within the bone and transformed into osteocytes (Fig. 1.2c). The cytoplasmic processes of osteocytes connect with the processes of other osteocytes and also with osteoblasts on the surface of the bone (Fig. 1.2d–f). Thus, a circulatory network within the osseous system, within the bone and to its surface, is built, providing the subsistence of the osteocytes and enables the transfer between bone, bloodstream, and interstitial fluid.

Osteoclasts are the bone-resorbing cells on or near the surface of the bone (Fig. 1.2g), often interposed between endothelial and endosteal cells and also between subcortical bone surface and endothelium on the trabecular surface. Osteoclasts, with their villous extensions bind to matrix adhesion proteins and produce resorption pits, shallow concavities, called Howship lacunae (Fig. 1.2h inset). The appearance of osteoclasts is either uni- or multinuclear. Multinuclear osteoclasts may even become larger than megakaryocytes (Fig. 1.2h). The relatively flat uni-nucleated osteoclasts equally do resorb bone as do the multinucleated forms. Bone marrow biopsies of children and young adults normally show marked bone remodeling with the presence of many osteoclasts, whereas in adults and older people the presence of many osteoclasts indicates a metabolic or a neoplastic disease.

Mean values from healthy adults for osteoblastic index (percentage of trabecular surface covered by cuboidal osteoblasts) is 5%. The osteoclastic index (number of osteoclasts/100 mm trabecular circumference) is 3–4/100 mm [4]. Although osteoclasts and osteoblasts share the surface of the trabeculae (Fig. 1.2g), these cells originate from different stem cells, osteoclasts from hematopoietic, and osteoblasts from mesenchymal stem cells.

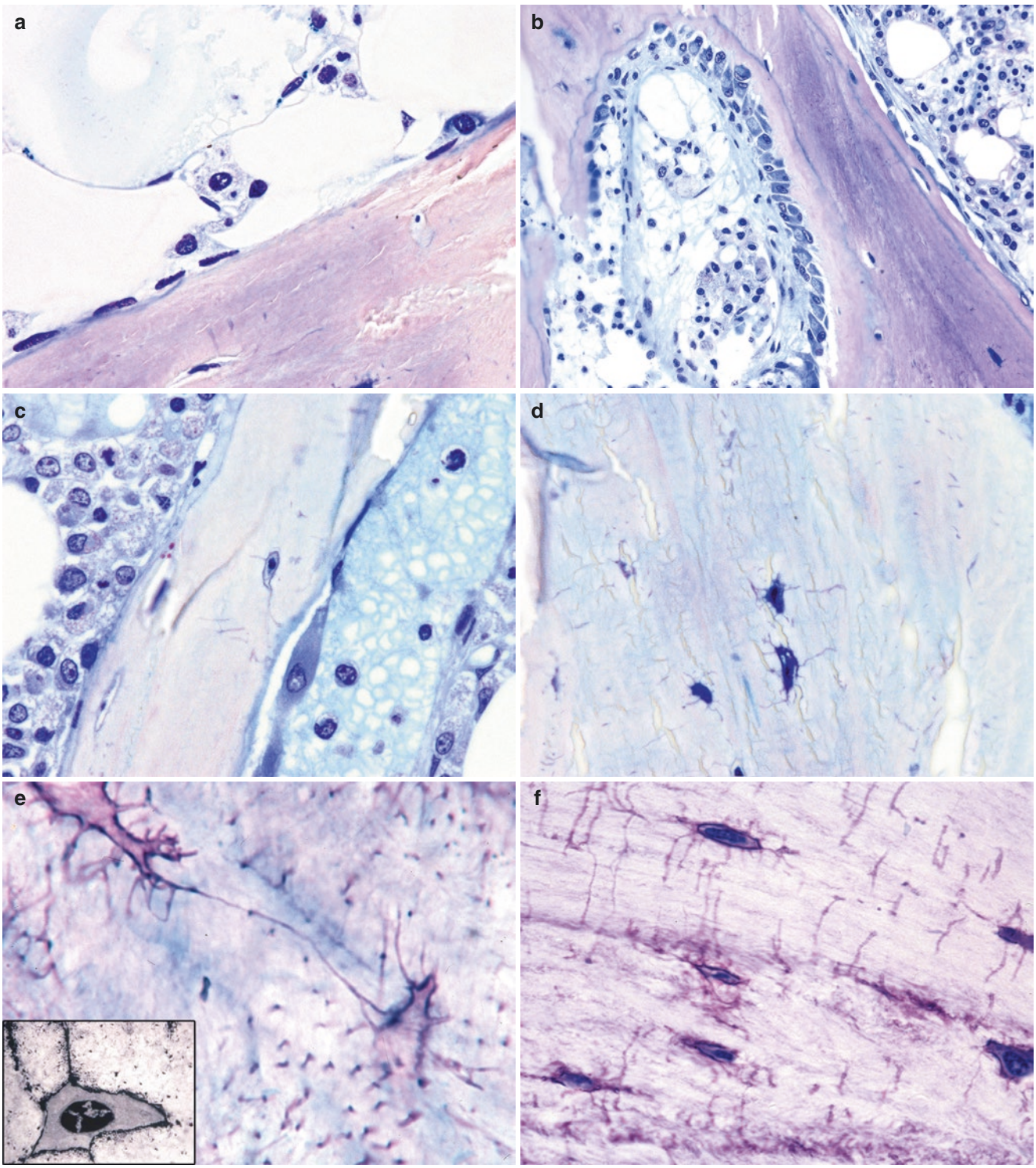

Fig. 1.2 (**a**) Osteoblasts lining the surface of bone (MGG). (**b**) Cuboidal activated osteoblasts (MGG). (**c**) Trabecular bone with osteocyte (MGG). (**d–f**) Cytoplasmic processes of osteocytes connecting with processes of adjacent osteocytes. Inset shows high magnification of osteocyte (MGG). (**g**) Multinucleated osteoclast on bone surface (MGG). (**h**) Huge multinucleated osteoclasts. Inset reveals Howship lacunae (MGG)

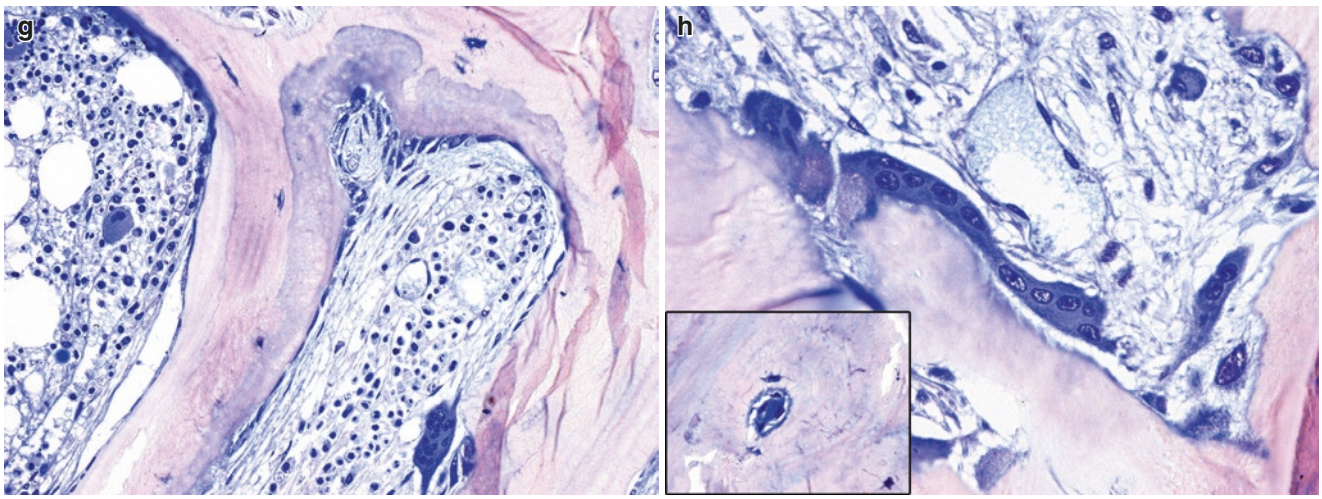

Fig. 1.2 (continued)

1.2 Cellularity of the Marrow

While BM aspirates (BMA) and BM trephine biopsies (BMTB) are excellent for assessment of lineage percentages and morphology, only BMTB can provide accurate information about the overall degree of cellularity and organization of all hematopoietic lineages. Also, if lymphocytic cells or plasma cells are increased, only BMTB will reveal the pattern of their distribution.

However, it is important that not only the width of the BMTB is adequate but also the length which ideally should measure at least 2 cm. Length is particularly important not only for the "staging" of neoplasms as to whether there is BM involvement but also in many infectious disease affecting BM (Fig. 1.3).

The term "cellularity" refers to hematopoietic as well as fat cells and indicates the relative amount of these components. Normal values are age-dependent (Fig. 1.3a) with individual deviations [5, 6]. For routine diagnosis, the cellularity is assessed subjectively; otherwise, there is the possibility of computerized image analysis or histomorphometry. Bone marrow cellularity is demonstrated as the percentage of a section occupied by hematopoietic tissue. This percentage can either refer to the entire biopsy including bone tissue, or, similar to an aspirate, to a marrow cavity excluding bone tissue [2]. The latter procedure is comparable to measurements of the cellularity of aspirated fragments. Slight differences in marrow cellularity have been described in different sites like sternum, lumbal vertebrae, and iliac crest [4].

The bone marrow of newborns mainly consists of cells with a negligent amount of fat cells (0–<5%). With increasing age, cellularity decreases with an accelerated rate of reduction beyond the age of 70. The decrease in hematopoietic tissue with advanced age is due to a loss of bone substance and also caused by a true loss of the amount of hematopoietic tissue. The marrow cavities consequently are filled with fat cells. At the age of 20, the average cellularity is 70–80%, at the age of 50 cellularity is 50–60%, and at 70 years and beyond, cellularity is reduced to 20–30% [2, 6–8] (Fig. 1.3a).

The spatial arrangement of hematopoiesis is a potential pitfall with regard to the normally present subcortical hypoplasia (subcortical fatty tissue) (Fig. 1.3b–d). To avoid the error of estimating cellularity in subcortical regions, it is necessary to pay attention to bone structures in the biopsy (e.g., a tangentially taken sample with plenty of cortical bone Fig. 1.3e). A representative biopsy (as mentioned before) should show at least three intertrabecular spaces [9, 10].

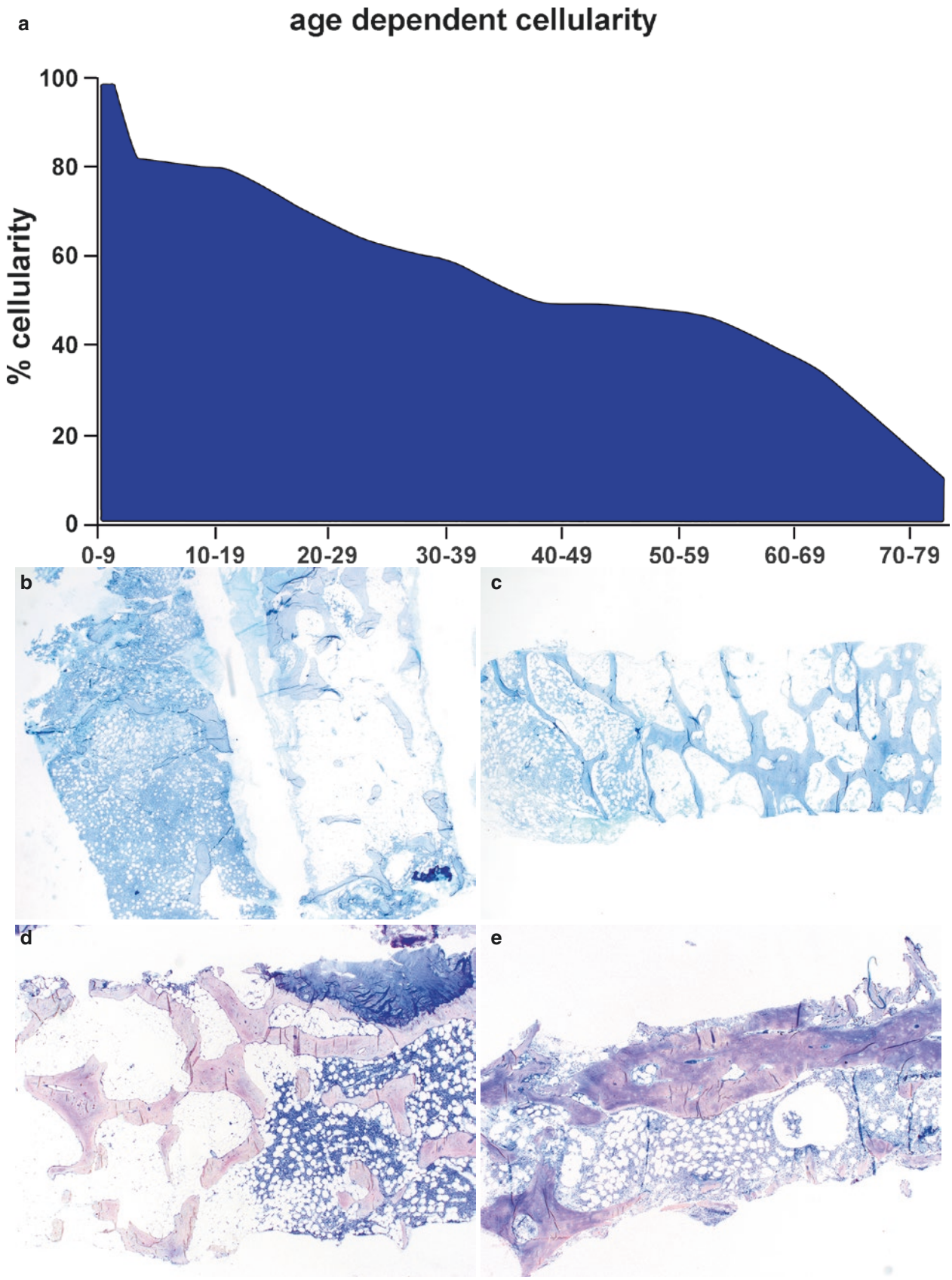

Fig. 1.3 (**a**) Schematic representation of cellularity in normal bone marrow biopsies showing decrease of hematopoiesis with advanced age. (**b**) BMB of a patient with myeloproliferative neoplasm (left side is representative for diagnosis, the biopsy on the right side reveals subcortical fatty tissue) (MGG). (**c**, **d**) Physiological subcortical hypoplasia: a common diagnostic pitfall (MGG). (**e**) The whole length of the biopsy shows cortical bone (tangentially taken sample) (MGG)

1.2.1 Topography (Fig. 1.4)

In the marrow cavities, hematopoietic tissue is distributed interstitial in the extravascular compartment (between the sinusoids) (Fig. 1.4a, b). In some pathological conditions, hematopoiesis can be found intrasinusoidal also. Myeloid precursor cells are closely attached to the endosteal surface and arterioles (Fig. 1.4c–f), more mature granulopoietic cells are seen in central intertrabecular areas. Attention should be paid to the term "myeloid," which, in the German- and English-speaking parts, has two different meanings. On the one hand, "myeloid" implies the complete hematopoiesis, on the other hand this term describes the granulopoietic and monocytopoietic lineage only, as demonstrated by the myeloid: erythroid (M:E) ratio. Usually, there is no interpretation problem, but ambiguousness in using the term "myeloid" should be avoided.

Groups of erythropoietic cells and megakaryocytes show a close association to the marrow sinusoids [3, 5, 8] (Fig. 1.4g, h). In normal bone marrow, considerable variations in the qualitative as well as quantitative distribution of cellular components can be observed.

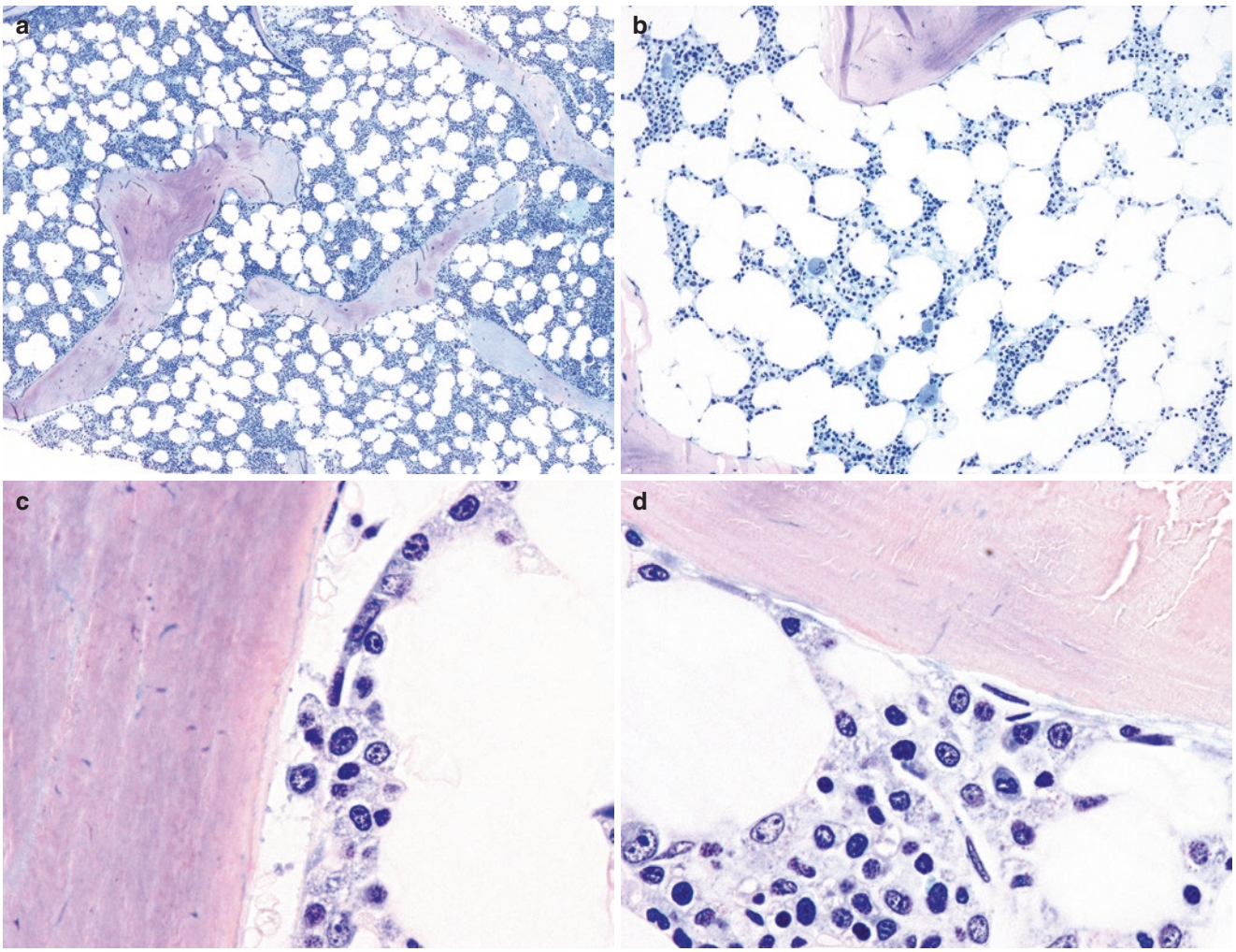

Fig. 1.4 (**a**, **b**) Distribution of hematopoiesis in the extravascular compartment (MGG). (**c**, **d**) Myeloid precursors are located closely to the surface of bone trabeculae (MGG). (**e**, **f**) Myeloid precursors located around arterioles (MGG). (**g**) Erythropoietic island closely attached to sinus (MGG). (**h**) Close association of megakaryocyte to sinus (MGG)

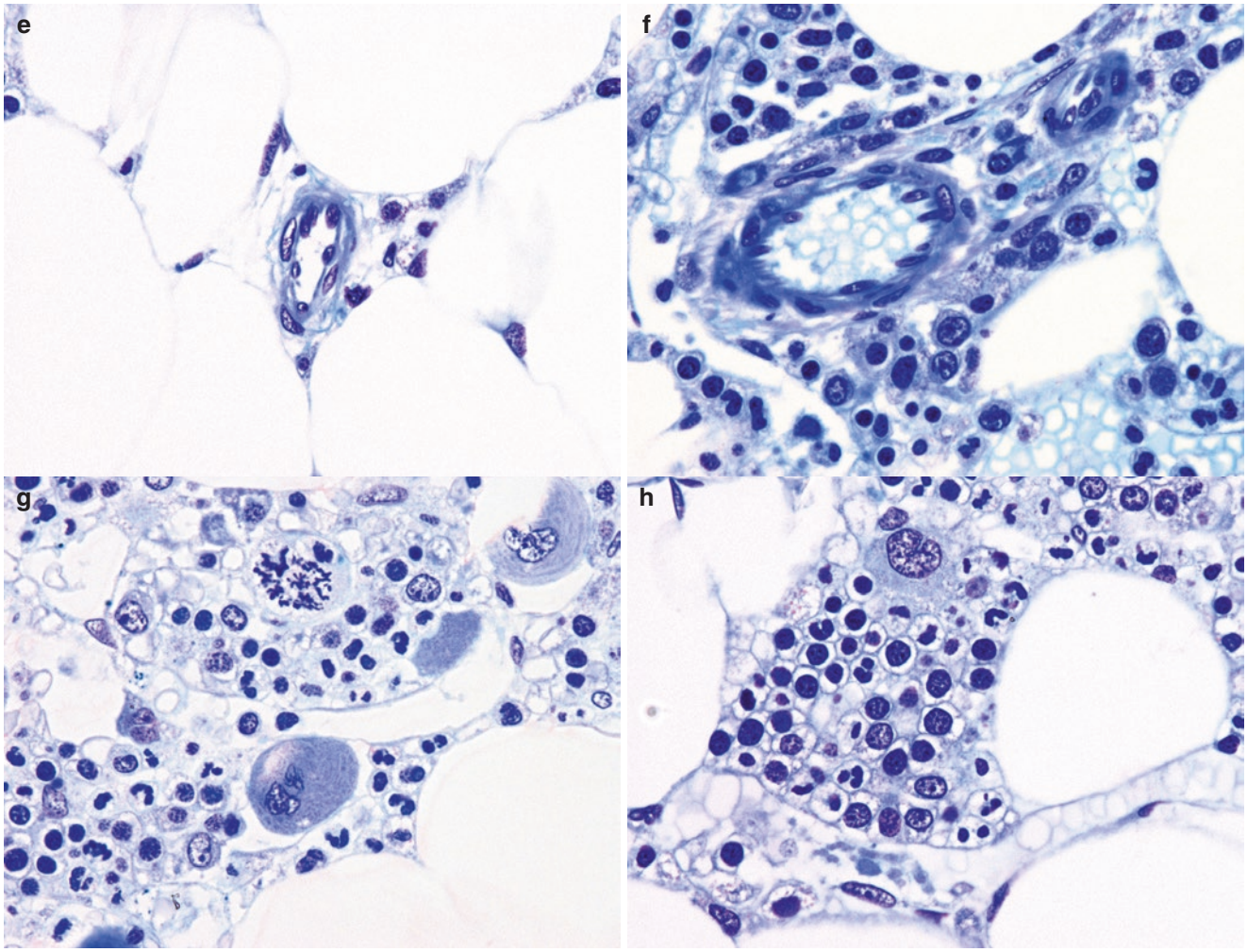

Fig. 1.4 (continued)

1.3 Cellular Components of the Bone Marrow

1.3.1 Hematopoiesis

Hematopoiesis occurs in the extravascular marrow spaces in a well-arranged order [11]. A common stem cell gives rise to all types of myeloid and lymphoid cells. Morphologically, the pluripotent stem cells and the stem cells committed to the specific cell lineages cannot be identified. For a healthy hematopoiesis, an efficient microenvironment is essential to provide all factors necessary for differentiation, proliferation, and maturation of stem cells to committed lineages. This environment mainly consists of adipocytes, macrophages, endothelial cells, bone lining cells, and extracellular matrix [12]. The normal values in the peripheral blood are reflected by the hematopoietic cells in the bone marrow. Hematopoiesis is rather sensitive to external influences. Proliferation occurs especially in neoplastic disease, suppression often is seen in chronic inflammation, malnutrition, toxic, or drug-induced conditions [13, 14].

Hematopoiesis in the elderly shows changes relating to physiological immunodeficiency as a result of aging with the occasional occurrence of dyshematopoiesis [15].

1.3.2 Erythrocytopoiesis (Fig. 1.5)

The nucleated precursors of the red cells are arranged in islands of various size comprising stages of maturation from the earliest recognizable erythroblast to the normoblast. These erythroblastic islands, called erythrones, usually enclose a centrally located macrophage. This macrophage (called "mother cell") often contains nuclear or cellular debris or hemosiderin (Fig. 1.5a). Usually, the red cells closely attached to the macrophage are more immature than the cells in the periphery. However, probably due to the plane of sectioning, the classical form of an erythropoietic island with centrally located macrophage is rarely found in biopsy sections. Normally, erythropoietic islands are located closely to marrow sinusoids (Fig. 1.5b–d). The normal myeloid: erythroid ratio in the BMB is 1.5:1 to 3:1. The early forms of nucleated red cells are large with small cytoplasm and large, rather round nuclei with dispersed chromatin and detectable nucleoli, which are occasionally adjoining the nuclear membrane. These early forms express both transferrin and glycophorin. More mature red cells show a rather condensed chromatin. With maturation, erythropoietic cells loose transferrin expression, while the expression of glycophorin remains stable [16] (Fig. 1.5e, f).

The following features are helpful in distinguishing erythroid precursors from other myeloid cells in the normal BMB: (1) occurrence of erythroid precursors normally in the form of clusters (islands) with cells of various maturation stage (2) usually, erythroblasts are closely attached to one another, (3) the nuclei are rather round, (4) late erythroblasts show regularly condensed chromatin, and lymphocytes (with a similar size) show a coarsely granular clumping of chromatin, (5) localization of erythrones is typically close to sinusoids [12, 17–19]. Since proerythroblasts and normoblasts are highly mitotic active cells, these cells show the highest amount of proliferation rate in normal BMBs (Fig. 1.5g, h).

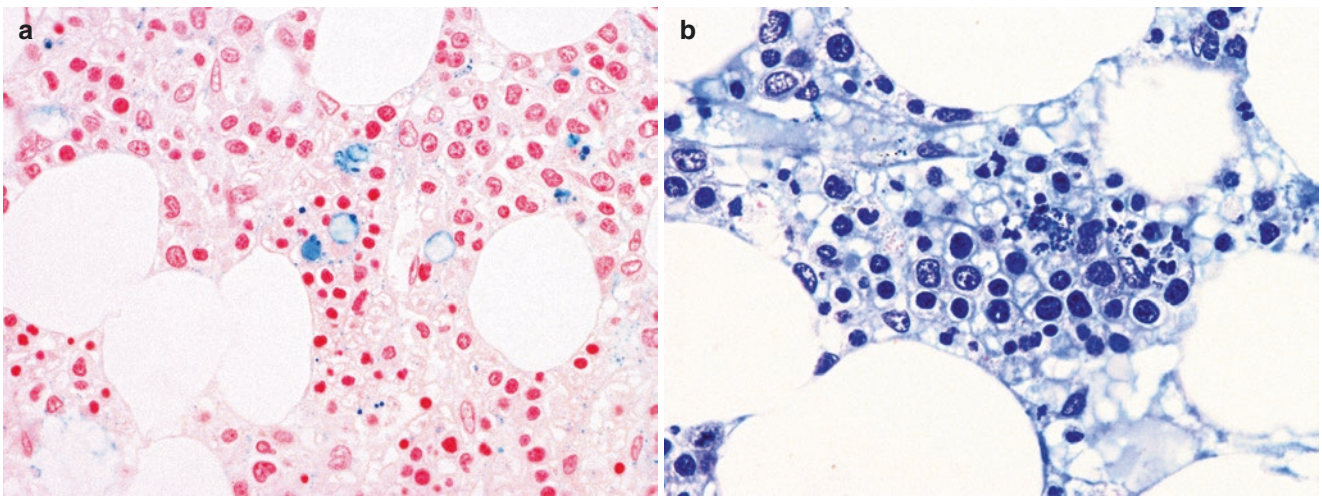

Fig. 1.5 (**a**) Erythron with enclosed macrophage (mother cell) containing hemosiderin (Prussian blue). (**b**–**d**) Erythropoietic islands are normally situated close to sinusoids (MGG). (**e**, **f**) Comparison of transferrin expression and glycophorin C expression in the same area of biopsy (left side: stained with antibody to transferrin [CD71], right side shows staining with antibody to Glycophorin C). (**g**, **h**) Normal BMB of older patient stained with H&E. On the right side, the same biopsy is immunohistochemically stained with the proliferation marker Ki67: Erythropoietic cells show the highest proliferation fraction

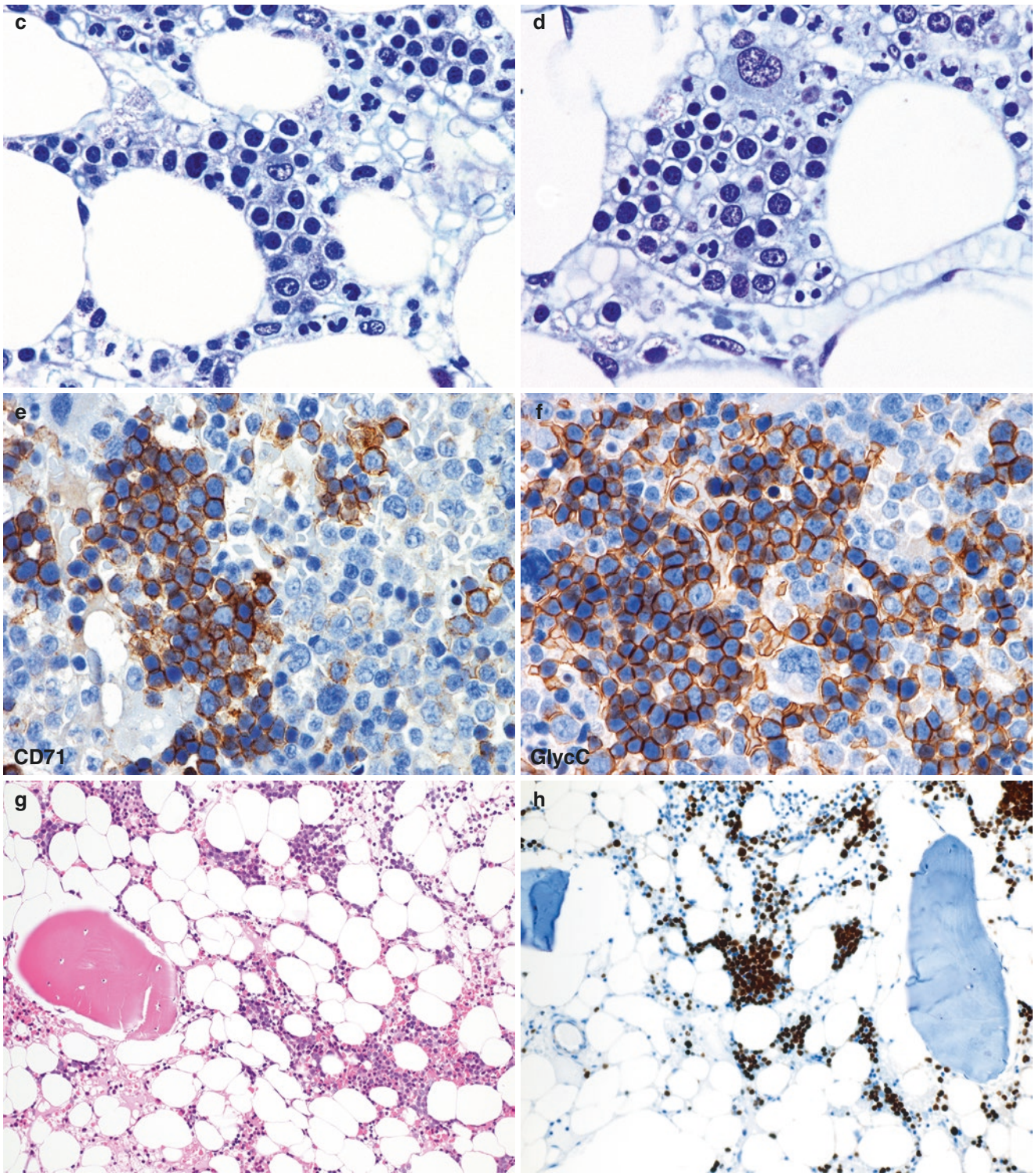

Fig. 1.5 (continued)

1.3.3 Granulocytopoiesis (Figs. 1.6 and 1.7)

Sections of normal BMBs contain neutrophils, eosinophils, and basophils, which can be identified by metachromatic stains (e.g., MGG) or immunohistochemically (Fig. 1.6a, b). The granulocytopoiesis, representing 50–70% of nucleated cells, quantitatively dominates the hematopoiesis. According to maturation, myeloblasts, promyelocytes, myelocytes, metamyelocytes, and segmented forms can be detected. The most immature myeloid cell detectable in bone marrow sections is the myeloblast, mostly located closely attached to the trabecular surface, or periarteriolar (Fig. 1.6c, d). In greater number promyelocytes and myelocytes are seen, which, in thin stained sections show a granulation of the cytoplasm. These cells are located also in the generation zone of myeloid cells. The more mature granulopoietic cells do not show any connections with the paratrabecular or periarteriolar areas. The distribution of granulopoietic cells can be highlighted immunohistochemically with antibodies to myeloperoxidase (MPO) and CD15. MPO shows a strong positivity in promyelocytes, and a rather weak positivity in more mature forms (Fig. 1.6e, f), whereas CD15 is strongly positive in metamyelocytes and granulocytes (Fig. 1.7a–d) [19]. Neutrophils and eosinophils are easily detectable in conventionally stained sections; however, for the detection of basophilic differentiated cells, special stains, or immunohistochemical investigations are necessary.

If the myeloid:erythroid ratio is increased without decrease in erythroid cells, granulocytic hyperplasia is indicated. In such conditions, either normal proportions of the various maturation stages are seen, or there can be a "shift to the left" with preponderance of immature forms, or a "shift to the right" with an increase of mature granulocytes. As mentioned before, the paratrabecular and periarteriolar areas constitute the generation zones of granulopoietic cells, more mature forms are seen in central areas of marrow spaces. However, single immature granulopoietic cells are found without recognizable connection to paratrabecular or periarteriolar areas. Normally, since granulocytopoiesis is very effective, all cells produced reach the circulation [4].

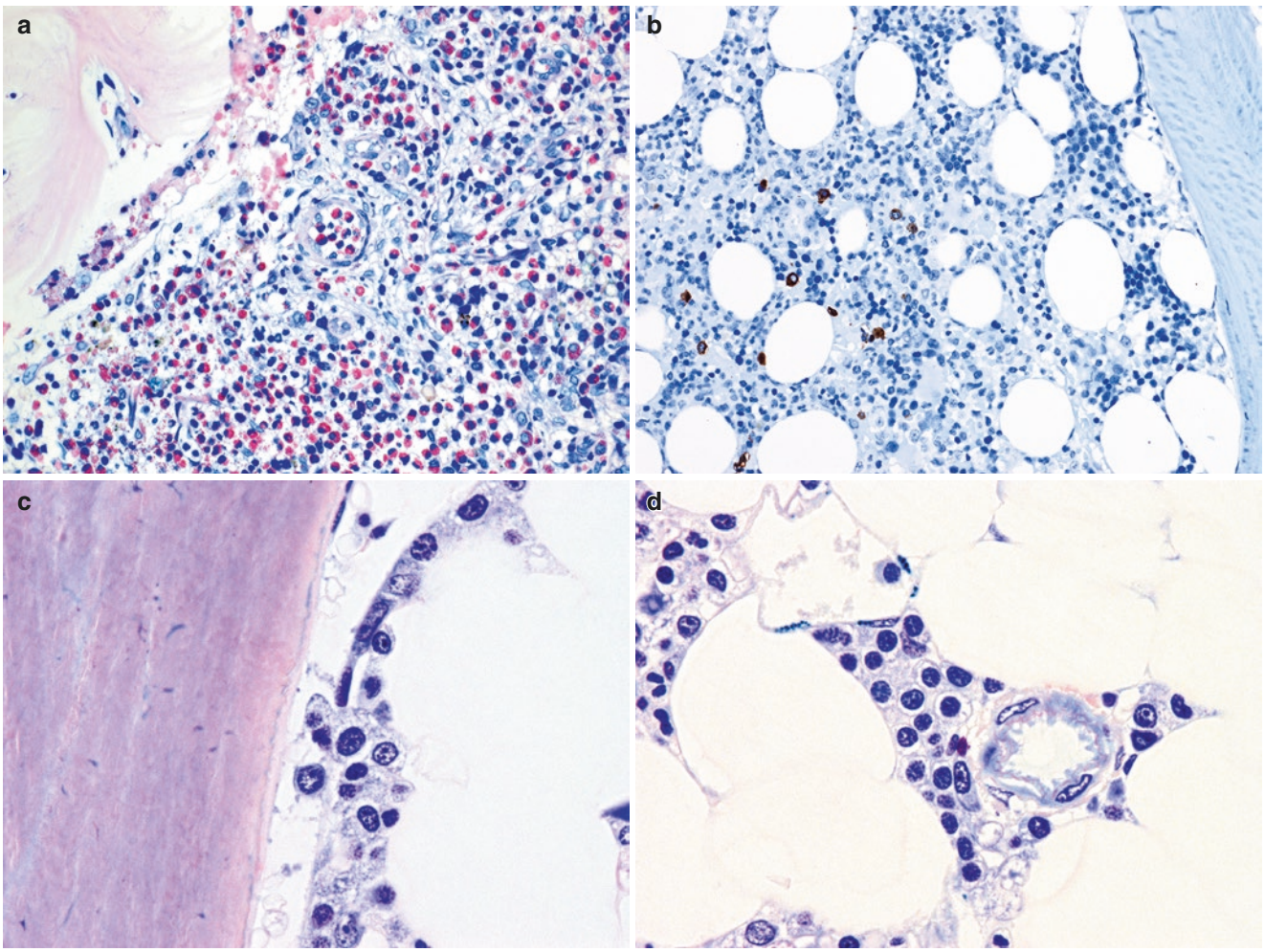

Fig. 1.6 (**a**) Eosinophils are easily identified with MGG. (**b**) A few basophils are detected in normal bone marrow immunohistochemically (2D7). (**c**, **d**) Myeloid precursors located peritrabecular (left biopsy) and periarteriolar (right side) (MGG). (**e**, **f**) Strong positivity of precursor myeloid cells using an antibody to MPO